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DAVI DA SILVA BARBIRATO

A MEDICINA PERIODONTAL NO CONTEXTO DA PANDEMIA DE COVID-19 E OBESIDADE, E A IMPORTÂNCIA DA AVALIAÇÃO HEPÁTICA EM PACIENTES COM PERIODONTITE

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Orientadora: Profª Drª Maria Cynésia Medeiros de Barros

Co-orientador: Prof Dr João Régis Ivar Carneiro

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CENTRO DE CIÊNCIAS DA SAÚDE
FACULDADE DE ODONTOLOGIA

DAVI DA SILVA BABIRATO

"A Medicina Periodontal no contexto da pandemia de COVID-19 e obesidade, e a importância da avaliação hepática em pacientes com periodontite"

Orientadores: Profª Drª Maria Cynésia Medeiros de Barros
Prof. Dr. João Regis Ivar Carneiro

Defesa de Doutorado, realizada por via remota, submetida ao Programa de Pós-Graduação em Odontologia da Faculdade de Odontologia da Universidade Federal do Rio de Janeiro – UFRJ como parte dos requisitos necessários à obtenção do grau de Doutor em Odontologia – área de concentração em Periodontia.

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“A menos que modifiquemos a nossa maneira de pensar, não seremos capazes de resolver os problemas causados pela forma como nos acostumamos a ver o mundo.”

Albert Einstein (1879-1955)

RESUMO

A presente Tese teve como objetivo desenvolver um ensaio teórico sobre a importância da patogênese da COVID-19 na pesquisa em Medicina Periodontal, e realizar uma síntese das evidências científicas sobre a relação entre obesidade e periodontite, a importância da PCR enquanto biomarcador de impacto sistêmico da periodontite, e os efeitos da bacteremia e endotoxemia por patógenos periodontais e suas toxinas no fígado. Desenvolvemos uma pesquisa bibliográfica sistematizada e de delineamento misto, cujos objetivos foram explorados em estudos individuais apresentados em seis capítulos. Os resultados sugerem que a COVID-19 e periodontite compartilham mecanismos de patogênese e fatores de risco que podem influenciar os estudos em Medicina Periodontal. Os efeitos da obesidade na periodontite parecem estar relacionados com o aumento de biomarcadores inflamatórios e complicações associadas às desordens no metabolismo da glicose. Existem evidências da associação entre obesidade e parâmetros clínicos periodontais, resistina e IL-1β no FCG, bem como de melhora da pressão arterial, colesterol total, LDL, triglicerídeos, HbA1c, resistência insulínica, PCR, IL-1β, TNF-α e C3 no sangue, quemerina, vaspina, omentina-1, visfatina, e 8-OHdG no FCG após o tratamento da periodontite. Alguns patógenos periodontais também reduziram em quantidade. As evidências atuais confirmam a redução de PCR após o tratamento da periodontite em pacientes com diabetes tipo 2, pré-hipertensão e hipertensão arterial, e insuficiência renal submetidos a hemodiálise e/ou diálise peritoneal. Além do aumento de PCR, o fígado desenvolve doença NAFL, NASH e fibrose avançada por ação direta de patógenos periodontais e LPS bacteriano, a partir da corrente sanguínea e do eixo boca-intestino-fígado. Casos graves de patologia hepática foram associados à bacteremia por patógenos bucais. Portanto, a obesidade e a avaliação hepática devem ser consideradas em novas pesquisas e na prática clínica em Medicina Periodontal. A evidência de associação entre a periodontite e níveis séricos de PCR reforça seu papel como biomarcador de risco sistêmico, e os efeitos da COVID-19 na patogênese das doenças periodontais e sistêmicas devem ser considerados.

Palavras-chave: COVID-19, Obesidade, Proteína C-Reativa. Hepatopatia Gordurosa Não Alcoólica.

ABSTRACT

This thesis aimed to develop a theoretical essay on the importance of the pathogenesis of COVID-19 in research in Periodontal Medicine, and to perform a synthesis of the scientific evidence on the relationship between obesity and periodontitis, the importance of CRP as a biomarker of the systemic impact of periodontitis. and the effects of bacteremia and endotoxemia by periodontal pathogens and their toxins on the liver. We developed a systematic literature search with a mixed design, whose objectives were explored in individual studies presented in six chapters. The results suggest that COVID-19 and periodontitis share pathogenesis mechanisms and risk factors that may influence studies in Periodontal Medicine. The effects of obesity on periodontitis seem to be related to the increase in inflammatory biomarkers and complications associated with disturbances in glucose metabolism. There is evidence of an association between obesity and periodontal clinical parameters, resistin and IL-1β in GCF, as well as improvement in blood pressure, total cholesterol, LDL, triglycerides, HbA1c, insulin resistance, CRP, IL-1β, TNF -α and Blood C3, chemerin, vaspin, omentin-1, visfatin and 8-OHdG in FCG after periodontitis treatment. Some periodontal pathogens were also reduced in quantity. Current evidence confirms the reduction of CRP after treatment of periodontitis in patients with type 2 diabetes, pre-hypertension and arterial hypertension and renal failure on hemodialysis and/or peritoneal dialysis. In addition to increased CRP, the liver develops NAFL disease, NASH and advanced fibrosis by the direct action of periodontal pathogens and bacterial LPS from the bloodstream and the mouth-gut-liver axis. Severe cases of liver pathology have been associated with bacteremia by oral pathogens. Therefore, obesity and liver assessment should be considered in new research and clinical practices in Periodontics. Evidence of an association between periodontitis and serum CRP levels reinforces its role as a biomarker of systemic risk, and the effects of COVID-19 on the pathogenesis of periodontal and systemic diseases should be considered.

Keywords: COVID-19, Obesity, C-reactive Protein, Non-alcoholic Fatty Liver Disease.

LISTA DE ABREVIATURAS E SIGLAS

ACE2 – Enzima conversora de angiotensina II

AGEs – Produtos finais da glicação avançada

A.a. – Aggregatibacter actinomycetemcomitans

Ang-(1-7) – Angiotensina-(1-7)

AT1R – Receptor AT1

B2R – Receptor de bradicinina 2

BMI – Índice de massa corporal

CD68 – *Cluster* de diferenciação 68

C.p. – Chlamydia pneumoniae

COVID-19 – Doença de coronavírus 2019 (COVID-2019)

C3 – Componente 3 do complemento

DCNT – Doença crônica não-transmissível

FGF – Fator de crescimento fibroblástico

FIB-4 – Fibrose-4

F.n. – Fusobacterium nucleatum

G-CSF – Fator estimulador de colônias granulocitárias

GM-CSF – Fator estimulador de colônias de granulócitos e macrófagos

HbA1c – Hemoglobina glicada

IC95% – Intervalo de confiança 95%

IFN-γ - Interferon-gama

IL-10 – Interleucina-10

IL-17 – Interleucina-17

IL-1β – Interleucina-1β

IL-2 – Interleucina-2

IL-6 – Interleucina-6

IL-6 – Interleucina-6

IL-7 – Interleucina-7

IL-8 – Interleucina-8

IL-9 – Interleucina-9

IL1RA – Antagonista do receptor de interleucina-1

IP-10 – Proteína 10 induzida por IFN-γ

Kg – Quilograma

LPS – Lipopolissacarídeo

LDL – Lipoproteína de baixa densidade

m^2 – Metro quadrado

MAFLD – Doença hepática gordurosa associada ao metabolismo

MasR – Receptor Mas

MCP-1 – Proteína quimiotática de monócitos-1

MIP-1-β – Proteína inflamatória de macrófagos-1-beta

MIP-1-α – Proteína inflamatória de macrófagos-1-alfa

ml – Mililitro

NAFL – Esteatose hepática não alcoólica

NAFLD – Doença hepática gordurosa não alcoólica

NAS – Escore de esteatose não alcoólica

NASH – Esteatohepatite

OR – Razão de chances

PCR – Proteína C reativa

PDGF – Fator de crescimento derivado de plaquetas

P.g. – Porphyromonas gingivalis

P.i. – Prevotella intermedia

RR – Risco relativo

Saa – Proteína amilóide A sérica

SARS-CoV-2 – Coronavirus 2 da síndrome respiratória aguda grave

SDRA – Síndrome do desconforto respiratório agudo

T.f. – Tannerella forsythia

Th1 – Linfócito Th1

Th17 – Linfócito Th17

TLR2 – Receptor tipo Toll 2

TMPRSS – Serino proteases transmembrana

TNF-α – Fator de necrose tumoral-α

T.d. – Treponema denticola

UTI – Unidade de terapia intensiva

VEGF – Fator de crescimento endotelial vascular

8-OHdG – 8-hidroxiguanosina

μg – Microgadia

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1. INTRODUÇÃO

O coronavírus SARS-CoV-2 é uma cepa do coronavírus relacionada à síndrome respiratória aguda grave, membro da família Coronaviridae e agente responsável pela doença referida como doença de coronavírus 2019 (COVID-2019) (Hu et al., 2021). Atualmente, a COVID-19 é o problema de saúde mais urgente e emergente em todo o mundo.

A maioria dos pacientes com COVID-19 apresenta sintomas leves (Huang et al., 2020). Aproximadamente 14% dos casos confirmados desenvolvem condições graves que requerem hospitalização e suporte de oxigênio, 5% precisam de internação em unidades de terapia intensiva e cerca de 2% morrem (NCPERE, 2020). Casos graves geralmente são complicados pela síndrome do desconforto respiratório agudo (SDRA), sepse e choque séptico, levando a danos em vários órgãos (Yang et al., 2020a). Estes casos estão associados a uma resposta imune exacerbada, caracterizada por níveis excessivos de citocinas pró-inflamatórias e dano tecidual generalizado (Mehta et al., 2020), chamada síndrome da "tempestade de citocinas" (Yang, et al., 2020b). A mortalidade por COVID-19 foi associada a níveis séricos elevados de interleucina-6 (IL-6), proteína C reativa (PCR), dímero D e ferritina (Chen et al., 2020b; Ruan et al., 2020), sugerindo uma ligação clara entre a gravidade da doença e uma hiperinflamação.

A associação entre periodontite e COVID-19 pode se dar pelo contato direto do vírus com os tecidos periodontais, devido à expressão de seus fatores de entrada [enzima conversora de angiotensina II (ACE2), serino proteases transmembrana (TMPRSS) e furina] na mucosa oral (Roganović, 2021; Park et al., 2022), e/ou pela superexpressão de citocinas inflamatórias como fator de necrose tumoral-α (TNF-α), antagonista do receptor de interleucina-1 (IL1RA), interleucina (IL)-1β, IL-2, IL-6, IL-7, IL-8, IL-9, IL-10, IL-17, interferon-gama (IFN-γ), proteína 10 induzida por IFN-γ (IP-10), fator de crescimento fibroblástico (FGF), fator estimulador de colônias granulocitárias (G-CSF), fator estimulador de colônias de granulócitos e macrófagos (GM-CSF), proteína quimiotática de monócitos-1 (MCP-1), proteína inflamatória de macrófagos 1-alfa (MIP-1-α), proteína inflamatória de macrófagos 1-beta (MIP-1-β), fator de crescimento derivado de plaquetas (PDGF) e fator de crescimento endotelial vascular (VEGF) (Huang et al., 2020; Regab et al., 2020; Chen et al., 2021). A relação entre o sistema renina-angiotensina, inibidores da ACE2 e a periodontite se dá pela reabsorção óssea alveolar regulada pelo eixo ACE2/Ang-(1-7)/MasR e IL1-β, pela regulação positiva da via cinina/B2R mediada por TLR2, pela resposta Th1/Th17, e pela expressão de AT1R no tecido gengival

inflamado (Hollá et al., 2001; Gürkan et al., 2009; Santos et al., 2009; Santos et al., 2015; Rodrigues et al., 2016). Este estímulo é capaz de modular a produção de IL-6 e IL-1β em fibroblastos gengivais humanos (Nakamura et al., 2011).

A periodontite é caracterizada por uma inflamação crônica em resposta a uma disbiose no biofilme subgengival (Curtis et al., 2020). A inflamação crônica frequentemente e persistente leva a inflamação sistêmica de baixo grau e ao aumento dos níveis de citocinas como TNF-α, IL-1β, IL-4, IL-6 e IL-10 (Chapple et al., 2013; Acharya et al., 2017), bem como PCR e ferritina (Thounaojam, 2019). A PCR ultra-sensível "representa um somatório da inflamação sistêmica geral do paciente, que pode em parte ser influenciada pela periodontite, mas por outro lado é uma carga inflamatória 'inexplicável' que é valiosa para avaliar em colaboração com os médicos do paciente", conforme descrito na classificação e definição de caso das doenças periodontais vigente. Prevê-se que no futuro será possível vincular o grau de periodontite ao potencial impacto sistêmico da doença (Tonetti et al., 2018). No entanto, de acordo com esses autores, a avaliação do risco de impacto sistêmico da periodontite com base nos níveis de PCR e biomarcadores ainda carece de evidências específicas.

A gravidade da COVID-19 tem sido associada à presença de doenças crônicas como as cardiovasculares, hipertensão arterial, diabetes mellitus, obesidade e doença renal crônica, além da idade (Wu et al., 2020; Zhou et al., 2020; Rapp et al., 2021). Ao tempo em que os fatores de risco que levam a piores resultados clínicos não foram totalmente elucidados, Marouf et al. (2021) descreveram uma OR de 8,81 (IC95%: 1,00-77,7), 3,54 (IC95%: 1,39-9,05) e 4,57 (IC95%: 1,19-17,4) para morte, admissão em unidade de terapia intensiva (UTI) e necessidade de ventilação assistida em pacientes com COVID-19 e periodontite, respectivamente. Estes resultados foram ajustados para potenciais confundidores. Larvin et al. (2021) descreveram efeitos aditivos da periodontite e da obesidade nos desfechos da COVID-19. Para pacientes com obesidade, a taxa de mortalidade foi muito maior (RR = 3,11; IC95%: 1,91-5,06) entre aqueles com periodontite do que naqueles sem periodontite. A obesidade foi associada a maiores taxas de hospitalização e mortalidade, e a periodontite parece exacerbar esse efeito.

A obesidade aumenta a susceptibilidade às formas graves de COVID-19 (Petrilli et al., 2020; Price-Haywood et al., 2020; Stefan et al., 2021). Um dos primeiros estudos de associação entre COVID-19 e obesidade, desenvolvido na França, reportou uma OR de 7,36 (IC95%: 1,63-33,14) para necessidade de ventilação mecânica invasiva em pacientes com BMI $\geq$ 35 kg/m^2, em comparação com BMI < 25 kg/m^2 (Simonnet et al., 2020). Esta associação foi independente

de idade, sexo e comorbidades como diabetes mellitus, hipertensão arterial ou dislipidemia. Em outro estudo, sobrepeso (BMI 24,0–27,9 kg/m^2) e obesidade (BMI ≥ 28 kg/m^2) apresentaram uma OR ajustada de 1,84 (IC95%: 0,99-3,43) e 3,40 (IC95%: 1,40-2,86), respectivamente, para desenvolver pneumonia grave em casos de internação hospitalar por COVID-19, em comparação com pacientes de peso normal (BMI 18,5-23,9 kg/m^2) (Cai et al., 2020). A pessoa com obesidade apresenta um risco aproximadamente três vezes maior de COVID-19 grave (OR = 3,00; IC95%: 1,22-7,38), mesmo após ajuste para idade, sexo, tabagismo, hipertensão arterial, diabetes mellitus e dislipidemia (Gao et al., 2020). Além destes, outros estudos e outros países reportaram resultados semelhantes, apontando a obesidade como uma doença crônica não transmissível de alto risco para a COVID-19 (Stefan et al., 2021).

Embora o mecanismo fisiopatológico seja desconhecido, estudos sugerem a obesidade como um fator de risco para periodontite (Al-Zahrani e Alghamdi, 2012; Martinez-Herrera et al., 2017). Alguns estudos propõem que os altos níveis de citocinas pró-inflamatórias circulantes como TNF-α, IL-1β, e IL-6 em pacientes com obesidade, podem aumentar a destruição periodontal (Zuza et al., 2011; Kose et al., 2015). O primeiro estudo a relatar a possível relação entre obesidade e periodontite data de 1977 (Perlstein e Bissada, 1977). Os autores observaram que o acúmulo de biofilme bacteriano esteve associado à maior destruição do osso alveolar em ratos com obesidade, comparados com ratos sem obesidade. Em associação com a hipertensão arterial, o dano periodontal foi mais pronunciado, mostrando um compartilhamento de fatores de risco para destruição periodontal entre hipertensão e obesidade. Além disso, revisões sistemáticas demonstraram o efeito negativo da obesidade na resposta ao tratamento periodontal (Papageorgiou et al., 2015), nos parâmetros clínicos periodontais e imunológicos, comparando indivíduos com e sem obesidade (Akram et al., 2016a,b; Gerber et al., 2016; Akram et al., 2017; Nascimento et al., 2016). O nível de evidência foi descrito como moderado para esta associação (Jepsen et al., 2017).

Pacientes gravemente doentes com COVID-19 podem morrer de falência de órgãos relacionada à doença subjacente, como a doença cardiovascular, diabetes mellitus, doença renal e doença hepática (Wang et al., 2020). A disfunção hepática, particularmente a doença hepática gordurosa não alcoólica (NAFLD), é aceita como causa do metabolismo prejudicado da glicose e dos lipídios, e como uma consequência da obesidade e da saúde metabólica prejudicada (Younossi et al., 2018; Stefan et al., 2019). A partir disso, uma nova definição para NAFLD é apresentada na literatura, a de uma doença hepática gordurosa associada ao metabolismo

(MAFLD) (Eslam et al., 2020). Um estudo desenvolvido na China com pacientes diagnosticados com COVID-19 e MAFLD, pareados por idade, sexo e status de obesidade para pacientes infectados com SARS-CoV-2 sem MAFLD, reportou um risco quatro vezes maior (OR = 4,07; IC95%: 1,20-13,79) de desenvolver COVID-19 grave para os pacientes com MAFLD (Zhou et al., 2020). O índice FIB-4 e o escore NAS apresentaram uma associação significativa com maior gravidade de COVID-19 independentemente do sexo, obesidade, diabetes mellitus e presença ou ausência de MAFLD (Targher et al., 2020). Além disso, biomarcadores de lesão hepatocelular são observados em 14% a 15% dos pacientes criticamente enfermos e hospitalizados com COVID-19 (Ayres, 2020; Bertolini et al., 2020).

O conhecimento sobre a patogênese da doença hepática e qualquer lesão hepática consequente é muito importante para pacientes com obesidade e saúde metabólica comprometida, especialmente no contexto da COVID-19 (Jothimani et al., 2020; Popkin et al., 2020; Sanchis-Gomar et al., 2020; Marjot et al., 2021; Stefan et al., 2021) e das doenças periodontais (Kuraji et al., 2021; Larvin et al., 2021; Marouf et al., 2021). Atualmente, uma teoria atualizada chamada de hipótese “multiple-hit” envolve uma série de fatores que podem atuar em paralelo na patogênese da NAFLD (Friedman et al., 2018; Chen et al., 2020a). Entre os muitos fatores que contribuem para “multiple hits” está o estresse oxidativo, que é considerado o principal contribuinte ao dano hepático e progressão da doença na NAFLD (Takaki et al., 2013). É possível que a translocação hematogênica de patógenos periodontais e suas toxinas influenciem a saúde hepática e os níveis séricos de PCR.

De acordo com Younossi et al. (2019), estamos apenas começando a entender os mecanismos de patogênese das doenças hepáticas e a contribuição de fatores ambientais e genéticos para o risco de desenvolver um curso progressivo da doença. Diante deste cenário, tem havido um intenso debate sobre periodontite como fator de risco para o início e progressão da NAFLD. No campo das pesquisas relacionadas à Medicina Periodontal, poucos trabalhos até o momento abordaram a relação entre as doenças periodontais e os órgãos do sistema digestivo (Kuraji et al., 2021).

Portanto, objetivamos desenvolver um ensaio teórico sobre a importância da patogênese da COVID-19 para a pesquisa em Medicina Periodontal, e realizar uma síntese das evidências científicas sobre a relação entre obesidade e periodontite, a importância da proteína C-reativa enquanto biomarcador de impacto sistêmico da periodontite, e os efeitos diretos de bactérias periodontopatogênicas no fígado.

2. OBJETIVO GERAL

Desenvolver um ensaio teórico sobre a importância da patogênese da COVID-19 na pesquisa em Medicina Periodontal, e realizar uma síntese das evidências científicas sobre a relação entre obesidade e periodontite, a importância da proteína C-reativa enquanto biomarcador de impacto sistêmico da periodontite, e os efeitos da bacteremia e endotoxemia por patógenos periodontais e suas toxinas no fígado.

2.1. Objetivos específicos:

2.1.1. Formular uma hipótese conceitual sobre a importância da patogênese da COVID-19 para a pesquisa em Medicina Periodontal.

2.1.2. Revisar os mecanismos biológicos envolvidos na relação bidirecional entre obesidade e periodontite e realizar uma síntese de evidências de nível 1 acerca dessa associação, baseada em estudos de meta-análise

2.1.3. Realizar uma síntese de evidências científicas sobre os benefícios sistêmicos do tratamento periodontal em pacientes com obesidade e periodontite a partir de ensaios clínicos.

2.1.4. Estabelecer o efeito do tratamento periodontal nos níveis séricos de proteína C-reativa em diferentes condições/doenças sistêmicas a partir de revisões sistemáticas de estudos de intervenção.

2.1.5. Realizar uma síntese de evidências disponíveis sobre os efeitos da endotoxemia e da bacteremia por patógenos periodontais no fígado, avaliar a qualidade e o nível das evidências disponíveis, e propor um modelo de patogênese das doenças hepáticas a partir dessa exposição.

3. MATERIAIS E MÉTODOS

3.1. Delineamento do projeto

A presente Tese de Doutorado trata de uma pesquisa bibliográfica, sistematizada, de delineamento misto ("*mixed-methods research*"). Os objetivos propostos foram contemplados em três eixos e apresentados em seis capítulos.

Eixos da pesquisa:

A. **COVID-19:** Formulação de uma hipótese conceitual sobre a importância da patogênese da COVID-19 para a pesquisa e a prática clínica em Medicina Periodontal.

B. **Obesidade e periodontite:** i) Revisão dos mecanismos biológicos envolvidos na relação entre obesidade e periodontite, e sumarização sistemática de evidências de nível 1 acerca dessa associação, sem restrição quanto ao delineamento dos estudos primários; ii) Sumarização dos benefícios sistêmicos do tratamento periodontal em pacientes com obesidade e periodontite; e iii) Sumarização dos efeitos do tratamento periodontal nos níveis séricos de proteína C-reativa em diferentes condições/doenças sistêmicas a partir de evidências de nível 1.

C. **Doença hepática gordurosa não alcoólica:** Síntese de evidências disponíveis sobre os efeitos da endotoxemia e da bacteremia por patógenos periodontais no fígado, avaliação da qualidade e do nível das evidências disponíveis, e proposta de um modelo de patogênese das doenças hepáticas a partir dessa exposição.

Capítulos da Tese:

1. Relação da patogênese da COVID-19 com a pesquisa em Medicina Periodontal.
   Capítulo dividido em dois artigos:
   - ***Relationship of COVID-19 pathogenesis for periodontal medicine research. Part I: Pathogenesis of COVID-19***
     (DOI: http://dx.doi.org/10.33448/rsd-v10i5.13729)

   - ***Relationship of COVID-19 pathogenesis for periodontal medicine research. Part II: Periodontal Medicine***

(DOI: http://dx.doi.org/10.33448/rsd-v10i5.13731)

2. **Mecanismos biológicos envolvidos na intercessão entre obesidade e periodontite**
   (DOI: http://dx.doi.org/10.33448/rsd-v9i11.10092)

3. **Interseção entre Obesidade e Periodontite: Uma *Umbrella Review* de Estudos de Meta-Análise**
   (Manuscrito)

4. ***Cardiometabolic, inflammatory, oxidative and microbiological benefits of periodontal therapy in patients with obesity and periodontitis: A systematic review***
   (Manuscrito)

5. ***Serum C-reactive Protein and Periodontitis-Treatment: An Umbrella Review***
   (Manuscrito)

6. ***Intersections between endotoxemia and bacteremia by periodontal pathogens and liver—A scoping review***
   (Manuscrito)

Cada capítulo que compõe a Tese apresenta um artigo completo, publicado ou em processo de revisão/submissão para publicação em periódico especializado da área. Apenas o Capítulo 1 possui dois artigos, por se tratar de duas publicações complementares (Parte I e Parte II). Os capítulos da Tese, em formato de artigos, contemplam Capa, Resumo, Introdução, Métodos, Resultados, Discussão, Conclusão, Agradecimentos, Conflito de interesse, Contribuição dos autores, Financiamento e Referências. A capa descreve o título do trabalho, lista de autores e referidos vínculos institucionais, e dados do(a) autor(a) de correspondência. Quanto à apresentação, as figuras e tabelas foram incluídas nos elementos textuais de forma intercalada com o texto, em posição aproximada a que seguem citados no texto.

A Discussão da Tese abrange todos os trabalhos apresentados, incluindo resultados de um estudo adicional disponibilizado como Apêndice 1, intitulado *Periodontitis-therapy for systemic improvement of inflammation and oxidative stress biomarkers in patients with type 2 diabetes mellitus: A systematic review and meta-analysis of randomized controlled*. As citações

feitas nas seções de Introdução e Discussão da Tese seguem listadas em Referências. A lista de abreviaturas e siglas segue como elemento pré-textual para consulta.

As atividades acadêmicas desenvolvidas no Doutorado estão descritas no Apêndice 2.

Dois artigos adicionais publicados pelo doutorando e pela orientadora durante o Doutorado seguem apresentados nos Anexos 1 [página de título do artigo *Toxicity potential of denture adhesives: A scoping review* (DOI: http://dx.doi.org/10.1016/j.prosdent.2021.03.003)] e 2 [página de título do artigo *Lateral periodontal cyst: A rare clinicopathological presentation mimicking a residual cyst* (DOI: https://doi.org/10.4317/jced.58668)].

CAPÍTULO 1

Relationship of COVID-19 pathogenesis for periodontal medicine research. Part I: Pathogenesis of COVID-19

Relação da patogênese de COVID-19 para pesquisa de medicina periodontal. Parte I: Patogênese da COVID-19

Relación de la patogénesis de COVID-19 para la investigación en medicina periodontal. Parte I: Patogénesis de COVID-19

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Abstract
Cell invasion mediated by angiotensin-converting enzyme 2 (ACE2) ectoenzyme and cellular proteases, such as trypsin-like proteases, cathepsins, transmembrane serine protease 2 and furin, target different tissues and organs as lung, gut, colon, ileum, kidney, gallbladder, heart muscle, epididymis, breast, ovary, stomach, bile duct, liver, oral cavity, lung, thyroid, esophagus, bladder, breast, uterus, prostate, pancreas, cerebellum, as well as calyx secreting cells in the nasal and sinus tissue. Loss of homeostasis of the renin-angiotensin system deregulates different axes compromising metabolic, cardiorespiratory, renal and hepatic control. SARS-CoV-2 infected cell undergoes pyroptosis and releases molecular patterns associated with damage: pro-inflammatory interleukin (IL) -1β, IL-6, IL-8, IL-10, IL-17, induced protein-10, interferon gamma, interferon gamma-induced protein-10, granulocyte colony-stimulating factor, granulocyte-macrophage colony-stimulating factor, macrophage inflammatory protein 1α and 1β, monocyte chemotherapy activating protein 1, inflammatory macrophage protein 1α, tumor necrosis-α, and mediators of immune-mediated inflammatory diseases. Cytokine storm and non-neutralizing antibodies produced by B cells circulate, cause/exacerbate damage to various organs. During viral replication and low oxygen saturation, loss of HIF-mediated cell homeostasis can lead to cell death/lysis and tissue damage, related to the hyperinflammatory response. The SARS-CoV-2-ACE2 can increase permeability, inflammation and microbial transmission by bacteremia or endotoxemia, in addition to dysbiosis. Thrombotic potential and the immunoinflammatory imbalance compromise function or lead to injuries and multiple organ failure. Infection by SARS-CoV-2 has the potential to modify the natural history of diseases, the relationships or interactions between the different systems and pathologies and the effects of their treatments, as in periodontal medicine approach.
Keywords: Coronavirus infections; Pathogenesis; Periodontics.

Resumo
A invasão celular mediada pela enzima conversora de angiotensina 2 (ACE2) ectoenzima e proteases celulares, tem como alvo diferentes tecidos e órgãos. A perda da homeostase do sistema renina-angiotensina desorganiza diferentes eixos, comprometendo o controle metabólico, cardiorrespiratório, renal e hepático. A célula infectada com SARS-CoV-2 sofre piroptose e libera padrões moleculares associados a danos: interleucina pró-inflamatória (IL) -1β, IL-6, IL-8, IL-10, IL-17, induzida por proteína-10, interferon gama, proteína induzida por interferon gama-10, fator estimulador de colônia de granulócitos, fator estimulador de colônia de granulócitos-macrófagos, proteína inflamatória de macrófagos 1α e 1β, proteína de ativação de quimioterapia de monócitos 1, células inflamatórias de proteína de macrófagos 1, necrose tumoral-α e mediadores de doenças inflamatórias mediadas. A tempestade de citocinas e os anticorpos não neutralizantes produzidos pelas células B circulam, exacerbando os danos a vários órgãos. Durante a replicação viral e a baixa saturação de oxigênio, a perda da homeostase celular mediada pelo HIF pode levar à morte/lise celular e danos aos tecidos, relacionados à resposta hiperinflamatória. O SARS-CoV-2-ACE2 pode aumentar a permeabilidade, inflamação e transmissão microbiana por bacteremia ou endotoxemia, além da disbiose. O potencial trombótico e o desequilíbrio imunoinflamatório comprometem a função ou levam a lesões e falência de múltiplos órgãos. A infecção por SARS-CoV-2 tem o potencial de modificar a história natural das doenças, as relações ou interações entre diferentes sistemas e patologias e os efeitos de seus tratamentos, como na abordagem da medicina periodontal.
Palavras-chave: Infecção por Coronavírus; Patogênese; Periodontia.

Resumen
La invasión celular mediada por la ectoenzima de la enzima convertidora de angiotensina 2 (ACE2) y las proteasas celulares, se dirige a diferentes tejidos y órganos. La pérdida de homeostasis del sistema renina-angiotensina desregula diferentes ejes, comprometiendo el control metabólico, cardiorrespiratorio, renal y hepático. La célula infectada con SARS-CoV-2 sufre piroptosis y libera patrones moleculares asociados con el daño: interleucina proinflamatoria (IL) -1β, IL-6, IL-8, IL-10, IL-17, proteína inducida-10, interferón gamma, proteína 10 inducida por interferón gamma, factor estimulante de colonias de granulocitos, factor estimulante de colonias de granulocitos-macrófagos, proteína inflamatoria de macrófagos 1α y 1β, proteína activante de quimioterapia de monocitos 1, proteína de macrófagos inflamatorios 1α, necrosis tumoral α y mediadores de enfermedades inflamatorias mediadas por el sistema inmunitario. La tormenta de citocinas y los anticuerpos no neutralizantes producidos por las células B circulantes agravan el daño a varios órganos. Durante la replicación viral y la baja saturación de oxígeno, la pérdida de homeostasis celular mediada por HIF puede provocar muerte/lisis celular y daño tisular, relacionado con la respuesta hiperinflamatoria. El SARS-CoV-2-ACE2 puede aumentar la permeabilidad, la inflamación y la transmisión microbiana debido a bacteriemia o endotoxemia, además de disbiosis. El potencial trombótico y el desequilibrio inmunoinflamatorio comprometen la función o conducen a lesiones e insuficiencia multiorgánica. La infección por SARS-CoV-2 tiene el potencial de modificar la historia natural de las enfermedades, las relaciones o interacciones entre diferentes sistemas y patologías y los efectos de sus tratamientos, como en el enfoque de la medicina periodontal.
Palabras clave: Infecciones por Coronavirus; Pathogenesis; Periodoncia.

1. Introduction

SARS-CoV-2 infection appears to directly affect tissues and organs by exposure and presence of the angiotensin-converting enzyme 2 (ACE2) ectoenzyme and cellular proteases (Bertram et al., 2011, Glowacka et al., 2011, Raj et al., 2013, Wang et al., 2013, Gheblawi et al., 2020, Gralinski & Menachery, 2020, Hoffmann et al., 2020, Wan, Shang, Graham, Baric & Li, 2020, Zhou et al., 2020). The lungs are the most affected organs and the clinical evolution of severe forms of COVID-19 leads to abnormalities in the blood hematological and biochemical index, and systemic conditions/diseases on kidney, liver and coagulation biomarkers (Tay, Poh, Rénia, MacAry & Ng, 2020, Pedersen & Ho, 2020, Schett, Sticherling & Neurath, 2020, Zhang et al., 2020). The pathogenesis of COVID-19 and its systemic impacts are associated with intense pro-inflammatory events and loss of homeostasis, associated with a hyperinflammatory state, secondary bacterial infections, bacteremia, endotoxemia, loss of function and multiple organ failure (Cao & Li, 2020, Chen et al., 2020, Hadjadj et al., 2020, Henry, de Oliveira, Benoit, Plebani & Lippi, 2020, Huang et al., 2020, Mehta, McAuley, Brown, Sanchez, Tattersall & Manson, 2020, Merad & Martin, 2020, Qin et al., 2020, Wang, Jiang, Chen & Montaner, 2020, Wu et al., 2020, Ye, Wang & Mao, 2020, Zhou et al., 2020, García-Sastre, 2017, Schulert & Grom, 2015, Mayer-Barber et al., 2014). The systemic impacts of the COVID-19 have the potential to influence the relationships and interactions between periodontal diseases and systemic conditions/diseases, previously reported in the literature. In addition, the periodontal medicine research, the natural history of periodontal disease and the response to

periodontal therapy during and after the COVID-19 pandemic may be affected by the disease. Therefore, the aim of this study was to review the literature and propose a conceptual hypothesis on the subject, based on the interception between the pathogenesis of COVID-19 and its main systemic repercussions, and periodontal medicine.

2. Methodology

Theoretical essay based on studies on the pathogenesis of COVID-19, potentially related to systemic interactions of periodontal diseases. Searches were performed in the MEDLINE|PubMed, Scopus, Embase, Web of Science, Cochrane Library, and BIREME|bvs databases for articles published up to 2020 December 20, using MeSH terms, Emtree terms and DeCS/MeSH terms related to 'COVID-19', 'SARS-CoV-2', and 'pathogenesis', combined by the Boolean operators "OR" and "AND". The studies, mostly experimental and review, published in the main journals, were qualitatively summarized. The comparison of these findings with the main systemic interactions of periodontal diseases previously described resulted in conceptual hypotheses based on the literature about the potential impacts of the COVID-19 pandemic on the scientific investigation of these interactions.

3. Results and Discussion

New coronavirus SARS-CoV-2 and host cell infection

The first cases of COVID-19 (coronavirus disease 2019) were reported to the World Health Organization (WHO) on December 31, 2019, where 27 individuals suffered pneumonia with no known cause and all were related to a wholesale market for wet animals in the city of Wuhan, China. All available evidence for COVID-19 suggests that SARS-CoV-2 has a zoonotic source. The clinical signs and symptoms and the genetic similarity of the pathogen to the SARS-CoV virus resulted in the taxonomic characterization of a new coronavirus identified as SARS-CoV-2 (severe acute respiratory syndrome coronavirus 2) (Peiris, Guan & Yuen, 2004, Cui, Li & Shi, 2019, Committee on Taxonomy of Viruses, 2020, Lai, Shih, Ko, Tang & Hsueh, 2020, World Health Organization, 2020a). In January 2020, the outbreak of COVID-19 was declared by WHO as a Public Health Emergency of International Importance, and on March 11 the pandemic of COVID-19 in the world was declared (World Health Organization, 2020b).

At least six other coronaviruses have been known to cause disease in humans, including viruses 229E, OC43, NL63 and HKU1; SARS-CoV and MERS-CoV are of zoonotic origin and can be fatal. SARS-CoV-2 (coronavirus genera β) is the seventh member of the family of coronaviruses that infect humans, (Fehr & Perlman, 2015, Rabi, Al Zoubi, Kasasbeh, Salameh & Al-Nasser, 2020, Tay, Poh, Rénia, MacAry & Ng, 2020) related to systemic complications in different tissues and organs, hyperinflammatory reactions (cytokine storm that resembles secondary haemophagocytic lymphohistiocytosis), bacterial superinfections, sepsis and multiple organ failure. In severe cases of COVID-19, respiratory infections are associated with pneumonia and acute respiratory distress syndrome (ARDS) (Tay, Poh, Rénia, MacAry & Ng, 2020, Pedersen & Ho, 2020, Schett, Sticherling & Neurath, 2020, Zhang et al., 2020). The severity and risk of death from COVID-19 may vary between individuals of same populations and are associated with risk factors, comorbidities and systemic abnormalities generally correlated/investigated in periodontal medicine research (Zhang, Penninger, Li, Zhong & Slutsky, 2020, Zhu et al., 2019, van Boheemen et al., 2012)

Specific genes in the regions downstream of ORF1 encode proteins for viral replication, formation of nucleocapsids and spikes in coronaviruses (van Boheemen et al., 2012). Glycoprotein spikes are responsible for binding and entering the virus into host cells through binding to the ACE2 ectoenzyme and membrane fusion and conformational changes dependent on cellular proteases, which include trypsin-like proteases of the human airways (HAT), cathepsins and serine transmembrane protease 2 (TMPRSS2) (Bertram et al., 2011, Glowacka et al., 2011, Raj et al., 2013, Wang et al., 2013, Gheblawi et al., 2020, Gralinski & Menachery, 2020, Hoffmann et al., 2020, Wan, Shang, Graham, Baric & Li, 2020, Zhou et al., 2020). The receptor-binding

domain (RBD) is loosely linked between viruses, so the virus's infectivity is highly efficient (Raj et al., 2013, Perlman & Netland, 2009). The RBD region maintains the van der Waals forces and the 394 glutamine residue is recognized by the critical lysine 31 residue in the human ACE2 receptor (Wan, Shang, Graham, Baric & Li, 2020).

Structural proteins are encoded by the structural genes spike (S), envelope (E), membrane (M) and nucleocapsid (N) (Chen, Liu & Guo, 2020, Hui et al., 2020, Li et al., 2020, Lu et al., 2020, Wu et al., 2020). SARS-CoV-2 differs from SARS-CoV in the absence of protein 8a and the number of amino acids in protein 8b and 3c varies (Wu et al., 2020). Spike is a transmembrane trimetric glycoprotein protruding from the viral surface. It is related to the diversity of coronaviruses and host tropism. SARS-CoV-2 Spike glycoprotein was modified by homologous recombination as a mixture of bat SARS-CoV and an unknown Beta-CoV; (Li et al., 2020) the N501T mutation in the SARS-CoV-2 Spike may have significantly increased its binding affinity for ACE2 (Wan, Shang, Graham, Baric & Li, 2020) SARS-CoV-2 also expresses other polyproteins, nucleoproteins and membrane proteins, such as RNA polymerase, protease type 3-chymotrypsin, protease type papain, helicase, glycoprotein and accessory proteins (Wu et al., 2020, Zhou et al., 2020).

Viral replication

The life cycle of SARS-CoV-2 in host cells begins when the cleavage at the S_1/S_2 cleavage site of the Spike protein for binding to the ectoenzyme ACE2 (step 1, attachment – stabilization of the membrane-anchored S_2 subunit), followed by changes in conformation through protease cleavage for activation at the S'_2 of the S_2 subunit, resulting in fusion of the viral envelope with the host cell membrane and endocytosis (step 2, penetration via endosomal). Among coronaviruses, only SARS-CoV-2 presents a furin cleavage site ("RPPA" sequence) at the S_1/S_2 site. Although the S_1/S_2 site was also subjected to cleavage by TMPRSS2 and cathepsin B and L, the ubiquitous expression of furin likely makes this virus very pathogenic (Gheblawi et al., 2020, Hoffmann et al., 2020, Zhou et al., 2020, Caly, Druce, Catton, Jans & Wagstaff, 2020, Moore, 2001). The virus's positive single-stranded RNA (RNA^+) is released into the host cell and its genome is translated into viral polyproteins replicase pp1a and 1ab, cleaved into small products by viral proteinases (step 3, biosynthesis). The viral replication of SARS-CoV-2 depends on the cytoplasmic mechanism of the infected cell and occurs through series of subgenomic mRNA production by discontinuous transcription. Viral replication of SARS-CoV-2 can occur in the cytoplasm of the host cell, with the viral RNA^+ acting as mRNA. After a polymerase action, the mRNAs are translated into relevant viral proteins that are assembled into virions with RNA from the genome in the endoplasmic reticulum (ER), intermediate compartment ER-Golgi and Golgi complex (step 4, maturation). The virus is released out of the cell via the membrane transport system (step 5, release) (Luo, Chen, Chen, Chen, Shen & Jiang, 2005, Frieman, Yount, Heise, Kopecky-Bromberg, Palese & Baric, 2007, Shereen, Khan, Kazmi, Bashir & Siddique, 2020, Yuki, Fujiogi & Koutsogiannaki, 2020).

SARS-CoV-2 intracellular replication also involves the cell nucleus by active transport of viral nucleoprotein through the nuclear pore complex using $\alpha/\beta 1$ importin complex (GTPase $\rightarrow$ GTP $\rightarrow$ intranuclear transport $\rightarrow$ GTP hydrolysis $\rightarrow$ GDP + Pi $\rightarrow$ extranuclear transport) (Frieman, Yount, Heise, Kopecky-Bromberg, Palese & Baric, 2007, Caly, Druce, Catton, Jans & Wagstaff, 2020, Uddin, Zonder & Azmi, 2020). Inside the nucleus, the GEF-Ran protein exchanges GDP for GTP, changing the conformation of Ran and releasing the nucleocapsid protein of the virus inside the nucleus. Free Ran-GTP and CAS-linked Ran-GTP _ protein related to cell apoptosis _ bind to free importin-α in the nucleus and act as an exportin, exporting this subunit to the cytoplasmic surface of the nuclear envelope (GTP hydrolysis in GDP); this active transport of molecules to the cell nucleus depends on the hydrolysis of two GTP molecules (Moore, 2001, Cavazza & Vernos, 2016). Some proteins important for viral replication reach the cytoplasm through nucleocytoplasmic transport (Frieman, Yount, Heise, Kopecky-Bromberg, Palese & Baric, 2007, Caly, Druce, Catton, Jans & Wagstaff, 2020, Uddin, Zonder & Azmi, 2020). Despite undergoing replication in the

cytoplasm, the positive single-stranded RNA (RNA^+) virus nucleocapsid protein is located in the nucleus or nucleolus of infected cells, usually at the beginning of the infectious cycle. After its translation to perform non-structural functions, the viral nucleocapsid protein returns to the cytoplasm and participates in the assembly of new virions (Tijms, van der Meer & Snijder, 2002, Yoo, Wootton, Li, Song & Rowland, 2003, Sato, Masuda, Miura, Yoneda & Kai, 2006, Wulan, Heydet, Walker, Gahan & Ghildyal, 2015). Recent computational models of localization of subcellular RNA, in silico, on the location properties of SARS-CoV-2 transcripts, revealed predicted transcription residency signals, specifically for the nucleolus and mitochondrial matrix (unique characteristics of SARS-CoV-2) (Wu, Fazal, Parker, Zou & Chang, 2020).

Response of the infected cell against viral replication, leading to the onset of a hyperinflammatory state

The coronavirus infecting human affects the cell division of the host, blocking molecular transport in the nucleocytoplasmic direction by viral nucleocapsid proteins. The antiviral activity mediated by STAT1 (signal transducer and activator of transcription 1) in infected cell is inhibited by the accessory virus ORF6, by sequestering importin-α and -β1 sub-unit in the membranes of the rough endoplasmic reticulum and the Golgi complex (Kopecky-Bromberg, Martínez-Sobrido, Frieman, Baric & Palese, 2007). This inhibits or reduces the expression of antiviral genes by STAT1, even if intracellular an intracellular STAT signaling/transduction from receptor tyrosine kinases activated by and pro-inflammatory molecules such as interleukin (IL) -6, interferon (IFN) -α (IFN-α), IFN-γ, and growth factors as PDGF (platelet-derived growth factor) occurs (Wulan, Heydet, Walker, Gahan & Ghildyal, 2015, Hiscox, Wurm, Wilson, Britton, Cavanagh & Brooks, 2001, Wurm, Chen, Hodgson, Britton, Brooks & Hiscox, 2001, Rowland, Chauhan, Fang, Pekosz, Kerrigan & Burton, 2005, Timani et al., 2005). Gene expressions by STAT1 are related to cell viability and survival, and responses to pathogens (Baris et al., 2016). Most interferon stimulated genes possess binding sites for STAT- or IFN- regulatory factor transcription factor-mediated expression (Kent et al., 2002, Read, Obeid, Ahlenstiel & Ahlenstiel, 2019).

PAMPs (pathogen associated molecular patterns) virus such as glycoproteins from the viral envelope (13 MHC-I and 3 MHC-II epitopes in SARS-CoV-2 Spike) and nucleic acids are recognized by cell surface and cytosolic pattern recognition receptors (TLR5/7/8 → innate immune), and endosomal toll-like receptors 7 and 8 (TLR7/8) that primarily bind viral nucleic acids (RNA^+) (Pande, Kawai & Akira, 2014, Moreno-Eutimio, López-Macías & Pastelin-Palacios, 2020, Noorimotlagh, Karami, Mirzaee, Kaffashian, Mami & Azizi, 2020). Thus, the downstream signaling intermediates activate both inflammatory and innate immune transcription factors and induce expression of IFN-α and IFN-β, IFN-γ, and/or IFN-λs, by a signaling cascade resulting in STAT1 and STAT2 heterodimerizing and binding interferon regulatory factor 9 (IRF9). Its translocation into the nucleus is related to gene promoter transcription, followed by immune cell chemotaxis and activation, and antiviral mechanisms to inhibit viral replication in the host cells (Read, Obeid, Ahlenstiel & Ahlenstiel, 2019). An association has been reported between ACE2 expression and IFN-stimulated canonical genes (ISGs) or components of the IFN signaling pathway, comparing $ACE2^+$ and $ACE2^-$ cells; both type I and type II IFNs induced ACE2 expression in human epithelial cells and keratinocytes. SARS-CoV-2 does not appear to induce type I, II or III interferons in infected human lung tissues, which suggests that ACE2 may not be increased in this organ in COVID-19 (Su & Jiang, 2020, Ziegler et al., 2020). The coronavirus infections induced expression of IFN, activating canonical IFN-induced genes (ISGs) and ACE2 expression, and contributing to the viral infection and acute lung injury (Su & Jiang, 2020).

SARS-CoV-2 uses ACE2 ectoenzyme (functional receptor) and TMPRSS2 to invade the host cell (endocytosis), followed by an acute respiratory distress syndrome (cytokine-related) induced by the hyper-activation of the transcription factor NF-κB, coactivated by STAT3 (Hirano & Murakami, 2020). The serum level of angiotensin 2 increases, and its accumulation induces inflammatory cytokines such as TNFα, IL-6 and metalloprotease 17 (ADAM17), followed by the activation of the IL-6

amplifier (IL-6 AMP). The HIF (hypoxia inducible factor) transcription factor family activates specific genes related to cellular oxygen homeostasis, and also participates in the pathogenesis of viral infection by coronavirus (Caly, Druce, Catton, Jans & Wagstaff, 2020). The nuclear import pathway is under-regulated by the nuclear accumulation of importin-α and by the under-regulation of importin-β in response to stimuli such as oxidative stress and thermal shock stress (Kodiha, Chu, Matusiewicz & Stochaj, 2004, Miyamoto et al., 2004). Hypoxia results in nuclear accumulation of HIF-1α (Caly, Wagstaff & Jans, 2012). The nuclear import of HIF proteins (HIF-1α, HIF-2α and HIF-1β) is triggered by the α/β1 importin complex [subfamily α (isoforms α1, α3, α5 and α7)] (Fagerlund, Kinnunen, Köhler, Julkunen & Melén, 2005). During coronavirus viral replication and low oxygen saturation, HIF-mediated cell homeostasis can be compromised and result in cell death/lysis and tissue damage, related to the hyperinflammatory response (oxidative stress, cytokine storm, enzymatic degradation and other factors) (Hirano & Murakami, 2020).

Immunoinflammatory response

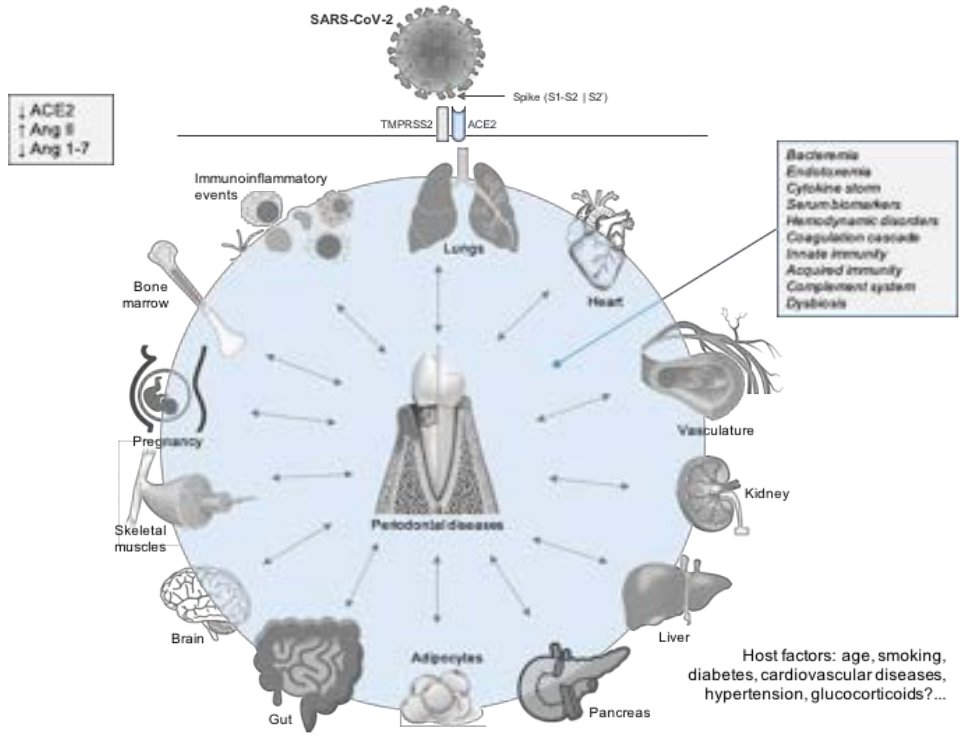
The SARS-CoV-2 infected host cell undergoes pyroptosis and releases molecular patterns associated with damage _ cytopathic virus _, releasing high levels of IL-1 β (Huang et al., 2020). Thus, ATP, nucleic acids and ASC oligomers are recognized by neighboring cells (epithelium, endothelium and macrophages) by the damage-associated molecular patterns (DAMPs), stimulating the release of pro-inflammatory cytokines and chemokines [IL-6, IP-10, macrophage inflammatory protein 1α (MIP1α), MIP1β and MCP1]. Monocytes, macrophages and T cells promote additional inflammation at the site of infection, increasing IFN-γ levels and promoting a pro-inflammatory feedback loop. Cumulative immune cells and chronic inflammation lead to overproduction of these cytokines and tissue damage. The resulting cytokine storm and non-neutralizing antibodies produced by B cells circulate to other organs, causing/exacerbating damage to various organs (Tay, Poh, Rénia, MacAry & Ng, 2020)

ACE2 is high expressed in different tissues and organs as lung (especially type II pneumocytes and endothelium), gut (absorbent enterocytes), colon, ileum, kidney, gallbladder, heart muscle, epididymis, breast, ovary, stomach, bile duct, liver, oral cavity, lung, thyroid, esophagus, bladder, breast, uterus, prostate, pancreas, cerebellum, as well as calyx secreting cells in the nasal and sinus tissue (Yuki, Fujiogi & Koutsogiannaki, 2020, Su & Jiang, 2020, Hamming, Timens, Bulthui, Lely, Navis & van Goor, 2004, Xu et al., 2020). Double positive cells ACE2 and TMPRSS2 are likely targets for SARS-CoV-2 (Su & Jiang, 2020). Zou et al. (2020) reported a single-cell RNA-seq data analysis on the receptor ACE2 expression. The authors identified the organs at risk to SARS-CoV-2 infection, and located specific cell types (e.g. type II alveolar cells (AT2), myocardial cells, proximal tubule cells of the kidney, ileum and esophagus epithelial cells, and bladder urothelial cells), which are vulnerable to 2019-nCoV infection.

Therefore, the loss of homeostasis of the renin-angiotensin system and the systemic spread of the virus may interfere with other organs and systems, probably including the periodontium, as ACE2, ET-1 and TNF-β have also been correlated with inflammatory processes in periodontal tissues (Hollá, Fassmann, Vašků, Znojil, Vaněk & Vácha, 2001, Gürkan et al., 2009, Santos et al., 2009, Santos et al., 2015, Rodrigues, Barbirato, Luiz, Scharfstein, Salles & Feres-Filho, 2016). In addition, the ACE2 ectoenzyme expressed in arterial and venous endothelial cells has important protective effects (angiotensin 1-7 mediated), including targeted anti-inflammatory drugs. ACE2 has been shown to regulate the renin-angiotensin system (Kuba, Imai & Penninger, 2006). Therefore, a reduction in ACE2 function after SARS-CoV-2 infection could influence blood pressure and fluid/electrolyte balance and enhance inflammation and vascular permeability in the airways (Tay, Poh, Rénia, MacAry & Ng, 2020).

The ACE2/angiotensin 1-7/Mas receptor axis was related to alveolar bone remodeling and decreased alveolar bone loss by improving the osteoblast/osteoclast ratio and reducing IL-6 expression (Queiroz-Junior, 2019). Therefore, in SARS-CoV-2 infection, ACE2 availability decreases and systemic complications can occur, mainly cardiovascular and metabolic diseases (Leisman, Deutschman & Legrand, 2020, Merad & Martin, 2020). The cytokine storm intensifies the homeostatic imbalance throughout the body and may interfere with the bidirectional immunoinflammatory relationship between periodontal diseases and systemic conditions (Hollá, Fassmann, Vašků, Znojil, Vaněk & Vácha, 2001, Kornman, 2008, Nakamura, Hasegawa-Nakamura, Sakoda, Matsuyama & Noguchi, 2011, Cekici, Kantarci, Hasturk & Van Dyke, 2002, Hajishengallis, 2014, Hajishengallis & Sahingur, 2014, Konkel, O'Boyle & Krishnan, 2019, Pan, Wang & Chen, 2019). The SARS-CoV-2-ACE2 bond can increase permeability, inflammation and microbial transmission by bacteremia or endotoxemia, in addition to dysbiosis. The hyperinflammatory response affects the cardiopulmonary system leading to endothelial dysfunction, vascular remodeling, pulmonary dysfunction and superinfections (viral and bacterial). Bacteremia, endotoxemia and a cytokine storm stimulate the production of immature megakaryocytes in the bone marrow and the activation of microglia in the paraventricular nucleus of the hypothalamus. The reduction in ACE2 associated with an increase in angiotensin II and angiotensin 1-7 affects important tissues and organs (Figure 1).

Figure 1: Compromise of homeostasis in different systems of the human body potentially related to periodontal diseases.



- Lungs: increased inflammation, vascular remodeling, endothelial dysfunction and cardiopulmonary dysfunction.
- Heart: increase in reactive oxygen species, hypertrophy, inflammation, matrix metalloprotein activity, metabolic shift and altered conductance.
- Vasculature: increase in reactive oxygen species, endothelial dysfunction and hypertrophy of vascular smooth muscle cells, and reduction in endothelial nitric oxide.
- Kidney: increase in reactive oxygen species, hypertrophy and inflammation.
- Liver: decreased insulin sensitivity and increased fibrosis.
- Pancreas: reduction of insulin secretion, increase of reactive oxygen species and inflammation.
- Adipocytes: decreased insulin sensitivity and increased glucose uptake.
- Brain: activated microglial, elevated cytokines and neuroinflammation.
- Skeletal muscles: decreased insulin sensitivity.
- Bone marrow: increased myeloidosis and decreased vascular repair cells.

Source: Authors.

In a systematic review, Smith et al. (2020) reported maternal and neonatal outcomes associated with COVID-19 infection, showing 63.8 % of premature births, 61.1 % of fetal distress, 76.9 % of in-neonatal intensive care units and 42.8 % low birth weight between 92 pregnant women with COVID-19 (67.4 % were symptomatic); 80 % needed cesarean section. The main chronic non-communicable diseases correlated with COVID-19 are hypertension (21.1 %; 95 % CI, 13.0–27.2), diabetes mellitus (9.7 %; 95 % CI, 7.2–12.2), cardiovascular diseases (8.4 %; 95 % CI, 3.8–13.8) and respiratory disease (1.5 %; 95 % CI, 0.9–2.1). Comparing severe and non-severe patients, the combined odds ratio of hypertension, respiratory system disease and cardiovascular disease were 2.36 (95 % CI, 1.46–3.83), 2.46 (95 % CI, 1.76–3.44) and 3.42 (95 % CI, 1.88–6.22), respectively (Yang et al., 2020).

Abnormalities of laboratory parameters were observed in hospital patients with COVID-19 such as glucose, albumin, aspartate aminotransferase, lipase, creatine kinase, lactate dehydrogenase, urea, creatinine, high-sensitive cardiac troponin I, prothrombin time/International Normalized Ratio, activated partial thromboplastin time, procalcitonin, D-dimer, C-reactive protein, ferritin, hemoglobin, leukocytes, neutrophil and lymphocyte count, and neutrophil/lymphocyte ratio and peak platelet/lymphocyte ratio (Bonetti et al., 2020, Huang, Pranata, Lim, Oehadian & Alisjahbana, 2020, Terpos et al., 2020, Zhang, Hou, Li & Li, 2020). The inflammatory biomarkers C-reactive protein and IL-6 are increased in COVID-19 patients' blood (Terpos et al., 2020, Zhang, Hou, Li & Li, 2020, Kermali, Khalsa, Pillai, Ismail & Harky, 2020).

The systemic interactions of COVID-19 with obesity, diabetes mellitus, metabolic syndrome, hypertension, cerebrovascular and cardiovascular diseases, acute kidney injury, chronic liver diseases, chronic kidney and liver diseases, maternal and perinatal results can be confirmed in blood biomarkers (Ali et al., 2020, Chen et al., 2020, Huang, Lim & Pranata, 2020, Malik, Ravindra, Attri, Bhadada & Singh, 2020, Mantovani, Beatrice & Dalbeni, 2020, Pranata, Huang & Lim, 2020, Zaigham & Andersson, 2020).

Patients with COVID-19 and acute respiratory distress syndrome may have lower levels of serum D-dimer and activated partial thomboplastin time, and higher levels of fibrinogen, antithrombin, prothrombin time and platelet count than non-COVID-19 patients with acute respiratory distress syndrome (Helms et al., 2020). Viral pulmonary sepsis can lead to vasoconstriction and thrombotic events potentially related to myocardial infarction and necrosis of the renal and hepatic tissues (Li et al., 2020).

PAMPs recognition receptors such as TLR4 and TLR7, DAMPs and cytokines (IL-6 and CCL2) activate blood monocytes that express tissue factor (TF) in the cell membrane. Cytokines (IL-6 and TNF) and viral particles stimulate endothelial cells to produce chemo-attractants of monocytes and adhesion molecules (P-selectin) and expose TF in the lumen, which recruits monocytes activated endothelial cells, TF and microvesicles derived from activated monocytes stimulate fibrin deposition and blood clotting (extrinsic coagulation pathway). Extracellular neutrophil traps (NETs) activate the coagulation contact pathway and bind and activate platelets (amplification of coagulation). In COVID-19, the inhibitor of the tissue factor pathway (TFPI), antithrombin and protein C (endogenous anticoagulant pathways) are reduced. The von Willebrand factor and the exposure of collagen from endothelial injury lead to the accumulation of platelets and fibrin and stimulate the intrinsic/contact coagulation pathway (Merad & Martin, 2020).

Thrombosis and pulmonary embolism in severe forms of COVID-19 are correlated with elevated levels of D-dimer and fibrinogen and abnormalities in the endothelium related to vasodilation, fibrinolysis and anti-aggregation. Significant endothelial lesions compromise thrombotic regulation leading to a hypercoagulable condition (Wang, Hao, Leeper & Zhu, 2018). Endothelial cells express the ACE2 ectoenzyme and correspond to one third of lung cells. The increase in ACE2-mediated microvascular permeability, inflammatory events and microbial challenge (viral infections and/or bacterial superinfections) can potentiate coronavirus infection, bacteremia, endotoxemia, hyperinflammatory status and systemic complications in multiple

tissues and organs (Yuki, Fujiogi & Koutsogiannaki, 2020, Yuki K, Fujiogi M, Koutsogiannaki et al., 2008, Sluimer et al., 2008, Zeng et al., 2012).

Pulmonary injury lesions in SARS-CoV-2 infection occur, in part, because ACE2 is highly expressed on the apical side of pulmonary epithelial cells in the alveolar space. The main cellular components of innate immunity in the lungs are epithelial cells, alveolar macrophages located on the apical side of the epithelium and subepithelial dendritic cells (Yoshikawa, Hill, Li, Peters & Tseng, 2009). These cells present the antigen (coronavirus) to T cells in the lymph nodes by phagocytosis of apoptotic cells infected by the virus, through PAMPs (Fujimoto, Pan, Takizawa & Nakanishi, 2000, Channappanavar, Zhao & Perlman, 2014). ACE2 expression in dendritic (splenic) cells and alveolar macrophages is limited, however, the SARS-CoV virus can bind to dendritic-cell specific intercellular adhesion molecule-3-grabbing nonintegrin (DC-SIGN) and DC-SIGN-related protein (DC-SIGNR, L-SIGN), highly expressed in dendritic cells and macrophages (Jeffers et al., 2004, Marzi et al., 2004, Yang et al., 2004). Therefore, it is possible that these antigen-presenting cells may be infected with coronary viruses, in addition to phagocyting them. $CD4^+$ cells activate B cells and promote the production of antibodies specific to the virus (IgM antibodies (recent exposure or acute events) and IgG (delayed immunity)). $CD8^+$ T cells can kill infected viral cells, especially in the early stages of the disease (Yuki, Fujiogi & Koutsogiannaki, 2020).

Severe forms of COVID-19 result in lymphopenia and reduction of peripheral blood T cells (lymphocyte count) (Gu et al., 2005, Frater, Zini, d'Onofrio & Rogers, 2020, Qin et al., 2020, Wilk et al., 2020). Increased plasma concentrations of pro-inflammatory cytokines, such as interleukin (IL) -1β, IL-6, IL-8, IL-10, IL-17, interferon gamma-induced protein (IP) -10, granulocyte colony-stimulating factor (G-CSF), granulocyte-macrophage colony-stimulating factor (GM-CSF), monocyte chemotherapy activating protein 1 (MCP1), inflammatory macrophage protein (MIP) 1α, tumor necrosis (TNF) -α, and mediators that are targeted in IMIDs (immune-mediated inflammatory diseases) (Schett, Sticherling & Neurath, 2020, Huang et al., 2020, Qin et al., 2020, Wilk et al., 2020). IL-6 levels correlate positively with the severity of the disease. Increased expression of CD69, CD38 and CD44 indicates that $CD4^+$ and $CD8^+$ cells have been activated. Higher percentage of $Tm3^+PD\text{-}1^+$ subsets and NK group 2 member A (NKG2A) in $CD4^+$ and $CD8^+$ T cells showed that T cells were also depleted (Zheng et al., 2020). Pathogenic $CD4^+$ T cells with co-expressing interferon (IFN) -γ and granulocyte-macrophage colony stimulating factor (GM-CSF) have been observed in patients with COVID-19 with severe disease (Wilk et al., 2020). GM-CSF helps cell differentiation in innate immunity, increases the function of T cells and release of IL-6, and can be associated with major tissue damage (Yuki, Fujiogi & Koutsogiannaki, 2020, Croxford et al., 2015, Huang et al., 2019). Serum levels of TNF, IL-6 and IL-10 negatively correlated with T cell count (Diao et al., 2020).

SARS-CoV-infected lung epithelial cells produce IL-6 and IL-8. IL-8-mediated neutrophil chemotaxis increases the number of innate and adaptive immune inflammatory cells in the lungs of critically ill patients with COVID-19 (Tian et al., 2020, Xu et al, 2020). The innate neutrophil-mediated immune response is correlated with lung injury, (Young et al., 2004, Koutsogiannaki, Shimaoka & Yuki, 2019, Fang et al., 2012) while the adaptive immune response mediated by $CD8^+$ T cells (primary cytotoxic) and pathological cytotoxic T cells derived from $CD4^+$ T cells kills the virus, cause lung injury, and recruit monocytes ($CD14^+CD16^+$) by GM-CSF. These inflammatory monocytes showed high expression of IL-6 and increased the systemic inflammatory response (Yuki, Fujiogi & Koutsogiannaki, 2020, Fang et al., 2012, Small et al., 2001).

ACE2 is also expressed in internal lymphoid cells (ILC) 2 and ILC3, responsible for mucosal homeostasis. Approximately 95 % of lung ILCs are Natural Killer (NK) cells, type ILC1. The relationship of coronaviruses infection with ILC2 and ILC3 cells has not yet been defined (Yuki, Fujiogi & Koutsogiannaki, 2020).

COVID-19 causes high levels of circulating pro-inflammatory cytokines and chemokines, such as IL-6, IFN γ, MCP1 and IP-10, (Zhang et al., 2020, Huang et al., 2020) related to a polarized response by helper T cells 1 (T_H1) (Huang et al., 2005).

These signaling molecules attract monocytes and T lymphocytes to the site of infection, but not neutrophils (Tian et al., 2020, Xu et al., 2020). The recruitment of immune blood cells and the lymphocytic infiltration in the lungs result in lymphopenia and an increase in the neutrophil-lymphocyte ratio in patients with COVID-19 (Hamming et al., 2004, Qin et al., 2020).

Critical COVID-19 patients admitted to the intensive care unit show dysfunctional immune responses and elevated plasma levels of IL-2, IL-6, IL-7, IL-7, IL-10, G -CSF, IP-10, MCP1, MIP1α and TNF. IL-6 levels increase according to the severity of the disease and are correlated with cases of death (Huang et al., 2020, Zhou et al., 2020, Zhou et al., 2020). In addition, these patients have a population of FCN1 macrophages derived from highly inflammatory monocytes in the bronchoalveolar region (Chua et al., 2020) and a significantly higher percentage of $CD14^{+}CD16^{+}$ inflammatory monocytes in the peripheral blood (Wilk et al., 2020). Cytokines secreted by these monocytes like MCP-1, IP-10 and MIP1α contribute to the cytokine storm (Tay, Poh, Rénia, MacAry & Ng, 2020).

As in SARS-CoV infection, it is possible that SARS-CoV-2 influences the stages of the interferon signaling pathway and prevents the recognition of viral RNA for PRR, (Wilk et al., 2020, Siu, Chan, Kok, Chiu-Yat Woo & Jin, 2014) by preventing its signaling through TBK1/inhibitor of nuclear factor-κB subunit-ε (IKKε), TRAF3 and IRF3, (Siu, Chan, Kok, Chiu-Yat Woo & Jin, 2014, Frieman, Ratia, Johnsto, Mesecar & Baric, 2009) resulting in an antagonism of the interferon responses downstream through STAT1 (Frieman et al., 2007) and inhibiting the host protein translation by mRNA degradation (Narayanan et al., 2008). This condition helps in viral replication and leads to aberrant inflammatory responses from pyroptosis. The species of virus, protease and reactive oxygen are associated with local tissue damage [diffuse alveolar damage (desquamation of alveolar cells), formation of hyaline membrane and pulmonary edema] (Tian et al., 2020, Xu et al., 2020). As a result, in addition to reducing oxygen saturation, secondary infections can occur (Tay, Poh, Rénia, MacAry & Ng, 2020).

The cytokine storm is related to local tissue damage and negative effects in the body, reaching septic shock and multiple organ failure associated with elevated levels of TNF. The dysfunctional immune response that causes pathology and also fails to successfully eradicate pathogens is more evident in people with comorbidities. It is still controversial whether the persistence of the virus is necessary to cause damage and loss of function in tissues and organs (Tay, Poh, Rénia, MacAry & Ng, 2020, Zhou et al., 2020). Viral infection of immune cells by SARS-CoV, even if it is not productive, leads to a hyperinflammatory response of monocytes and macrophages, for example; (Cheung et al., 2005, Law et al., 2005, Tseng, Perrone, Zhu, Makino & Peters, 2005, Yilla et al., 2005) the same should occur with exposure to SARS-CoV-2 (Tay, Poh, Rénia, MacAry & Ng, 2020).

The acute respiratory distress syndrome associated with impaired lung function in COVID-19 was attributed to a non-adaptive immune response (Guan et al., 2020). Vascular and cellular events of inflammation mediated by pro-inflammatory cytokines produced by immune cells resident in the lung lead to the leakage of neutrophils and monocytes from the blood into the bronchi, breaking through the air-blood barrier and causing damage to epithelial cells and local vascular endothelial cells (express ACE2); vascular endothelial injury may result in thrombotic microangiopathies. In the innate immune response to viruses, the complement system appears to induce pro-inflammatory responses via activation of the C3 component (observed in SARS-CoV-2 infections), associated with the acute respiratory distress syndrome (Mastellos, Ricklin & Lambris, 2019, Li et al., 2020). These findings did not occur in mice with C3 deficiency infected with SARS-CoV, where the neutrophilic infiltrate and the levels of IL-6 in the lung were significantly reduced (Gralinski et al., 2018). The immunoinflammatory events previously described for other coronavirus infections can be repeated in the pathogenesis of COVID-19; however, clinical data on the role of complement activation associated with SARS-CoV-2 are still limited. Despite this, lung biopsies from patients with COVID-19 confirmed complement activation with a generation of C3a and deposition of C3 fragments, in addition to a significant increase in serum C5a levels. Treatment of COVID-19 with anti-C5a antibody (well-established axis C5a-C5aR in the

pathophysiology of acute respiratory distress syndrome) resulted in an increase in pulmonary oxygenation and a decrease in systemic inflammation and in the clinical improvement of patients (Campbell CM, Kahwash, 2020, Risitano et al., 2020).

4. Final Considerations

The affinity of SARS-CoV-2 for ACE2 and the complications of loss of homeostasis of the renin-angiotensin system result in decompensations or deregulations of different axes compromising metabolic, cardiorespiratory, renal and hepatic control. The thrombotic potential and the hyperinflammatory cell response potentiate this imbalance and can compromise function or lead to injuries and multiple organ failure. Based on the pathogenesis of coronavirus infections, this theoretical essay proposes the conceptual hypothesis that infection by SARS-CoV-2, especially in cases of severe COVID-19, is able to modify the natural history of diseases, the relationships or interactions between the different systems and pathologies, and the consequences of their treatments.

New experimental studies, epidemiological studies, epigenetic, immunoinflammatory and microbiological characterization, and the comparison of the results of clinical trials during or after the COVID-19 pandemic with the results of the pre-pandemic period, will contribute to establish the impacts of SARS-CoV-2 infection in periodontal medicine.

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Relationship of COVID-19 pathogenesis for periodontal medicine research. Part II: Periodontal Medicine

Relação da patogênese de COVID-19 para pesquisa de medicina periodontal. Parte II: Medicina Periodontal

Relación de la patogénesis de COVID-19 para la investigación en medicina periodontal. Parte II: Medicina Periodontal

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Abstract
The dysfunctional immunoinflammatory response to SARS-CoV-2 infection leads to excessive infiltration of monocytes, macrophages and T cells, non-neutralizing antibody, systemic cytokine storm, microthrombi mediated by tissue factor and oxidative stress, lower platelet counts, increased D-dimer, C-reactive protein and coagulation abnormalities, increased vascular permeability, pulmonary edema and pneumonia, and widespread inflammation and multi-organ damage. Periodontal diseases have a chronic and multifactorial inflammatory profile, of infectious origin, with bidirectional systemic interactions linked to over 50 systemic conditions/diseases. Immunoinflammatory response of periodontal tissues to the microbial challenge, protective/repair response and the local destruction of periodontium influence and are influenced by systemic conditions/diseases. Renin-angiotensin system/ACE inhibitors are also related to pathogenesis of COVID-19 by SARS-CoV-2-ACE2 and to pathogenesis of periodontitis, through bone resorption regulated by the ACE2/Ang-(1-7)/MasR axis and IL1-β, positive regulation of the kinin/receptor pathway B2 due to Toll-like receptor 2 inflammation and Th1/Th17 responses, the expression of the type 1 angiotensin II receptor in the inflamed gingival tissue, and modulating IL-1β-induced IL-6 production in human gingival fibroblasts. It is possible that SARS-CoV-2 infection increases local inflammatory events in periodontal tissue leading to destruction of periodontal tissues, probably enhanced by the systemic effects of periodontitis. Despite limited or non-existent scientific evidence on the effects of COVID-19 on periodontal diseases and their systemic interactions to date, it is possible to expect its impact on periodontal medicine research from the natural history of periodontal diseases to their pathogenesis and relationship with systemic conditions and response to treatment, as an environmental and acquired risk factor.
Keywords: Coronavirus infections; Pathogenesis; Periodontics.

Resumo
A resposta imunoinflamatória à infecção por SARS-CoV-2 leva à infiltração excessiva de monócitos, macrófagos e células T, anticorpo não neutralizante, tempestade de citocinas sistêmica, microtrombos mediados por fator de tecido e

estresse oxidativo, contagem de plaquetas mais baixa, dímero D, aumentado proteína C reativa e anormalidades de coagulação, aumento da permeabilidade vascular, edema pulmonar, pneumonia, inflamação generalizada e danos a múltiplos órgãos. As doenças periodontais apresentam um perfil inflamatório crônico e multifatorial, de origem infecciosa, com interações sistêmicas vinculadas a mais de 50 condições sistêmicas. A resposta imunoinflamatória dos tecidos periodontais ao desafio microbiano, a resposta de proteção e a destruição local do periodonto influenciam e são influenciadas por condições sistêmicas. O sistema renina-angiotensina/inibidores da ECA também estão relacionados à patogênese do COVID-19 pelo SARS-CoV-2-ACE2 e à patogênese da periodontite, por meio da reabsorção óssea regulada pelo eixo ACE2/Ang (1-7) / MasR e IL1 - β, regulação positiva da via do receptor de quinina/B2 devido à inflamação do receptor Toll-like 2 e respostas Th1/Th17, expressão do receptor de angiotensina II tipo 1 em tecido gengival inflamado e modulação induzida por IL-1β 6 produção em fibroblastos gengivais humanos. É possível que a infecção por SARS-CoV-2 aumente os eventos inflamatórios locais no tecido periodontal, levando à destruição dos tecidos periodontais, provavelmente potencializado pelos efeitos sistêmicos da periodontite. Apesar das evidências científicas limitadas ou inexistentes sobre os efeitos do COVID-19 nas doenças periodontais e suas interações sistêmicas até o momento, é possível esperar seu impacto na pesquisa da medicina periodontal.
Palavras-chave: Infecção por Coronavírus; Patogênese; Periodontia.

Resumen
La respuesta inmunoinflamatoria a la infección por SARS-CoV-2 conduce a una infiltración excesiva de monocitos, macrófagos y células T, anticuerpos no neutralizantes, tormenta de citocinas sistémicas, menor recuento de plaquetas, aumento del dímero D, Proteína C reactiva y anomalías en la coagulación, aumento de la permeabilidad vascular, edema pulmonar, inflamación generalizada y daño multiorgánico. Las enfermedades periodontales tienen un perfil inflamatorio crónico, de origen infeccioso, con interacciones sistémicas vinculadas a más de 50 afecciones sistémicas. La respuesta inmunoinflamatoria de los tejidos periodontales al desafío microbiano, la respuesta protectora y la destrucción local de la influencia del periodonto están influenciadas por condiciones sistémicas. Los inhibidores del sistema renina-angiotensina/ECA también están relacionados con la patogenia de COVID-19 por SARS-CoV-2-ACE2 y con la patogénesis de la periodontitis, a través de la resorción ósea regulada por el eje ACE2/Ang- (1-7)/MasR e IL1 - β, regulación positiva de la vía cinina / receptor B2 debido a la inflamación del receptor 2 tipo Toll y respuestas Th1/Th17, la expresión del receptor de angiotensina II tipo 1 en el tejido gingival inflamado y la modulación de IL-1β inducida por IL- 6 producción en fibroblastos gingivales humanos. Es posible que la infección por SARS-CoV-2 aumente los eventos inflamatorios locales en el tejido periodontal que conducen a la destrucción de los tejidos periodontales. Apesar de la evidencia científica limitada o inexistente sobre los efectos del COVID-19 en las enfermedades periodontales y sus interacciones sistémicas hasta la fecha, es posible esperar su impacto en la investigación de la medicina periodontal.
Palabras clave: Infecciones por Coronavirus; Pathogenesis; Periodoncia.

1. Introduction

SARS-CoV-2 infection appears to directly affect tissues and organs by exposure and presence of the angiotensin-converting enzyme 2 (ACE2) ectoenzyme and cellular proteases (Bertram et al., 2011, Glowacka et al., 2011, Raj et al., 2013, Wang et al., 2013, Gheblawi et al., 2020, Gralinski & Menachery, 2020, Hoffmann et al., 2020, Wan, Shang, Graham, Baric & Li, 2020, Zhou et al., 2020). The lungs are the most affected organs and the clinical evolution of severe forms of COVID-19 leads to abnormalities in the blood hematological and biochemical index, and systemic conditions/diseases on kidney, liver and coagulation biomarkers (Tay, Poh, Rénia, MacAry & Ng, 2020, Pedersen & Ho, 2020, Schett, Sticherling & Neurath, 2020, Zhang et al., 2020). The pathogenesis of COVID-19 and its systemic impacts are associated with intense pro-inflammatory events and loss of homeostasis, associated with a hyperinflammatory state, secondary bacterial infections, bacteremia, endotoxemia, loss of function and multiple organ failure (Cao & Li, 2020, Chen et al., 2020, Hadjadj et al., 2020, Henry, de Oliveira, Benoit, Plebani & Lippi, 2020, Huang et al., 2020, Mehta, McAuley, Brown, Sanchez, Tattersall & Manson, 2020, Merad & Martin, 2020, Qin et al., 2020, Wang, Jiang, Chen & Montaner, 2020, Wu et al., 2020, Ye, Wang & Mao, 2020, Zhou et al., 2020, García-Sastre, 2017, Schulert & Grom, 2015, Mayer-Barber et al., 2014). The systemic impacts of the COVID-19 have the potential to influence the relationships and interactions between periodontal diseases and systemic conditions/diseases, previously reported in the literature. In addition, the periodontal medicine research, the natural history of periodontal disease and the response to periodontal therapy during and after the COVID-19 pandemic may be affected by the disease.

This paper is a continuation of Part 1, in which the authors summarize and describe the immunoinflammatory and

clinical impacts of SARS-CoV-2 infection shared or correlated with systemic interactions of periodontal diseases. Two illustrations describe the immunoinflammatory response in COVID-19 disease and the COVID-19 multifactorial pathogenesis potentially associated with the pathogenesis of periodontal diseases and their bidirectional systemic interactions. Therefore, the aim of this study was to review the literature and propose a conceptual hypothesis on the subject, based on the interception between the pathogenesis of COVID-19 and its main systemic repercussions, and periodontal medicine.

2. Methodology

Theoretical essay based on studies on the pathogenesis of COVID-19, potentially related to systemic interactions of periodontal diseases. Searches were performed in the MEDLINE|PubMed, Scopus, Embase, Web of Science, Cochrane Library, and BIREME|bvs databases for articles published up to 2020 December 20, using MeSH terms, Emtree terms and DeCS/MeSH terms related to 'COVID-19', 'SARS-CoV-2', and 'pathogenesis', combined by the Boolean operators "OR" and "AND". The studies, mostly experimental and review, published in the main journals, were qualitatively summarized. The comparison of these findings with the main systemic interactions of periodontal diseases previously described resulted in conceptual hypotheses based on the literature about the potential impacts of the COVID-19 pandemic on the scientific investigation of these interactions.

3. Results and Discussion

Hyperinflammatory state in COVID-19

Increased C-reactive protein, ferritin and D-dimer (inflammatory markers) in the blood, the proportion of neutrophils/lymphocytes (Cao & Li, 2020, Henry, de Oliveira, Benoit, Plebani & Lippi, 2020, Wu et al., 2020, Zhou et al., 2020) and serum levels of inflammatory cytokines and chemokines (Chen et al., 2020, Ye, Wang & Mao, 2020, Huang et al., 2020, Qin et al., 2020, Wang, Jiang, Chen & Montaner, 2020) are associated with greater severity and death from COVID-19. There are similarities between the increased profile of cytokines in the macrophage activation syndrome and that observed in COVID-19: increase in IL-6, IL-7, the soluble form of the α-chain of the IL-2 receptor, TNF, inflammatory chemokines such as CC-chemokine 2 (CCL2), CCL3 and CXC-chemokine 10 ligand (CXCL10) (Merad & Martin, 2020).

Some studies suggest that unregulated activation of mononuclear phagocytes contributes to the hyperinflammatory state of patients with COVID-19 (Schulert & Grom, 2015, Mehta, McAuley, Brown, Sanchez, Tattersall & Manson, 2020). Patients who died with COVID-19 showed high levels of lymphocytic apoptosis in the spleen and lymph nodes related to increased expression of the death receptor FAS (cell death induced by activation). The recognition of antigens and high levels of IL-6, mediated by macrophages, may be associated with lymphopenia (Merad & Martin, 2020, Haigh et al., 2020).

Monocytes represent 80 % of the total cells present in the bronchoalveolar fluid of patients with COVID-19, enriched in CCL2 and CCL7 [chemokines for recruiting CC-chemokine receptor 2-positive ($CCR2^+$) monocytes]. Monocyte chemotaxis and cell count increase with disease severity; tissue-resident macrophages are depleted and there is a significant increase in monocyte-derived macrophages (Azkur et al., 2020). The bronchoalveolar fluid of patients with mild COVID-19 has clonal expansion of subsets of $CD8^+$ T cells (signature of the T cell gene with memory residing in the tissue) and minimal inflammatory monocyte infiltration. These characteristics seem to be associated with better control of viral load, less tissue damage and systemic complications mediated by inflammation. Severe cases of COVID-19 in ICUs show a significant increase in $CD14^+CD16^+$ monocytes producing IL-6 in the peripheral blood (Chu et al., 2020, Alzaid et al., 2020, Bouadma et al., 2020). COVID-19 leads to populations of subcapsular and splenic macrophages in the marginal zone of the $CD169^+$ lymph node (tissue post-mortem immunostaining), by the expression of the ACE2 or CD147 receptor (Haigh et al., 2020, Helal et al., 2020). $IL6^+$ macrophages with endocytosed viral particles were associated with depletion of spleen and lymph node lymphocytes (Hadjadj

et al., 2020). $CD68^{+}NP^{+}$ macrophages and monocytes have been associated with acute renal tubular injury in patients with COVID-19 (Mehta, McAuley, Brown, Sanchez, Tattersall & Manson, 2020). Lung damage (focal necrosis and lymphocytic and monocytic infiltration), spleen (necrosis), heart, liver and muscles, caused by COVID-19, were also observed. SARS-CoV-2 infection leads to high levels of IFN-γ, IL-1β, IL-6, IL-10, IL-12, TGFβ, CCL2, CXCL10, CXCL9 and IL-8, in addition to hyperinflammatory macrophages in the lungs of those killed by COVID-19. In view of the blocking of the production of type I interferon in coronavirus-infected cells (García-Sastre, 2017), the hyperinflammatory responses of COVID-19 (Hadjadj et al., 2020) may be associated with the activation of the inflammasome (Merad & Martin, 2020, Mayer-Barber et al., 2014).

Pulmonary epithelial cells secrete IL6, MCP1, IP-10, MIP1β and MIP1α that stimulate T cells, monocytes and macrophages, which in turn increase IFN-γ levels, establishing positive feedback that sustains the hyperinflammatory state. If the cellular response mediated by $CD4^{+}$ and $CD8^{+}$ T cells is efficient, the alveolar macrophages recognize and phagocytize the apoptotic cell (no virus release), and the alveolar macrophages eliminate the virus neutralized by the antibodies. However, the evolution of the infection results in cytokine storms (IL-6, IP-10, IFN-γ, IL-2, IL-10, G-CSF, MIP1α and TNF) and leakage caused by vascular permeability, with non-neutralizing antibody. The dysfunctional immune response leads to excessive infiltration of monocytes, macrophages and T cells, systemic cytokine storm, pulmonary edema and pneumonia, and widespread inflammation and multi-organ damage (Tay, Poh, Rénia, MacAry & Ng, 2020). Li et al. (2020) observed typical clinical manifestations of shock in critically ill COVID-19 patients and described it as a viral sepsis.

Lower platelet counts, increased D-dimer (fibrin degradation product) and coagulation abnormalities are associated with organ failure and death in patients with severe COVID-19 (Xiang-Hua et al., 2010, Helms et al., 2020, Tang, Bai, Chen, Gong, Li & Sun, 2020). Many of these patients have microthrombi in the lungs, lower limbs, hands, brain, heart, liver and kidneys (Liu, Blet, Smyth & Li, 2020, Zhang et al., 2020). The cytokine storm can activate intravascular coagulation and lead to organ damage and sepsis, (Levi & van der Poll, 2010) mediated by the expression of the TF pathway (or CD142 or coagulation factor III) (Simmons & Pittet, 2015, Iba, Levy, Raj & Warkentin, 2019). Mononuclear cells and vascular endothelial cells express TF in response to pro-inflammatory cytokines (especially IL-6), capable of transforming prothrombin into thrombin, which in turn converts circulating fibrinogen into fibrin (van der Poll, van de Veerdonk, Scicluna & Netea, 2017). Antithrombin and the TF pathway inhibitor (natural anticoagulants) can be impaired during inflammation. Coagulation can start with vascular injury or with the recruitment of TF-expressing inflammatory monocytes by activated endothelial cells (von Brühl et al., 2012). In SARS-CoV infection, oxidized phospholipids present in the lungs as a result of oxidative stress increase TF expression, monocyte recruitment and activation of endothelial cells and macrophages via the TLR4–TRIF–TRAF6–NF-κB pathway (Merad & Martin, 2020, Berliner, Leitinger & Tsimikas, 2009, Imai et al., 2008, Owens et al., 2012).

During neutrophil and monocyte/macrophage response in severe stage of COVID-19, T cells activated by SARS-CoV-2^{+} antigen presenting cells lead to an increase in IL-6 and GM-CSF and the accumulation of hyaline membrane in the bronchi. IL-1 and TNF are also elevated in the lung during acute respiratory distress syndrome and both induce HA-synthase-2 in $CD31^{+}$ endothelial cells, responsible for the production of hyaluranonan. In addition to local tissue damage by the hyperinflammatory response, the accumulation of hyaluronan contributes to the reduction of oxygen saturation, as it absorbs water up to 1,000 times its molecular weight (Shi et al., 2020).

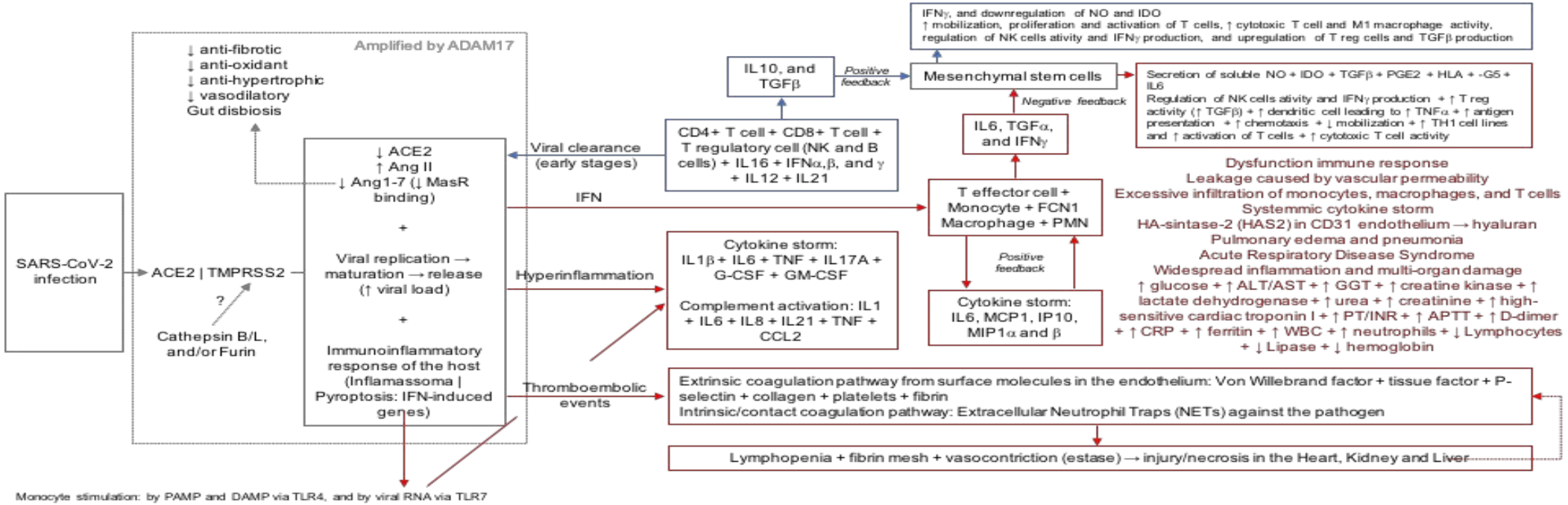
Rao et al. (2020) described the role of mesenchymal stem cells as bridge catalysts between innate and adaptive immunity in COVID-19. The reduction of the immune response in the early infectious phase of COVID-19, marked by IL-10 and TNF-β, exerts positive feedback on mesenchymal stem cells, resulting in: i) increased mobilization, proliferation and activation of T cells; ii) increased activity of cytotoxic T cells; iii) IFN-γ and negative regulation of nitric oxide and enzyme indoleamine 2, 3-dioxygenase, resulting in the activation of M1 macrophages, regulation of NK cell activity and production of IFN-γ based on the

type of stimulus, and; iv) upregulation of T regulatory cells and TGF-β production. This positive feedback results in the up regulation of immune system with increase in production of proinflammatory cytokines. The increase in pro-inflammatory cytokines, such as IL-6, TGF-α and IFN-γ, leads to negative feedback from mesenchymal stem cells. In this case, the following occurs: i) decrease the activity of regulatory T cells and reduce TGF-β; ii) secretion of soluble factors such as nitric oxide, enzyme indoleamine 2, 3-dioxigenase, TGF-β, prostaglandin E2 (PGE_2), human leukocyte antigens (HLA) and soluble IL-6, resulting in regulation of NK cell activity and production of IFN-γ based in the type of stimulus, inhibition of the dendritic cell, leading to decreased TNF-α and decreased presentation of antigens, and decreased chemotaxis and increased neutrophil mobilization; iii) decreased TH1 cell lines and decreased T cell activation; iv) decreased activity of cytotoxic T cells. This negative feedback results in the downregulation of excessive immune response, decrease in pro-inflammatory cytokines, increased tissue regeneration and repair.

The immunological profile of patients with moderate and severe COVID-19 shows an overall increase in innate cell lines and a concomitant reduction in T cell counts, early and elevated pro-inflammatory cytokines and an increase in chemokines and growth factors; the latter was correlated with a better course of the disease. In the most severe cases, type 1 (antiviral) and type 3 (antifungal) responses remain elevated throughout the disease. In addition to multiple type 2 effectors (anthelmintics), such as IL-5, IL-13, IgE and eosinophils. Early immune signatures and abnormal immune responses influence the trajectory of COVID-19 (Lucas et al., 2020).

The immunoinflammatory events involved with the pathogenesis of COVID-19 are compiled in Figure 1:

Figure 1: Immunoinflammatory response in COVID-19 disease.



Monocyte stimulation: by PAMP and DAMP via TLR4, and by viral RNA via TLR7

Monocyte chemotaxis: CCR2, P-selectin, and IL6-IL6R

Macrophage stimulation:
- Phospholipids oxidized via TLR4 (intracellular signal transduction: TRIF→TRAF6 → NFκB → inflammatory genes)
- TNF + IFNγ + CM-CSF + IFN via receptors (intracellular signal transduction: JAK → STAT → Interferon Stimulated Genes)
- Tissue factor → inflammatory genes
- Intracellular signaling via stimulation of the immunoreceptor tyrosine-based activation motif _ ITAM by Anti-spike IgG (intracellular signal transduction: SYK+SYK → PI3K+PLCγ → DAG → PKC → inflammatory genes)
- Virus binding to CD147 and NLRP3 inflammassome stimulation → activate capase 1 → Pro-IL1β → IL1β and IL-8 (IL1β autocrine effect activating IRAK4 → TRAF6)
- Recognition of viral RNA by TLR7 (intracellular signal transduction: IRAK4-TRAF6-NFkb-inflammatory genes)

Hyperstimulated macrophages: IL1RA, IL6, IL8, IL10, TNF, CXCL10, and oxidative stress

Cytokine storm: IL18, MCP1, IP10, and MIP1α

Source: Authors.

SARS-CoV-2 infection and periodontal medicine research

Considering all that has been exposed the pathogenesis of COVID-19 may directly influence the natural history of periodontal diseases, response to periodontal therapy, and the investigation of the causal and bidirectional relationships between periodontitis and systemic diseases. Even the diagnosis and classification of periodontal and peri-implant diseases and conditions can be influenced by SARS-CoV-2 infection and the development of COVID-19. Given the complexity of the pathogenesis of COVID-19 and the uncertainties of its effects on patients, perhaps SARS-CoV-2 infection in its different clinical manifestations (e.g. asymptomatic, mild and severe cases) should represent an exclusion criterion in certain studies of periodontal medicine.

For Page and Kornman (1997), "Antigens and various other virulence factors, and in some cases invading bacteria, comprise the microbial challenge, and the host responds with an immediate inflammatory and immune response that can influence the challenge. The host response results in production of cytokines, eicosanoids, other inflammatory mediators such as the kinins, complement activation products and matrix metalloproteinases, which perpetuate the response and mediate connective tissue and bone destruction. All of these events are influenced by disease modifiers, both genetic and environmental or acquired." Through a microbial challenge, antigens, lipopolysaccharides and other virulence factors stimulate the host's immune-inflammatory response, and then polymorphonuclear cells and antibodies fight microorganisms while cytokines and prostanoids and matrix metalloproteinases act on connective tissue and metabolism bone, resulting in clinical signs of disease initiation and progression. Genetic risk factors and environmental and acquired risk factors influence this process. Considering this non-linear or multifactorial model of the pathogenesis of periodontal diseases, the SARS-CoV-2 infection and social isolation may represent acquired risk factors for periodontal diseases and/or its association with systemic diseases (Kornman, 2008).

Social isolation must compromise the treatment and supportive periodontal therapy of patients with periodontitis. Likewise, patients with chronic non-communicable diseases, for example, should also stop treatment and follow-up. In this context, the bidirectional relationship between periodontitis and systemic diseases, such as diabetes mellitus and cardiovascular diseases, suggests a critical situation during the COVID-19 pandemic (Grasselli et al., 2020). The immunoinflammatory and infectious component, as well as the impairment of homeostasis between the systems, observed in these diseases, offer an even greater risk for these patients to develop severe forms of COVID-19. In addition, the pathogenic profile of oral bacteria associated with periodontitis also poses a risk of systemic infectious complications, both due to aspiration and bacteremia.

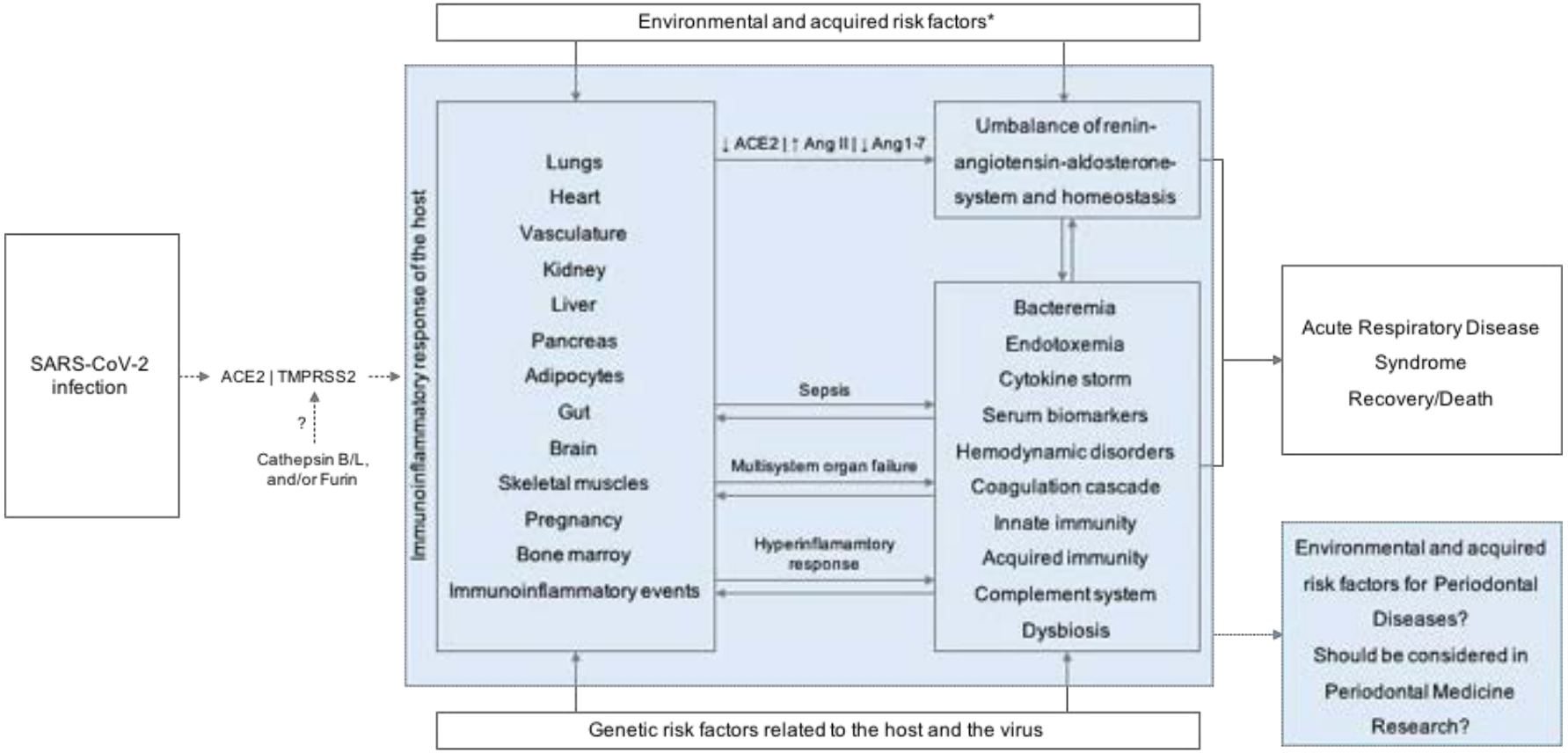
Given the intensity of the effects of COVID-19 in different host systems, it is possible that the relationships between periodontal diseases and systemic diseases, investigated in periodontal medicine, are modified or amplified (Figure 2). Despite scientific evidence about the infectious nature of periodontitis, bacteria can be considered essential, but not sufficient, for the clinical evolution of the disease (Page, Offenbacher, Schroeder, Seymour & Kornman, 1997).

Although there are still no studies on the interaction between SARS-CoV-2 infection and periodontal tissues, the pathogenesis of COVID-19 has numerous factors directly related to the biological plausibility of the bi-directional relationships investigated in periodontal medicine. The interpretation of serum levels of pro-inflammatory cytokines and C-reactive protein in patients with periodontitis and systemic diseases should be changed by COVID-19. Likewise, the loss of homeostasis and the impairment of tissues and organs diagnosed also by specific biomarkers in the blood may compromise the causality studies between periodontitis and systemic diseases.

In addition, the treatment of COVID-19 should be considered an important modifying factor in the systemic immunoinflammatory profile of these patients. Different protocols and therapeutic drugs have been used worldwide in the treatment of COVID-19 and may also vary according to the severity of each case. Antibiotics, antivirals, chloroquine/hydroxychloroquine, ivermectin, anti-inflammatories, glucocorticoids, anticoagulants, immunomodulatory drugs and convalescent plasma transfusion have been widely used. Patients recovering from COVID-19 may have systemic

abnormalities or sequelae caused by the disease or related to treatment, for a period not yet known. Gut dysbiosis was also observed in patients with COVID-19, and associated with ACE2 imbalance (Viana, Nunes & Reis, 2020). The relationship between the renin-angiotensin system/ACE inhibitors and periodontitis can occur through bone resorption regulated by the ACE2/Ang-(1-7)/MasR axis and IL1-β, positive regulation of the kinin/receptor pathway B2 (B2R) due to TLR2 inflammation and Th1/Th17 responses, (Hollá et al., 2001, Gürkan et al., 2009, Santos et al., 2009, Santos et al., 2015, Rodrigues et al., 2016) but also by the expression of the type 1 angiotensin II receptor (AT1R) in the inflamed gingival tissue, modulating IL-1β-induced IL-6 production in human gingival fibroblasts (Nakamura et al., 2011).

Figure 2: COVID-19 multifactorial pathogenesis potentially associated with the pathogenesis of periodontal diseases and their bidirectional systemic interactions.



Environment risk factors (e.g., environmental exposure, wild animals, climate, social and physical contact, etc.), and acquired (e.g.,age, smoking, commorbidities, glucocosticoids, etc.).

Source: Authors.

If the effects of SARS-CoV-2 infection or the COVID-19 disease on periodontal tissues are confirmed, this condition may be classified as "Periodontal manifestations of systemic diseases and acquired and developmental conditions - Systemic disorders that have a major impact on the loss of periodontal tissues by influencing the periodontal inflammation" (Jepsen et al., 2018). The new classification for periodontal and peri-implant diseases and conditions considers C-reactive protein as an important biomarker in the diagnosis of periodontitis. However, COVID-19 increases serum levels of C-reactive protein, which can remain high in cases of liver damage or other pathologies. In addition, cytokines such as IL-1β, IL-2, IL-6, IL-7, IP-10, G-CSF, IFN-α, IFN-β, IFN-γ, MCP-1, MIP-1A and TNFα, as well as chemokines (IL-8 and CCL2) and the activation of endothelial adhesion molecules (intracellular adhesion molecule-1 (ICAM-1) and TF) increased in COVID-19 (Huang et al., 2020, Channappanavar & Perlman, 2017). Pyroptosis, lymphopenia, neutrophilic infiltration in tissues, increased neutrophil/lymphocyte ratio and recruitment of hyperactive monocytes/macrophages contribute to a hyperinflammatory response and local tissue damage.

Epidemiological and experimental studies have linked periodontitis to the development or exacerbation of other chronic inflammatory diseases. This relationship was attributed to the patient's systemic inflammatory state, with consequences distal to oral inflammation resulting from bacteremia and endotoxemia (bacterial lipopolysaccharides), increased pro-inflammatory mediators IL-1β e IL-6, IL-17, IFN-γ, TNF-α, GM-CSF, acute phase proteins, such as C-reactive protein, haptoglobin, fibrinogen, serum amyloid A, and serum amyloid P. A prolonged or excessive acute phase response is associated with sepsis and reperfusion injuries. Like COVID-19, activated monocytes, $CD4^+$ T, Th2/B and Th17 cells, aberrant immune responses, neutrophil-mediated hyperinflammation (NETs), complementary factors and inflammatory mediators (IL-1β, IL-6, IL-17, IFN-γ, TNF-α, GM-CSF, PGE_2, thymic stromal lymphopoietin (TSLP), short chain fatty acids and nitrite) increased in the blood by host factors and microbial factors in periodontitis can result in hematopoiesis alterations of the dysfunction endothelial by cytokines or neuronal stimulus, altered immune cell trafficking, reactive microglia, altered immune cell function, altered vascular tone, altered myelopoiesis and trained monocytes. Atherosclerosis, Alzheimer's disease, stroke, obesity, lung infections, rheumatoid arthritis, inflammatory bowel disease, colon cancer, pregnancy complications and diabetes are related to the distal effects of inflammatory mediators, bacteria or antigens that can enter the bloodstream in patients with periodontitis (Van Dyke, 2008, Van Dyke & Kornman, 2008, Cekici, Kantarci, Hasturk & Van Dyke, 2014, Hajishengallis, 2014, Hajishengallis & Sahingur, 2014, Hirschfeld et al., 2015, Meyle & Chapple, 2015, White et al., 2016, Magán-Fernández, O'Valle, Abadía-Molina, Muñoz, Puga-Guil & Mesa, 2019, Konkel , O'Boyle & Krishnan, 2019, Pan, Wang & Chen, 2019).

The alveolar bone loss in periodontitis is also mediated by the host's immunoinflammatory response to a local stimulus, but it can be increased by a systemic inflammatory condition. M-CSF, ligand RANK and osteoprotegerin are responsible for the cell differentiation of monocytes/macrophages in osteoclasts. These cells are activated by TNF-α, IL-1 and PGE_2, mainly in inflammatory osteolysis found in periodontitis. The regulation of the Th1-Th2-Th17 regulatory axis of the adaptive immune response promotes bone loss mediated by macrophages and neutrophils of Th1, B cells that release pro-inflammatory mediators and activate RANK-L expression pathways (Hienz, Paliwal & Ivanovski, 2015, Hajishengallis, Moutsopoulos, Hajishengallis & Chavakis, 2016). Thus, it is possible that the hyperinflammatory state related to the cytokine storm and the systemic complications of COVID-19 potentiate inflammatory events and periodontal tissue destruction, as well as the systemic effects of periodontitis.

Monsarrat et al. (2016) described 57 systemic conditions potentially related to periodontal diseases, in a systematic review of clinical trials from World Health Organization International Clinical Trials Registry Platform. In 2019, Beck et al. published an article entitled "Periodontal Medicine: 100 Years of Progress", based on the 'periodontal medicine' concept proposed by Dr. S. Offenbacher as "[…] a term used to describe how periodontal infection/inflammation may impact extraoral health." The authors reported that "Periodontitis has been linked to over 50 systemic diseases and conditions" with emphasis on

the timeline of cardiovascular disease, diabetes *mellitus*, adverse pregnancy outcomes and biologic mechanisms mediating the systemic effects of periodontitis (Beck, Papapanou, Philips & Offenbacher, 2019). Therefore, given the significant number of interrelationships between periodontal diseases and systemic conditions/diseases established or proposed in the literature, it is very likely that the systemic effects of COVID-19 or SARS-CoV-2 infection will directly or indirectly influence these diseases/conditions.

Changes in the microbial profile,(Dhar & Mohanty, 2020, Gu et al., 2020, Zuo et al., 2020) social isolation, (Magán-Fernández, O'Valle, Abadía-Molina, Muñoz, Puga-Guil & Mesa, 2019, Wilder-Smith & Freedman, 2020) the use of different drugs during the treatment (Jean, Lee & Hsueh, 2020, McKee, Sternberg, Stange, Laufer & Naujokat, 2020, Zhang et al., 2020) and recovery of patients infected with SARS-CoV-2 may also influence the course of periodontal diseases, their responses to treatment and their systemic relationship as a cause or consequence of pathological conditions (Gu et al., 2020, Zuo et al., 2020, Tamburini, Shen, Wu & Clemente, 2016, Acharya, Sahingur & Bajaj, 2017, Blasco-Baque et al., 2017, Lamont, Koo & Hajishengallis, 2018, He et al., 2020, Wong, Lui & Sung, 2020). For the clinical immunologists, the anti-inflammatory treatment of severe COVID-19, including glucocorticoids, IL-6 antagonist, JAK inhibitors and choloroquine/hydrochloroquine can compromise the patient's immune system for other diseases (Zhang et al., 2020). Furthermore, the widespread use of antibiotics during the COVID-19 pandemic can contribute to microbial resistance to these drugs and changes in the microbial configuration in different areas/systems of the individuals (Rawson, Ming, Ahmad, Moore & Holmes, 2020).

4. Final Considerations

Based on the pathogenesis of COVID-19 and its systemic effects, the population infected by SARS-CoV-2, from asymptomatic disease to severe cases of a long period in-hospital patients, represents a challenge to investigate its relationship with periodontal diseases. Besides that, another point represents a new reality in studies in periodontal medicine: Patients previously infected with SARS-CoV-2 and/or who developed COVID-19 represent a bias in studies of the association between periodontal and systemic diseases? What variables directly or indirectly influence these relationships and to what extent? Which diagnostic protocols should be included in the eligibility criteria in periodontal research, mainly in longitudinal studies?

The late effects of COVID-19 and its treatment are not yet known. Perhaps the ideal sample for clinical studies in periodontal medicine research should be patients who have not been infected with asymptomatic SARS-CoV-2 or COVID-19, with no clinical signs and symptoms of the disease, its complications, or use of drugs for its treatment. Previous exposure to SARS-CoV-2 can be assessed by serological tests, regardless of whether or not there is efficient immunity against the virus. However, the diagnosis of COVID-19 and confirmation of infection by SARS-CoV-2 are made by RT-PCR test. Its sensitivity differs between biological samples: 93 % for bronchoalveolar lavage, 72 % for sputum, 63 % for nasal swab, 32 % for oropharyngeal swab, 29 % for feces, 1 % for blood and 0 % for urine (Wang et al., 2020). The time interval for peak viral load levels in COVID-19 is still unknown and the ideal time for diagnosing the infection by RT-PCR has not been established (an average interval of 5 to 7 days) (Xie et al., 2020). The period in which patients remain infectious is not yet fully understood (Zou et al., 2020). Multiple samples for RT-PCR at different times seems to be necessary for the diagnosis of COVID-19 and its monitoring over time, in the case of longitudinal studies in which the disease may represent a confounding variable. We must consider the possibility of assessing previous or current exposure to SARS-CoV-2, drugs used, complementary exams and medical records data in cases of hospitalization for COVID-19 in periodontal researches from now on. Until an effective vaccine is widely distributed to the entire population, RT-PCR tests will be required to screen participants for clinical research and throughout the follow-up period in longitudinal studies.

In the case of investigating the interceptions between the pathogenesis of COVID-19 and periodontal diseases, even during the pandemic, experimental tests can be performed and play a vital role in the discovery of pathogenic mechanisms and

can be applied to investigate the systemic interaction between SARS-CoV-2 infection and periodontal diseases. Due to the genomic similarity of SARS-CoV-2 with SARS-CoV, the experimental models used previously represent alternatives for new studies *in vivo* and *in vitro*: genetically modified hamsters mediated by TALEN or CRISPR, mice (F344), mice and clinical isolates (cell culture) (Shereen, Khan, Kazmi, Bashir & Siddique, 2020).

Recently, Marouf et al. (2021) published a paper on the association between periodontitis and severity of COVID-19 infection. In this case-control study, the authors evaluated 568 patients and reported an odds ratio of 8.81 (95% CI 1.00-77.7), 3.54 (95% CI 1.39-9.05) and 4.57 (95% CI 1.19-17.4) for death, admission to the intensive care unit and the need for assisted ventilation in patients with COVID-19 and periodontities, respectively. This result was significant and adjusted for potential confounders (Marouf et al., 2021).

We should also take into account that the oral cavity is colonized by a large number and variety of micro-organisms, including bacteria, fungi, and viruses (Sultan, Kong, Rizk & Jabra-Rizk, 2018). In addition to host–microbe interactions, we know from the literature that the interfaces of periodontal pathogens with other non-host pathogens, such as herpesviruses like Epstein–Barr virus and cytomegalovirus, can contribute to the pathogenesis of the periodontal disease, or can affect the outcome of viral infection and dissemination (Tonoyan, Vincent-Bugnas, Olivieri & Doglio, 2019).

This theoretical essay supports the conceptual hypothesis that high rate of SARS-CoV-2 contamination or herd immunity should change pre-COVID-19 health status of periodontal patients, due to the direct effects or indirect effects of the virus/disease. Despite limited or non-existent scientific evidence on the effects of COVID-19 on periodontal diseases and their systemic interactions, it is possible to expect its impact on periodontal medicine research from the natural history of periodontal diseases to their pathogenesis and relationship with systemic conditions and response to treatment.

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CAPÍTULO 2

Mecanismos biológicos envolvidos na intercessão entre obesidade e periodontite

Biological mechanisms involved in the intercession between obesity and periodontitis

Mecanismos biológicos implicados en la intercesión entre obesidad y periodontitis

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Resumo

Introdução: O indivíduo obeso apresenta um estado hiper-inflamatório e anormalidades metabólicas relacionadas com o metabolismo glicêmico e funções hepáticas que suportam as hipóteses de maior susceptibilidade e gravidade da periodontite nesses pacientes. Entretanto, a plausibilidade biológica para essa condição ainda não foi estabelecida. Objetivo: Descrever os principais eventos biológicos envolvidos na relação da obesidade com a periodontite. Material e métodos: Ensaio teórico a partir de uma revisão sistematizada de artigos científicos indexados nas bases de dados PubMed|MEDLINE, Scopus, Embase, Web of Science, Cochrane Library, e bvs|LILACS. Resultados e Discussão: Citocinas pró-inflamatórias como IL-1β, IL-6 e TNF-α, perda da homeostasia entre os níveis séricos de leptina e adiponectina,

bem como o aumento dos níveis de ácidos graxos livres e de espécies reativas de oxigênio parecem exercer um *feedback* positivo entre os efeitos deletérios da obesidade e periodontite, com participação importante do fígado e da resistência insulínica nesse processo, potencializando cada vez mais esse sistema. O acúmulo de AGEs, aumento da colagenólise e complicações vasculares decorrentes da hiperglicemia relacionam-se de forma direta com a gravidade da periodontite e a destruição tecidual. O estresse oxidativo participa desse processo não apenas nos tecidos periodontais mas também no fígado, onde o comprometimento funcional desse órgão é acompanhado por aumento dos níveis séricos de proteína C reativa e angiotensinogênio, estimulados também pela endotoxemia, bacteremia e aumento dos níveis séricos de citocinas pró-inflamatórias a partir das bolsas periodontais. Conclusão: Os efeitos da obesidade sobre a periodontite parecem estar relacionados, principalmente, com o estado hiperinflamatório e o comprometimento do metabolismo da glicose.

Palavras-chave: Obesidade; Periodontite; Citocinas; Quimiocinas; Adipocinas.

Abstract

Introduction: The obese individual has a hyper-inflammatory state and metabolic abnormalities related to glycemic metabolism and liver functions that support the hypotheses of greater susceptibility and severity of periodontitis in these patients. However, the biological plausibility for this condition has not yet been established. Objective: To describe the main biological events involved in the relationship between obesity and periodontitis. Material and methods: Theoretical essay based on a systematic review of scientific articles indexed in the PubMed|MEDLINE, Scopus, Embase, Web of Science, Cochrane Library, and bvs|LILACS databases. Results and Discussion: Pro-inflammatory cytokines such as IL-1β, IL-6 and TNF-α, loss of homeostasis between serum leptin and adiponectin levels, as well as increased levels of free fatty acids and reactive oxygen species they seem to exert positive feedback between the deleterious effects of obesity and periodontitis, with an important participation of the liver and insulin resistance in this process, increasing this system more and more. The accumulation of AGEs, increased collagenolysis and vascular complications resulting from hyperglycemia are directly related to the severity of periodontitis and tissue destruction. Oxidative stress participates in this process not only in periodontal tissues but also in the liver, where the functional impairment of this organ is accompanied by an increase in serum levels of C-reactive protein and angiotensinogen, stimulated also by endotoxemia, bacteremia and an increase in serum levels of pro-inflammatory cytokines from periodontal pockets.

Conclusion: The effects of obesity on periodontitis seem to be related mainly to the hyperinflammatory state and impaired glucose metabolism.

Keywords: Obesity; Periodontitis; Cytokines; Chemokines; Adipokines.

Resumen

Introducción: el individuo obeso presenta un estado hiperinflamatorio y alteraciones metabólicas relacionadas con el metabolismo glucémico y las funciones hepáticas que sustentan las hipótesis de mayor susceptibilidad y gravedad de la periodontitis en estos pacientes. Sin embargo, aún no se ha establecido la plausibilidad biológica de esta condición. Objetivo: Describir los principales eventos biológicos involucrados en la relación entre obesidad y periodontitis. Material y métodos: Ensayo teórico basado en una revisión sistemática de artículos científicos indexados en las bases de datos PubMed|MEDLINE, Scopus, Embase, Web of Science, Cochrane Library y bvs|LILACS. Resultados y Discusión: Citocinas proinflamatorias como IL-1β, IL-6 y TNF-α, pérdida de homeostasis entre los niveles séricos de leptina y adiponectina, así como niveles elevados de ácidos grasos libres y especies reactivas de oxígeno. parecen ejercer una retroalimentación positiva entre los efectos deletéreos de la obesidad y la periodontitis, con una importante participación del hígado y la resistencia a la insulina en este proceso, aumentando cada vez más este sistema. La acumulación de AGE, el aumento de la colagenólisis y las complicaciones vasculares resultantes de la hiperglucemia están directamente relacionados con la gravedad de la periodontitis y la destrucción de tejidos. El estrés oxidativo participa en este proceso no solo en los tejidos periodontales sino también en el hígado, donde el deterioro funcional de este órgano se acompaña de un aumento de los niveles séricos de proteína C reactiva y angiotensinógeno, estimulado también por endotoxemia, bacteriemia y un aumento de los niveles séricos de citocinas pro-inflamatorio de bolsas periodontales. Conclusión: Los efectos de la obesidad sobre la periodontitis parecen estar relacionados principalmente con el estado hiperinflamatorio y el metabolismo alterado de la glucosa.

Palabras clave: Obesidad; Periodontitis; Citocinas; Quimiocinas; Adipocinas.

1. Introdução

A partir do aumento da expectativa média de vida observada nos últimos anos em decorrência de avanços científicos e tecnológicos nas áreas médicas, as doenças crônicas passaram a representar os agravos à saúde de maior impacto global (Petersen, 2004). Chamadas assim devido aos efeitos da patogênese serem de baixa intensidade e longa duração

e, pela incapacidade de serem tratadas em curto período de tempo, contemplam comorbidades não transmissíveis como a obesidade. Esta condição tem sido relatada como um problema epidêmico de alta complexidade, morbidade e limitante. Aproximadamente 56 % e 78 % da população mundial do sexo feminino e masculino, respectivamente, apresentam obesidade (NCD-RisC, 2017).

A obesidade é um distúrbio causado pelo acúmulo excessivo de gordura corporal devido a desregulação entre gasto e ganho energético, e, sofre influência de fatores ambientais, genéticos e comportamentais. O aumento do número de obesos nos últimos anos se deve ao estilo de vida adquirido pela maioria da população, sobretudo relacionado com a alimentação inadequada e o sedentarismo (WHO, 2015).

A periodontite também é considerada uma doença crônica não transmissível, em que a inflamação do periodonto causada pelo acúmulo de biofilme dentário associado à resposta do hospedeiro são capazes de levar à destruição dos tecidos periodontais de suporte (Eke et al., 2012). O processo inflamatório, inicialmente agudo e local, visa conter e eliminar microrganismos patogênicos, em especial frente à invasão tecidual. As limitações dos mecanismos imunológicos pré-resolutivos são consideradas responsáveis pela transição para um estado inflamatório crônico (Van Dyke 2008, Medzhitov 2010, Hajishengallis 2015).

Citocinas pró-inflamatórias como a interleucina-1 beta (IL-1β), interleucina-6 (IL-6), fator de necrose tumoral alfa (TNF-α) e ligante do receptor ativador do fator nuclear kappa B (RANKL) são produzidas localmente nos tecidos periodontais, a fim de conter e eliminar a injúria tecidual. A ativação de metaloproteinases da matriz (MMPs) também está associada com perda de inserção periodontal e reabsorção óssea (Page 1991, Birkedal-Hansen 1993, Ebersole et al. 1993, Seymour & Gemmell 2001, Hanada & Yoshimura 2002, Theoleyre et al. 2004, Buduneli et al. 2007, Graves 2008, Noh et al. 2013).

Dentre os prováveis fatores de risco para periodontite, denominados indicadores de risco (Suvan et al., 2018), destacam-se a idade (Grossi et al., 1994), sexo (Kocher et al., 2005), etnia (Grossi et al., 1995), status socioeconômico (Norderyd, 1998), microbiota subgengival específica (Van Winhelhoff et al., 2002), consumo de álcool (Pitiphat et al., 2003), genótipos de interleucina-1 (IL-1) (Kornman et al., 1997; Mcdevitt et al., 2000), exercícios físicos inadequados (Merchant et al., 2003), osteoporose (Reinhardt et al., 1999), síndrome metabólica, obesidade e estresse (Genco & Borgnakke 2013, Genco et al., 1999).

Indivíduos obesos apresentam um estado hiperinflamatório (Lundin et al., 2004), devido aos efeitos metabólicos e imunoinflamatórios provenientes do acúmulo de adipócitos e das comorbidades associadas. Nesta condição, ocorre um desequilíbrio entre os níveis e

proporções de mediadores pró-inflamatórios e anti-inflamatórias, em favor da inflamação (Tilg & Moschen 2006, Varady et al., 2009), e, duas a três vezes mais chance de desenvolver periodontite independente de fatores de risco como idade, sexo e tabagismo (Saito et al., 1998, Al-ZAharani et al., 2003, Wood et al., 2003, Dalla et al., 2005, Torrungruang et al., 2005, Kim & Kim 2017, Martinez-Herrera 2017, Nascimento et al., 2017).

O fato de a obesidade e a periodontite compartilharem mecanismos biológicos, condições sistêmicas e fatores de risco relacionados com sua patogênese, estabelece uma provável relação entre ambas. O estado hiperinflamatório e as complicações metabólicas associadas tanto à obesidade quanto com a periodontite resultam na perda da homeostasia, desfavorável ao indivíduo. Portanto, dada a importância dos mecanismos biológicos envolvidos para o diagnóstico e tratamento da periodontite em pacientes obesos, o objetivo deste estudo foi descrever os principais eventos biológicos envolvidos na relação da obesidade com a periodontite.

2. Metodologia

Este ensaio teórico foi conduzido como uma revisão integrativa de artigos científicos publicados (Whittemore & Knafl, 2005), indexados nas bases de dados PubMed|MEDLINE, Scopus, Embase, Web of Science, Cochrane Library, e bvs|LILACS. Consultamos estudos experimentais, revisões de literatura ou estudos clínicos que avaliaram parâmetros biológicos hematológicos, bioquímica do sangue, variáveis metabólicas, citocinas, quimiocinas, adipocinas e eventos celulares em ensaios experimentais *in vitro* ou *ex vivo*. Os descritores foram estabelecidos por meio das ferramentas MeSH|PubMed, Emtree|Embase, e DeCS|bvs, e, associados utilizando os operadores Booleanos “OR” ou “AND” (Tabela 1).

Tabela 1: Descritores utilizados na busca e seleção de artigos nas bases de dados.

Estratégias de busca
MeSH terms and Emtree terms: (periodontal diseases OR disease, periodontal OR diseases, periodontal OR periodontal disease OR parodontosis OR parodontosis OR pyorrhea alveolaris OR periodontitis OR periodontitis OR pericementitis OR pericementitis OR chronic periodontitis OR chronic periodontitis OR periodontitis, chronic OR periodontitis, chronic OR adult periodontitis OR adult periodontitis OR periodontitis, adult OR periodontitis, adult OR aggressive periodontitis OR periodontitis, aggressive OR periodontitis, prepubertal OR periodontitis, circumpubertal OR circumpubertal periodontitis OR prepubertal periodontitis OR early-onset periodontitis OR early onset periodontitis OR early onset periodontitis OR periodontitis, early-onset OR periodontitis, early-onset OR juvenile periodontitis OR periodontitis, juvenile OR juvenile periodontitis OR periodontitis, juvenile OR periodontosis OR periodontosis OR periodontitis, aggressive, 1 OR periapical periodontitis OR periapical periodontitis OR periodontitis, periapical OR periodontitis, periapical OR periodontitis, apical OR apical periodontitis OR apical periodontitis OR periodontitis, apical OR periodontitis, acute nonsuppurative OR acute non suppurative periodontitis OR acute non suppurative periodontitis OR nonsuppurative periodontitis, acute OR nonsuppurative periodontitis, acute OR periodontitis, acute nonsuppurative OR periodontitis, aggressive, 2) AND (obesity) AND (cytokines OR biological factors OR biological products OR chemokines OR cytokines, chemotactic OR intercrines OR chemotactic cytokines

OR chemotactic factors OR receptors, chemokine OR chemokine receptors OR receptors, cytokine OR cytokine receptors OR cytokine receptor OR receptor, cytokine OR receptors, cytokines OR cytokines receptors OR receptors, immunologic OR immunomodulation OR immunomodulations OR inflammation mediators OR mediators, inflammation OR mediators of inflammation OR peptide hormones OR adipokines OR adipocytokines OR adipokine OR receptors, adipokine OR adipokine receptors OR c-reactive protein OR c reactive protein OR protein, c-reactive OR acute-phase proteins OR acute phase proteins OR proteins, acute-phase OR proteins, acute phase OR reactants, acute-phase OR reactants, acute phase OR acute-phase reactants OR acute phase reactants OR acute-phase protein OR acute phase protein OR protein, acute-phase OR acute-phase glycoproteins OR acute phase glycoproteins OR glycoproteins, acute-phase OR immunoproteins)

DeCS terms: (periodontal diseases OR enfermedades periodontales OR doenças periodontais OR periodontitis OR periodontite OR aggressive periodontitis OR periodontitis agresiva OR periodontite agressiva OR chronic periodontitis OR periodontitis crónica OR periodontite crônica OR gingivitis OR gengivite OR gingivitis, necrotizing ulcerative OR gingivitis ulcerosa necrotizante OR gengivite ulcerative necrosante) AND (obesity OR obesidad OR obesidade OR obesity, morbid OR obesidad mórbida OR obesidade mórbida OR obesity, abdominal OR obesidad abdominal OR obesidade abdominal OR pediatric obesity OR obesidad periátrica OR obesidade pediátrica OR obesity, metabolically benign OR obesidad metabólica benigna OR obesidade metabolicamente benigna OR obesity, maternal OR obesidad materna OR obesidade materna) AND (cytokines OR citocinas OR receptors, cytokine OR receptores de citocinas OR chemokines OR quimiocinas OR biological factors OR factores biológicos OR fatores biológicos OR biological products OR productos biológicos OR produtos biológicos OR immunomodulation OR inmunomodulación OR imunomodulação OR inflammation mediators OR mediadores de inflamación OR mediadores da inflamação OR peptide hormones OR hormonas peptídicas OR hormônios peptídicos OR adipokines OR adipoquinas OR adipocinas OR c-reactive protein OR proteína c-reactiva OR proteína c-reativa OR acute-phase proteins OR proteínas de fase aguda)

Fonte: Autores.

A busca e seleção dos artigos foi realizada sem restrição de data ou idioma de publicação, e, os autores selecionaram os estudos em reuniões de consenso, com o objetivo de descrever os principais eventos biológicos envolvidos na relação da obesidade com a periodontite.

3. Resultados e Discussão

Obesidade e periodontite estão entre as desordens crônicas mais comuns no mundo (Papapanou 1996, Albandar & Rams 2002, Petersen et al., 2005), onde a periodontite é citada como a sexta condição crônica mais prevalente, desde o ano de 2010 (Kassebaum et al., 2014). Dados dos Centros de Controle e Prevenção de Doenças dos Estados Unidos da América sugerem que aproximadamente 47 % da população adulta apresenta essa doença (Albandar & Rams 2002, Dye et al., 2007).

Em 1977, Perlstein e Bissada publicaram um estudo experimental *in vivo* reportando a primeira associação entre obesidade e periodontite, onde foi observada uma maior reabsorção óssea alveolar em ratos obesos, comparados a não obesos. Este resultado foi corroborado por Amar et al. (2007), os quais reportaram a desregulação da resposta imune em modelo animal obeso, relacionada com maior perda óssea alveolar.

A obesidade é descrita como uma condição associada ao acúmulo e expansão excessiva dos adipócitos, e, aumento da infiltração de células macrofágicas nos tecidos

adiposos, o que também define seu estado inflamatório e oferece risco à saúde (Boulomié et al., 2005, Heilbronn & Campbell 2008, Gregor & Hotamisligil 2011).

A avaliação corporal _ parâmetros antropométricos _ na obesidade pode ser feita de diversas maneiras, sendo o índice de massa corporal (IMC) a principal avaliação do estado nutricional do adulto (Expert Panel, 1998). Entretanto, Pischon et al. (2007) propuseram que apesar de ser o principal mecanismo de avaliação, o IMC não é capaz de mensurar a distribuição da gordura corporal e possui uma acurácia limitada pelas diferentes configurações de relação entre peso e altura, que sofrem influência do percentual de gordura mas também de outras variáveis como o volume/densidade muscular. Apesar disso, o IMC é a variável padronizada mais utilizada nos diagnósticos de baixo peso, sobrepeso e obesidade.

Acreditava-se que o tecido adiposo era inerte e que atuava apenas como reserva energética. O tecido adiposo é, em verdade, um órgão endócrino altamente ativo, capaz de secretar substâncias químicas que impulsionam a inflamação (Berg & Scherer 2005, Pischon et al., 2007, Rosen et al., 2006). Dentre essas substâncias há uma variedade de fatores pró-inflamatórios e antinflamatórios como a leptina, adiponectina, citocinas e quimiocinas) (Falagas et al., 2006). A produção ativa de hormônios e citocinas pelo tecido adiposo atua como elo entre a obesidade e suas comorbidades (Genco et al., 2005, Hotamisligil 2006, Madsen et al., 2008, Van Dyke 2008, Nigro et al., 2014, Estefahani et al., 2015).

Os adipócitos em indivíduos obesos secretam quantidades elevadas de adipocinas como adiponectina, leptina, visfatina, levando ao aumento dos níveis séricos e teciduais de citocinas como IL-6 e TNF-α, bem como ao aumento da resposta hepática. A maior atividade inflamatória induz um aumento da síntese e liberação de proteínas de fase aguda pelo fígado, onde a proteína C reativa é a mais estudada e considerada um biomarcador para doenças periodontais, associada ao aumento das espécies reativas de oxigênio, produção e acúmulo de ácidos graxos. O aumento de ácidos graxos potencializa as espécies reativas de oxigênio (*feedback* positivo) e contribui para a resistência insulínica (Soares et al., 2020). No periodonto, subprodutos bacterianos são capazes de ganhar a corrente sanguínea (endotoxemia) e aumentar os estímulos inflamatórios e a geração de espécies reativas de oxigênio no fígado. Portanto, as respostas e disfunções que relacionam obesidade com a periodontite agem em ciclo.

Além do aumento dos mediadores pró-inflamatórios, os adipócitos potencializam o recrutamento de macrófagos, reduzem os níveis de citocinas anti-inflamatórias, e, elevam os níveis de citocinas pró-inflamatórias como IL-6 e TNF-α (Suvan et al., 2018). IL-6 e TNF-α se relacionam com a menor sinalização de insulina, maior oxidação de ácidos graxos e

aumento de secreção de proteína C reativa no fígado, o que acarreta intensificação da resposta inflamatória (Ouchi et al., 2011).

O controle fisiológico do aumento de citocinas pró-inflamatórias é feito, também, pela adiponectina. Entretanto, esta adipocina foi identificada em níveis mais baixos em indivíduos com sobrepeso e obesos, com periodontite (Nakamura et al., 2014, Nigro et al., 2014, Thanakun et al., 2017). É possível que a adiponectina exerça um mecanismo de *feedback* negativo na obesidade, pois seus níveis plasmáticos são menores nessa condição, apesar de ser sintetizada exclusivamente por tecido adiposo. Além disso, a adiponectina apresenta uma relação inversa com a inflamação periodontal, sugerindo um papel protetor contra doenças periodontais (Yesim et al., 2006, Karthikeyan & Pradeep 2007, Martin et al., 2008). Pischon et al. (2014) descreve a adiponectina como um hormônio envolvido no metabolismo da glicose e dos lipídios que é capaz de melhorar sensibilidade a insulina. Se considerarmos que a hiperglicemia e o acúmulo de produtos finais da glicação avançada (AGEs – *advanced glycation end-products*) são fatores de risco para a periodontite e se associam com maior gravidade da doença, é esperado então que a diminuição dos níveis de adiponectina da obesidade favoreçam a periodontite não apenas por um aumento significativo do estado inflamatório do paciente, mas também pelo comprometimento do metabolismo da glicose e prováveis efeitos deletérios do diabetes nos tecidos periodontais.

Outra adipocina importante no estudo da obesidade é a leptina, secretada pelo tecido adiposo e envolvida na patogênese de inflamações crônicas (Iikuni et al., 2008). A quantificação de leptina no fluido crevicular gengival tem sido inconsistente (Akram et al., 2016), embora tenham sido associados níveis elevados dessa adipocina no soro de pacientes obesos com periodontite. Thanakun et al. (2017) reportaram níveis elevados de IL-6, TNF-α, proteína C reativa e leptina relacionados com a associação entre obesidade e periodontite, quando comparados com seus equivalentes eutróficos. A leptina controla o apetite e o metabolismo energético, e desempenha um papel importante no crescimento das células das ilhotas e secreção de insulina (Ruhl & Everhart, 2001). Ela ainda é capaz de alterar o mecanismo imunológico ativando monócitos e macrófagos e modulando a fagocitose, produção de citocinas, quimiotaxia e produção de espécies oxidativas.

Os níveis elevados de leptina são prejudiciais em pacientes com periodontite pois são capazes de exacerbar a resistência a insulina prejudicando a resposta do hospedeiro a infecção local; resultado similar ao dos níveis reduzidos de adiponectina, que também interfere o metabolismo da glicose nessa mesma direção.

Já a visfatina é uma adipocina estudada mais recentemente por ter ação semelhante à insulina e ser produzida pelo tecido adiposo. Sua atuação desencadeia o crescimento das células B de defesa, além de exercer efeito hipoglicêmico (Suresh & Mahendra, 2014). Estudos mostraram que a visfatina pode ter papel patogênico nas doenças periodontais, mas essa afirmação necessita de mais pesquisas para ser comprovada.

A resistina é rica em cisteína e apesar de ser encontrada no tecido adiposo também é produzida por células do sistema imunológico, como macrófagos e monócitos, em processos inflamatórios (Saito et al., 2008). Reilly et al. (2004) reportaram uma correlação entre os níveis plasmáticos de resistina e marcadores de inflamação, como TNF-α, IL-6, lipoproteína associada a fosfolipase A2, a partir da avaliação de 879 indivíduos.

Um estudo comparando ratos obesos com ratos eutróficos (controle) demonstrou níveis mais elevados resistina no plasma de animais obesos (Goncalves et al., 2015). O mesmo resultado foi observado em um estudo clínico em que pacientes obesos com periodontite apresentaram níveis plasmáticos de resistina mais elevados, quando comparados com pacientes saudáveis (Patel & Raju, 2014). A associação entre níveis de resistina e o IMC é ocorre de forma diretamente proporcional (Azuma et al., 2003) e sua secreção está relacionada com a resistência à insulina (Guimarães et al., 2007). A administração de anticorpos antirresistina diminuem a glicemia e melhoram a sensibilidade à insulina em modelos animais (Janke et al., 2002).

A proteína C reativa é uma das proteínas de fase aguda liberadas pelo fígado em que a concentração sérica varia (aumenta ou diminui) em cerca de 25 %, em decorrência de eventos de inflamação. Aproximadamente 95 % ou mais dos indivíduos obesos apresentam doença hepática gordurosa, onde a evolução e a gravidade dessa condição se associam com um aumento dos níveis séricos de proteína C reativa. Na fase aguda da inflamação, o aumento da proteína C reativa foi capaz de intensificar a destruição tecidual periodontal, por atuar como um sinalizador não específico de infecções (Aguiar et al., 2013). Essa relação com a intensificação da degradação do periodonto foi reafirmada em estudos que mostraram que a redução do peso e da gordura corporal são capazes de melhorar o metabolismo e diminuir marcadores de inflamação como a proteína C reativa (Sheu et al., 2008).

Na periodontite, os patógenos presentes na bolsa periodontal levam a um desafio microbiano direto sobre as células epiteliais gengivais e os fibroblastos, que respondem a esse estímulo através de uma resposta inflamatória intensa. Essa resposta pode ser capaz de conter ou eliminar os periodontopatógenos, levar à destruição dos tecidos periodontais, ou participar dos eventos de reparo pós-cessação do estímulo. Fatores de virulência bacterianos, em

especial os lipopolissacarídeos, resultam em um aumento significativo de citocinas inflamatórias locais como IL-1β e TNF-α. O aumento dessas citocinas na corrente sanguínea causada pelo estado inflamatório do corpo obeso pode ser capaz de aumentar a gravidade da inflamação periodontal.

O TNF-α é uma das citocinas secretadas pelo tecido adiposo visceral e participa de lesões induzidas por endotoxinas nos tecidos periodontais (Gemmell & Seymour, 1998). A produção dessa citocina é menos presente em pacientes com saúde periodontal e diminuída após terapia periodontal (Nishimura et al., 2003). Os níveis de TNF-α e proteína C reativa de alta sensibilidade são mais elevados no fluido crevicular gengival de indivíduos obesos, com ou sem periodontite, estando associados com aumento do IMC e resistência insulínica (Grimble 2002, Martinez-Herrera et al., 2017).

Papageorgiou et al. (2017) reportaram uma redução de TNF-α em pacientes obesos e eutróficos, após terapia periodontal. Apesar dos níveis elevados de TNF-α se relacionarem com fatores de risco para periodontite, Genco et al. (2005) propuseram que a elevação dos níveis de TNF-α interferem nos estágios iniciais do desenvolvimento das doenças periodontais, mas em menor proporção no progresso da periodontite quando em estágios mais avançados.

A IL-1β induz a produção de colagenase, interferindo na reabsorção óssea. IL-1β em conjunto com o TNF-α são capazes de interferir na densidade e função celular de fibroblastos, produção de IL-6 e IL-11. Consequentemente, ambas participam do controle das reações inflamatórias (Nicolau et al., 2003).

IL-1β e TNF-α realizam uma regulação positiva de mediadores pró-inflamatórios e produção de proteases envolvidas no processo de destruição dos tecidos periodontais de suporte (Garlet, 2010). O aumento da diferenciação e ativação de osteoclastos e dos níveis locais de metaloproteinases de matriz também participam desse processo (Hotamisligil et al., 2000, Kobayashi et al., 2006). Zimmermann et al. (2013) compararam dois grupos de indivíduos obesos e não obesos, ambos com periodontite, e identificaram níveis elevados de TNF-α no fluido crevicular e de leptina circulante nos indivíduos obesos. Outro fator complicador é o fato de TNF-α e IL-6, aumentados em indivíduos obesos e na resposta imune contra periodontopatógenos, também estarem relacionados com a resistência à insulina e maiores níveis de proteína C reativa circulante (Boesing et al., 2009, Roozbeh Khosravi et al., 2013).

Os níveis plasmáticos de ácidos graxos livres estão aumentados em pacientes obesos (Guenther, 2008). Além de causar resistência à insulina por alterar o transporte e sinalização de glicose dependentes de insulina, também ocorre o aumento de espécies reativas de oxigênio e a diminuição de óxido nítrico (Inoguchi et al., 2000). O aumento dos ácidos graxos livres também é capaz de ativar o fator de transcrição nuclear kappa B (NF-κB), que desencadeia maior expressão hepática de citocinas pró-inflamatórias como TNF-α, IL1-β, IL-6 e MCP-1 (proteína quimioatraente de monócitos-1), intensificando a resposta de defesa e resultando em complicações como a resistência insulínica (Guenther, 2008, Boden et al., 2005). TNF-α e IL-6 produzidas no tecido adiposo também são capazes de prejudicar a sinalização intracelular da insulina, contribuindo para a resistência à insulina (Hotamisligil 2000, Rotter et al., 2003).

Genco *et al*. (2005) sugerem que o estado hiperinflamatório da obesidade deva ser resultado do aumento da resistência insulínica e da predisposição ao diabetes *mellitus*, os quais, então, aumentariam o risco para doenças periodontais. A redução da sensibilidade à insulina associada ao aumento da produção e acúmulo de AGEs no tecido gengival, em diabéticos, pode resultar em maior destruição dos tecidos periodontais (Grossi & Genco 1998, Genco et al., 2005, Reaven 2005, Martinez-Herrera et al., 2017). A resistência à insulina é capaz de provocar diversas alterações, já demonstradas pela relação bi-direcional entre periodontite e diabetes (Taylor, 2001). Dentre elas estão: glicosilação não enzimática, produção de mediadores inflamatórios, alteração estrutural do colágeno, lesões vasculares, mudanças no tecido conjuntivo devido a menor função de fibroblastos e maior quantidade de plasmócitos que prejudicam a cicatrização. Além disso, as alterações vasculares causadas por mudanças no transporte de oxigênio e nutriente às células aumentam a susceptibilidade à degradação periodontal (Alves et al., 2007, Brandão et al., 2011). A periodontite é mais prevalente nos obesos com resistência insulínica, comparados a eutróficos e obesos sem resistência à insulina. Nesses casos, são observados níveis mais elevados de TNF-α, proteína C reativa, glicose, insulina e pressão arterial sistólica (Martinez-Herrera et al., 2017).

As alterações induzidas pela obesidade incluem mudanças no número de linfócitos totais na circulação periférica (Tanaka et al., 2001, O'Rourke et al., 2005). Além disso, ocorre uma desregulação da resposta imunológica frente ao desafio microbiano por periodontopatógenos, mediada pelo aumento dos níveis de ácidos graxos livres que comprometem a sensibilidade de receptores para padrões moleculares associados a patógenos, como os resceptores *toll-like* (Amar et al., 2013, Green et al., 2017). Estas duas

características, somadas aos demais efeitos diretos ou indiretos da obesidade nos tecidos periodontais, se relacionam com uma resposta imunoinflamatória menos eficiente no controle da infecção e preservação dos tecidos periodontais de suporte.

Entretanto, além da resistência insulínica, diabetes e doenças hepáticas gordurosas serem prevalentes em pacientes obesos e todas associadas com seu estado hiperinflamatório, outra condição diagnóstica é bastante comum e reúne mais de uma alteração sistêmica, chamada síndrome metabólica: paciente apresenta aumento de pressão arterial, dislipidemia [(aumento dos triglicérides e diminuição do colesterol HDL (lipoproteína de alta densidade)], obesidade central e aumento da glicemia em jejum (Alberti et al., 2009).

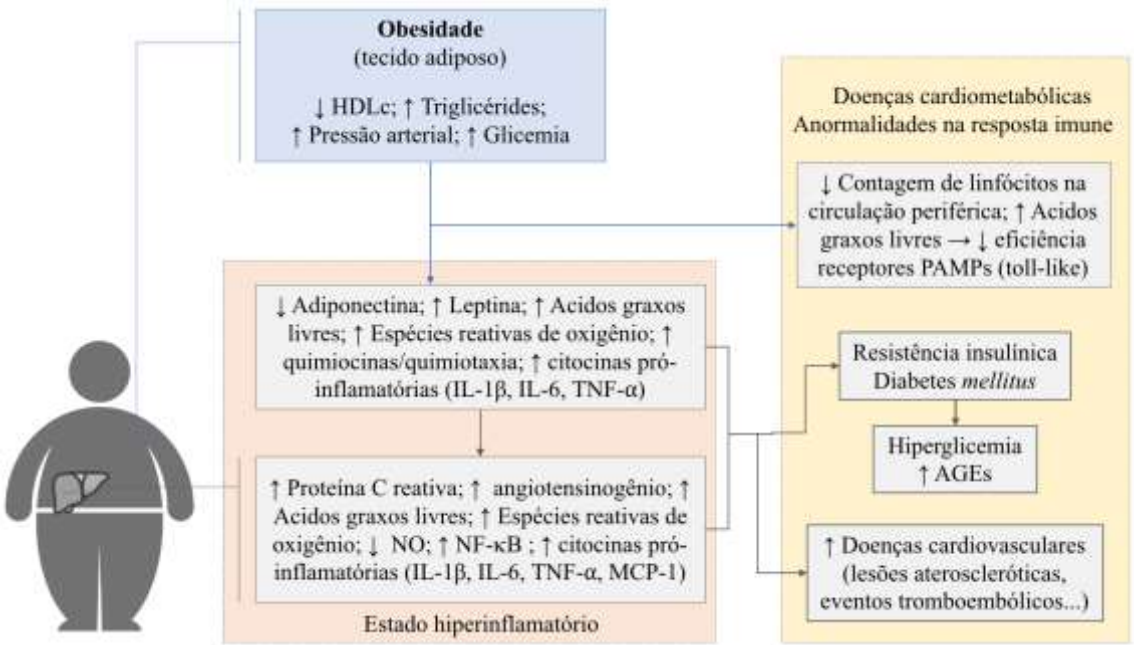
Zeckel et al. (2005) definiu síndrome metabólica como alterações que ocorrem em maior frequência do que pelo acaso devido a fatores pré-dispostos, podendo aumentar as chances de um indivíduo desenvolver doenças cardiovasculares. O estado inflamatório do organismo é a principal relação da síndrome metabólica com a doença periodontal destrutiva. Apesar das evidências e estudos que comprovam essa relação, o mecanismo biológico que explica as influências pontuais ainda não foi totalmente compreendido (Roozbeh Khosravi et al., 2013).

A cronicidade da inflamação decorrente da obesidade acarreta o aumento de espécies reativas de oxigênio, levando a um quadro de estresse oxidativo. Essa condição está associada, também, ao aumento dos níveis de IL-6 e TNF-α, ácidos graxos não esterificados, angiotensinogênio e proteína C reativa (Ando & Fujita 2009). A avaliação de biomarcadores de estresse oxidativo no fluido crevicular gengival ocorre pelos níveis de malondialdeído (MDA), proteína carbonil (PC) e capacidade antioxidante total. Pacientes obesos apresentam maiores níveis de MDA e PC no fluido crevicular gengival comparados a não obesos tanto na condição de saúde periodontal quanto na gengivite ou na periodontite. Além disso, a capacidade antioxidante total é maior em indivíduos saudáveis quando comparados com obesos nas três condições periodontais (Atabay et al., 2017). Tais comprovações reafirmam a condição de maior estresse oxidativo em pacientes com obesidade intensificando o comprometimento da condição periodontal. Outra hipótese acerca da influência da obesidade na periodontite relaciona-se com as alterações da microcirculação bucal. Apesar de Akman et al. (2012) terem reportado valores mais elevados do inibidor do ativador do plasminogênio tipo 1 (PAL-1), que altera a fibrinólise em organismos obesos, e, uma menor espessura da membrana basal de arteríolas terminais, os mecanismos biológicos envolvidos numa possível relação entre o comprometimento microvascular e as doenças periodontais em indivíduos obesos não estão estabelecidos. O tratamento periodontal pode resultar em redução dos níveis

plasmáticos de proteína C reativa, hemoglobina glicada e hiperlipidemia em pacientes cardiopatas (da Silva et al., 2020).

Portanto, a perda da homeostasia em diferentes sistemas decorrente de um número significativo de fatores de risco relacionados com a obesidade, levam a um estado hiperinflamatório caracterizado por um desequilíbrio entre moléculas anti- e pró-inflamatórias circulantes, mas também pelo comprometimento hepático relacionado com o acúmulo de gordura visceral, comum nos pacientes obesos. Estes fatores implicam em aumento do risco de complicações cardiovasculares e metabólicas, especialmente relacionadas com a resistência à insulina e decorrente diabetes *mellitus* tipo II, conforme ilustrado na Figura 1.

Figura 1: Efeitos sistêmicos da obesidade relacionados com o estado hiperinflamatório sistêmico e desordens imunológicas e metabólicas potencialmente relacionadas com maior risco e gravidade de periodontite.



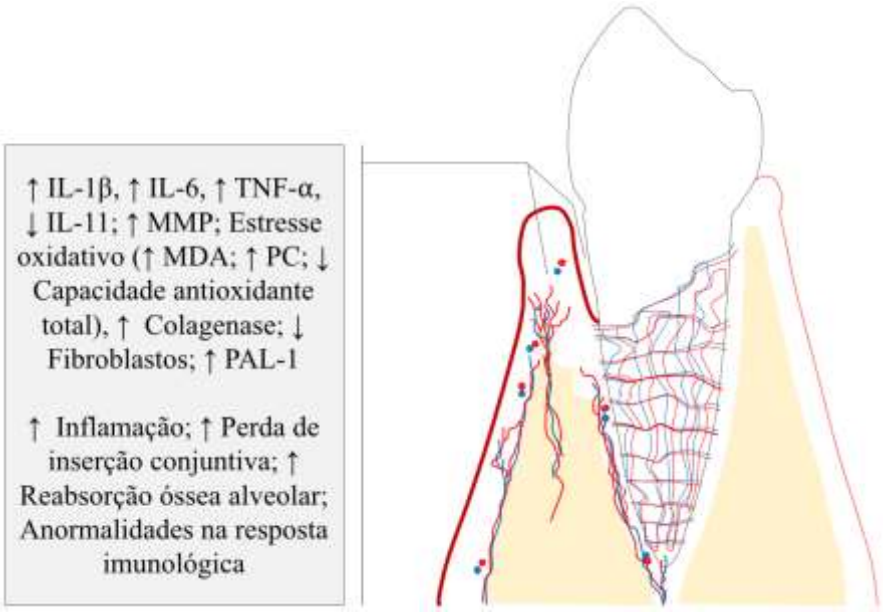
Legenda: HDLc, colesterol lipoproteína de alta densidade; IL, interleucina; TNF-α, fator de necrose tumoral alfa; NO, óxido nítrico; MCP-1, proteína quimioatraente de monócitos-1; PAMPs, padrões moleculares associados a patógenos; AGEs, produtos finais da glicação avançada. Fonte: Autores.

Todos os fatores descritos na Figura 1 apresentam-se circulantes, ou seja, são capazes de influenciar os tecidos periodontais através da microcirculação. Por ser uma doença inflamatória crônica de origem infecciosa, a partir de um desafio microbiano oriundo do biofilme dental, o estado hiperinflamatório sistêmico pode potencializar a resposta

inflamatória nos tecidos periodontais e direcionar o perfil imunoinflamatório de forma desfavorável para o hospedeiro.

A Figura 2 reúne as principais moléculas inflamatórias e eventos locais que resultam em eventos inflamatórios vasculares e celulares mais intensos, maior degradação tecidual e perda dos tecidos de suporte dos dentes, com importante potencial de interferir sistemicamente através da endotoxemia, bacteremia ou mesmo pelo aumento dos níveis séricos de citocinas pró-inflamatórias capazes de prejudicar o metabolismo da glicose e a função hepática, dentre outros.

Figura 2: Perfil hiperinflamatório dos tecidos periodontais em pacientes obesos com periodontite.



Legenda: IL, interleucina; TNF-α, fator de necrose tumoral alfa; MMP, metaloproteinases de matriz; PAL-1, inibidor do ativador do plasminogênio tipo 1. Fonte: Autores.

4. Considerações Finais

Os efeitos da obesidade sobre a periodontite parecem estar relacionados, principalmente, com o estado hiperinflamatório e o comprometimento do metabolismo da glicose tendo como principais fatores biológicos associados as citocinas pró-inflamatórias IL-1β, IL-6 e TNF-α, perda da homeostasia de leptina e adiponectina, aumento dos níveis de ácidos graxos livres e de espécies reativas de oxigênio, acúmulo de AGEs, aumento da

colagenólise e complicações vasculares decorrentes da hiperglicemia, estresse oxidativo, proteína C reativa e angiotensinogênio. É possível que o efeito da obesidade nos tecidos periodontais represente um somatório de fatores de risco e condições favoráveis ao desenvolvimento da periodontite, e não apenas pelo acúmulo de adipócitos e aumento do IMC. Condições sistêmicas como o estado hiper-inflamatório, resistência insulínica e diabetes *mellitus*, e as doenças hepáticas não gordurosas parecem interferir de forma sinérgica e cumulativa com a obesidade nos tecidos periodontais, frente a um biofilme periodontopatogênico.

A investigação da contribuição de cada um destes fatores na patogênese da periodontite em indivíduos obesos pode ser complexa por meio de estudos clínicos, tanto por razões biológicas quanto por questões éticas. Portanto, se fazem necessários e indicados novos estudos experimentais e observacionais capazes de estabelecer os mecanismos biológicos envolvidos na interação entre a obesidade e a periodontite, que irão sustentar protocolos preventivos e terapêuticos multi-/interprofisisonais mais eficazes. Temos como perspectiva nesse sentido, que o tratamento periodontal dos pacientes obesos seja ampliado e passe a integrar na rotina odontológica também a abordagem da equipe médica dos diferentes sistemas envolvidos.

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CAPÍTULO 3

Interseção entre Obesidade e Periodontite: Uma *Umbrella Review* de Estudos de Meta-Análise

Intersection of Obesity and Periodontitis: An Umbrella Review of Meta-Analysis Studies

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ABSTRACT

Objetivo. Este estudo objetivou responder à pergunta norteadora: Qual é a evidência a partir de estudos secundários sobre a relação entre obesidade e periodontite e seus efeitos bidirecionais?

Tipos de estudos revisados. Esta *umbrela review* sumarizou resultados de revisões sistemáticas com meta-análises sobre a relação entre obesidade e periodontite. Seguimos o manual Joanna Briggs para *Umbrella Reviews*, utilizamos o fluxograma PRISMA e planilha padronizada para extração de dados conforme recomendado pelo manual da *Cochrane Collaboration*, seguimos a diretriz de reporte SWiM para síntese dos dados, e utilizamos a ferramenta ROBIS para análise de risco de viés. A seleção dos estudos seguiu critérios de elegibilidade pré-estabelecidos, consultando as bases de dados MEDLINE|PubMed, CENTRAL Cochrane e Embase, outras fontes e busca manual em Janeiro de 2022; a revisão segue atualizada até o momento da submissão, com base nos alertas das bases de dados.

Resultados. A busca inicial resultou na recuperação de 132 registros, dos quais 12 revisões sistemáticas com meta-análises foram incluídas. A chance de desenvolver periodontite e ocorrer piora de parâmetros clínicos periodontais e resistina e IL-1β no fluido crevicular gengival, e maior índice de massa corporal entre indivíduos com periodontite foi observada. Adiponectina, leptina, TNF-α, IL-6 e IL-8 não foram influenciadas de forma significativa pela obesidade em indivíduos com periodontite. Além disso, a obesidade parece não exercer efeito significativo sobre a resposta ao tratamento

periodontal e parâmetros locais. A cirurgia bariátrica não resultou em benefício significativo para a saúde periodontal, tendo sido reportadas pioras nos parâmetros clínicos após a bariátrica por alguns autores, especialmente no longo prazo. Concluímos que existe evidência científica para a associação entre obesidade e parâmetros clínicos peridontais, resistina e IL-1β no fluido crevicular gengival, mas não para a adiponectina, leptina, TNF-α, IL-6 e IL-8.

Conclusões. Não há evidência para efeitos da obesidade sobre a resposta ao tratamento da periodontite e para benefícios da cirurgia bariátrica para os tecidos periodontais.

Registro de protocolo. OSF.IO/486KW

Palavras-chave (termos MeSH). obesity; periodontal diseases; periodontitis; meta-analyis [publication type]; meta-analyis as topic.

INTRODUÇÃO

Na contemporaneidade, mais do que nunca, as doenças crônicas não transmissíveis (DCNTs) representam o maior impacto global nas questões em saúde, e remediações a curto prazo estão sendo substituídas por estratégias de longo prazo.[1] Estima-se que as DCNTs, incluindo doenças cardíacas, doenças respiratórias, obesidade e câncer, sejam responsáveis por 60% das mortes no mundo todo.[2] Dentre estas, a crescente prevalência da obesidade e suas complicações (incluindo diabetes tipo 2, doenças cardiovasculares, maior risco de morte prematura, doença hepática gordurosa não alcoólica) estão cada vez mais influenciando nos problemas de saúde globais, bem como nos custos em saúde.[1,3]

Pesquisas demonstraram vários fatores de risco comuns para DCNTs como a genética, o tabagismo, níveis de estresse, etilismo, sedentarismo, dieta hiperlipídica, dentre outros. As doenças periodontais e a obesidade também são fatores de risco associados ao desenvolvimento e progressão da inflamação crônica e seus desfechos. As respostas do hospedeiro são entendidas como governadas por diversos fatores, os quais se manifestam diferentemente em cada indivíduo.[1] Neste contexto, é necessário investigar e entender a associação entre estas doenças.

A obesidade é uma doença multifatorial, crônica e não transmissível, caracterizada pelo excesso de gordura corporal, inicialmente causada por um desequilíbrio exacerbado entre a ingestão calórica e o gasto de energia[2]. Isto, por sua vez, pode desencadear interações entre fatores ambientais, genéticos e neuroendócrinos em resposta à ingestão de alimentos ou atividade dos adipócitos[4]. Mais do que nunca, entende-se que a inflamação sistêmica ocorre como uma consequência da obesidade por efeitos diretos das adipocinas produzidas e liberadas no tecido adiposo, e por efeitos indiretos do comprometimento

homeostático de diferentes sistemas e eixos metabólicos do corpo humano.[5] Atualmente, é considerada pela Organização Mundial da Saúde (OMS) como um dos mais graves problemas de saúde pública.[2.]

A periodontite, por sua vez, é uma doença inflamatória crônica multifatorial caracterizada pela destruição do periodonto de sustentação, associada à periodontopatógenos.[7] Caracterizada pela associação entre a infecção bacteriana e a resposta imunológica, pode ser modificada, também, por fatores comportamentais como o tabagismo[6]. Estes patógenos produzem fatores de virulência pró-inflamatórios que interagem com o sistema imunológico do hospedeiro induzindo uma resposta inflamatória, com infiltrado de polimorfonucleares, linfócitos, mediadores químicos e modulação da resposta imune.[8,9] Tal cenário resulta em um sítio periodontal (bolsa periodontal) cronicamente inflamado revestido por epitélio ulcerado, caracterizando uma porta de entrada de bactérias (bacteremia) e seus subprodutos (endotoxemia) para dentro da circulação sistêmica[10].

A partir da necessidade de estudos correlacionando as condições fisiológicas e patológicas entre a saúde do periodonto e a saúde sistêmica dos pacientes, utilizando os diferentes tratamentos periodontais como alternativa para a redução da morbimortalidade das doenças crônicas, nasce a "Medicina Periodontal".[11] Neste contexto, revisões sistemáticas e meta-análises sugerem a existência de uma associação entre obesidade e periodontite.[12-23]

Um estado pró-inflamatório sistêmico estabelecido como resultado da liberação de fatores inflamatórios pelos adipócitos, na obesidade, demonstrou afetar os processos de cicatrização, embora os mecanismos não sejam totalmente compreendidos,[24] bem como favorecer o crescimento quantitativo e de complexidade da microbiota oral.[25] Estudos intervencionais sugerem que indivíduos com obesidade apresentam uma resposta clínica deficiente em relação ao tratamento periodontal quando comparados a indivíduos sem obesidade ou com sobrepeso. Nos pacientes com obesidade, pode haver uma menor redução na profundidade de bolsa à sondagem após o tratamento periodontal não cirúrgico (TPNC).[26]

Apesar da possível interação entre obesidade e periodontite ter sido demonstrada, a heterogeneidade metodológica dos estudos, a força de evidência variável entre as publicações, os resultados divergentes e a multifatoriedade destas duas condições tornam difícil a tomada de decisão clínica baseada em evidência neste cenário. Neste sentido, a presente *umbrela review* teve como objetivo sumarizar a melhor evidência acerca da relação entre obesidade e periodontite e seus efeitos bidirecionais, com base em resultados apresentados em artigos de revisão sistemática com meta-análise.

MÉTODOS

***Protocolo e registro*.** Este estudo foi conduzido de acordo com The Joanna Briggs Institute

Reviewers' Manual 2014: Methodology for JBI Umbrella Reviews.[27] O registro de protocolo do presente estudo é OSF.IO/486KW, na plataforma Open Science Framework – OSF (https://osf.io/wbfde/).

***Pergunta norteadora*.** Qual é a evidência a partir de estudos secundários sobre a relação entre obesidade e periodontite e seus efeitos bidirecionais? Estratégia PI/ECOD: P (população)- pacientes com periodontite e obesidade; I/E (intervenção/exposição)- tratamento periodontal sem restrição à técnica/protocolo, ou tratamento da obesidade / exposição à periodontite ou à obesidade; C (controle)- ausência de tratamento da periodontite considerada a instrumentação subgengival, tratamento periodontal tardio ou ausência de tratamento da obesidade, no caso de estudos de intervenção, e ausência de exposição à periodontite ou à obesidade no caso de estudos observacionais; O (desfecho)- efeitos locais ou sistêmicos do tratamento da periodontite ou da obesidade, ou correlação/associação entre periodontite e obesidade; D (delineamentos de interesse)- revisões sistemáticas com meta-análise.

***Critérios de seleção do estudo*:**

- Critérios de inclusão: estudos de meta-análise sobre a relação entre periodontite e obesidade, baseados em estudos observacionais ou de intervenção.
- Critérios de exclusão: i- pacientes em tratamento com imunomoduladores, glicocorticóides, aintinflamatórios não-esteroidais ou outras drogas com efeito imunoinflamatórios; ii- uso de antimicrobianos ou anti-inflamatórios nos seis meses anteriores ao diagnóstico e tratamento periodontal realizado; iii- critérios diagnósticos de periodontite não reportados; iv- pacientes com síndromes congênitas ou doenças autoimunes que acometam os dentes e/ou tecidos periodontais, ou sejam associadas a patologias ósseas dos maxilares; e v- indisponibilidade do texto completo.
- Nenhuma restrição de data ou idioma de publicação foi aplicada.

***Fontes de informação*.** As buscas foram realizadas no MEDLINE usando o mecanismo de busca PubMed (http://www.ncbi.nlm.nih.gov/sites/pubmed), Cochrane CENTRAL (https://www.cochranelibrary.com) e Embase (https:// www.embase.com). Outras fontes (literatura cinza) foram consultadas por meio do Google Scholar (https://scholar.google.com.br), System for Information on Grey Literature in Europe (SIGLE) por meio das bases de dados OpenGrey (www.opengrey.eu). As bases de dados de registro do protocolo incluíram PROSPERO (https://www.crd.york.ac.uk/prospero/) e Open Science Framework – OSF (https://osf.io/). Também foram realizadas buscas manuais em periódicos especializados (ex.: *Journal of Periodontology; Jornal de Periodontologia Clínica; Jornal de Pesquisa Periodontal; Periodontologia 2000; Journal of Periodontal & Implant Science; O Jornal Internacional de Periodontia e Odontologia Restauradora; O Jornal da American Dental Association; Jornal de Patologia Oral e Medicina; Cirurgia Oral,*

Medicina Oral, Patologia Oral e Radiologia Oral) e nas listas de referências dos artigos selecionados. Os especialistas foram identificados usando expertscape.com (https://expertscape.com) e contatados para outras fontes de dados.

Estratégia de busca. A estratégia de busca foi criada utilizando termos MeSH e entry, termos Emtree e Index, e termos DeCS/MeSH, somadas a termos livres, combinados pelos operadores booleanos "OR" e "AND" (Quadro 1), para consulta nas bases de dados MEDLINE|PubMed, Web of Science, Cochrane Library, Embase, Scopus e bvs. As buscas em bases de registro de protocolo e de literatura cinza (outras fontes) utilizaram estratégias de busca adaptadas do MEDLINE|PubMed. A busca eletrônica foi realizada em Janeiro de 2022 e foram criados alertas nas bases de dados para identificar estudos publicados após o momento da submissão do manuscrito para publicação em periódico científico da área.

QUADRO 1

Quadro de estratégias de busca personalizadas por base de dados

Base de dados	Estratégia de busca
MEDLINE|PubMed	(((obesity[Mesh] OR obesity [TiAb]) AND (periodontal diseases[Mesh] OR periodontal diseases[TiAb] OR disease, periodontal[TiAb] OR diseases, periodontal[TiAb] OR periodontal disease[TiAb] OR periodontitis[TiAb])) AND (systematic review[Publication type] OR systematic reviews as topic[MeSH] OR systematic reviews[TiAb] OR systematic review[TiAb] OR meta-analysis[Publication type] OR meta-analysis as topic[MeSH] OR meta-analysis[TiAb] OR meta-analyses[TiAb] OR meta analysis[TiAb] OR meta analyses[TiAb]))
Cochrane Library	ID Search #1 MeSH descriptor: [obesity] explode all trees #2 obesity #3 #1 OR #2 #4 MeSH descriptor: [periodontal diseases] explode all trees #5 periodontal diseases OR periodontitis #6 #4 OR #5 #7 MeSH descriptor: [Systematic Review] explode all trees #8 MeSH descriptor: [Systematic Reviews as Topic] explode all trees #9 MeSH descriptor: [Systematic Reviews as Topic] explode all trees #10 MeSH descriptor: [Meta-Analysis] explode all trees #11 MeSH descriptor: [Meta-Analysis as Topic] explode all trees #12 MeSH descriptor: [Network Meta-Analysis] explode all trees #13 (systematic reviews OR systematic review OR meta-analysis OR meta-analyses OR meta analysis OR meta analyses):ti,ab,kw #14 #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 #15 #3 AND #6 AND #14
Embase	#4: #1 AND #2 AND #3 #3: 'systematic review' OR 'systematic review (topic)' OR 'meta analysis' OR 'meta analysis (topic)' #2: 'periodontal disease' OR periodontite #1: obesity

Processo de seleção dos estudos. Os artigos recuperados foram exportados para o gerenciador de referências rayyan™ (https://www.rayyan.ai) e as duplicatas foram removidas pelo programa e manualmente. Autores de estudos que não foram recuperados na íntegra foram contatados por e-mail em até cinco tentativas. Se dois estudos tivessem sobreposição de amostras, e os mesmos critérios de metodologia avaliados, o estudo menos completo foi excluído. O processo de seleção foi realizado em duas fases (*conventional double-screening*): Fase 1, dois pesquisadores (YVDO e DSB) examinaram de forma independente os títulos e resumos de todas as referências identificadas, aplicando o processo de inclusão (mascaramento ou cegamento); e Fase 2, os mesmos dois revisores aplicaram independentemente os critérios de exclusão aos demais estudos, com base na leitura do texto completo (mascaramento ou cegamento). A confiabilidade entre revisores no processo de seleção dos estudos foi determinada pelo teste κ de Cohen, assumindo um valor limite mínimo aceitável de 0,80.[28] A discordância em qualquer etapa foi resolvida por discussão e decisão mútua (reunião de consenso) com um terceiro revisor (MFF). A decisão/seleção final foi sempre baseada no texto integral da publicação. Os motivos de exclusão dos estudos foram relatados no fluxograma PRISMA (Figura 1) e na seção de Resultados.

Processo de coleta de dados. Os textos completos foram avaliados e julgados em todo o documento. Foi considerado contatar os autores por correio eletrônico, durante cinco semanas consecutivas, quando necessário obter detalhes sobre o desenho do estudo e esclarecimento de dados. Os dados foram extraídos por dois revisores independentes (YVDO e DSB) dos estudos incluídos e descritos no artigo em uma reunião de consenso com o terceiro revisor (MFF). Quando havia informações pouco claras ou omitidas, falta de dados ou quando o texto completo não estava disponível, tentativas semanais foram feitas por até cinco semanas para entrar em contato com os autores. Caso não houvesse retorno dos autores para identificar os dados em gráficos, o programa digital WebPlotDigitizer™ online (https://automeris.io/WebPlotDigitizer/) poderia auxiliar a extração de dados quantitativos a partir de gráficos—apesar de previsto, este recurso não foi necessário na presente pesquisa. A precisão dos dados extraídos foi confirmada pelo terceiro revisor (MFF). Além disto, vale destacar que o programa tradutor do Google foi utilizado no caso de estudos em língua estrangeira não dominada pelos pesquisadores ou em casos de dúvida (https://translate.google.com.br/?hl=pt-BR).

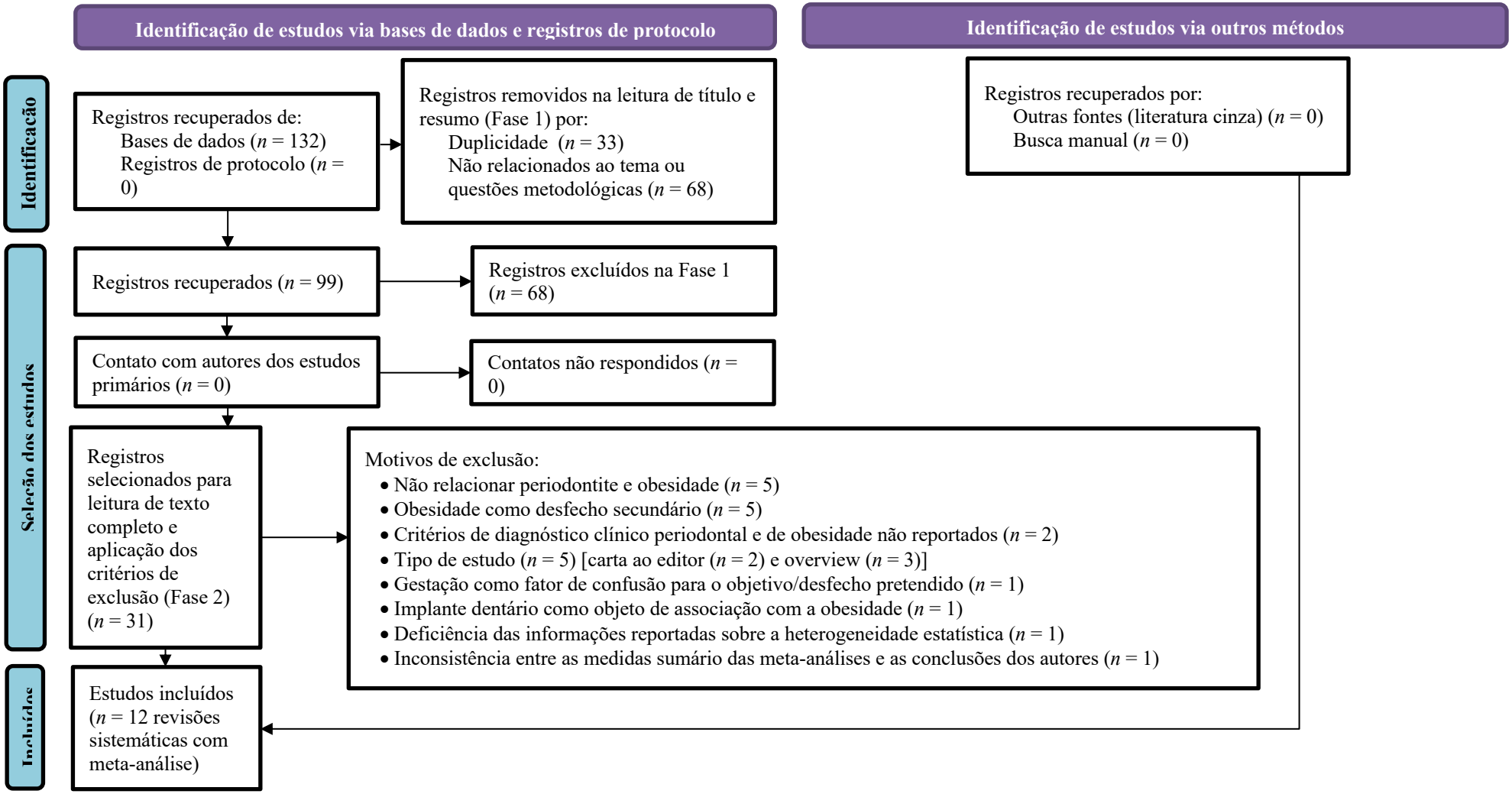
Itens e síntese de dados. Os dados foram extraídos independentemente pelos dois revisores (YVDO e DSB [mascaramento ou cegamento]) usando uma planilha padronizada (gabarito ou *template*), conforme recomendado pelo manual da *Cochrane Collaboration* para revisões sistemáticas.[29] Dos artigos selecionados foram extraídos os seguintes dados: Tabela 1 – estudo | base de dados registrada, objetivo do estudo, guia ou roteiro de estrutura do artigo, PICO ou PECO, consulta da literatura, número e desenho dos estudos incluídos, ferramenta de avaliação de qualidade/risco de viés | qualidade geral/risco de viés, meta-análises, certeza das evidências (GRADE), conclusão dos autores;

conflito de interesses, apoio financeiro; Tabela 2 – estudo, (P) diagnósticos/parâmetros periodontais e/ou diagnósticos/parâmetros de obesidade, (P) controlado para tabagismo, (I) tipos de intervenções periodontais ou abordagem da obesidade | (E) exposição, (C) grupo comparativo, (I/C) terapia periodontal de suporte, evidência de melhora nos parâmetros periodontais | existência da associação entre obesidade e periodontite, acompanhamento, principais resultados; e Tabela 3 – dados e resultados de meta-análises. A síntese qualitativa dos resultados foi adaptada da diretriz de reporte SWiM.[30] Dados e resultados descritivos foram apresentados na forma de texto, figura e tabelas seguindo o ordenamento da estratégia PI/ECO, em reuniões de consenso entre os três revisores (YVDO, DSB e MFF).

***Risco de viés dos estudos*.** A avaliação da qualidade e risco de viés em estudos clínicos foi realizada por três autores (YVDO, DSB e MFF) em reunião de consenso, utilizando-se uma ferramenta específica para risco de viés e avaliação de qualidade metodológica para revisões sistemáticas e meta-análises: Risk of Bias in Systematic Reviews (ROBIS).[31,32] Os autores dos relatórios foram contatados para recuperar qualquer possível viés de dados faltantes; o contato foi feito por e-mail em até cinco tentativas. Os autores dos estudos incluídos foram contatados para esclarecer possíveis dúvidas ou dados ausentes; o contato foi feito por e-mail em até cinco tentativas.

RESULTADOS

***Seleção de estudos*.** No total, foram recuperados 132 registros das bases de dados consultadas: MEDLINE/PubMed (n = 60) e Embase (n = 72). A consulta de registros de protocolo e outras fontes (literatura cinza), bem como a busca manual em periódicos especializados da área e nas listas de referências de estudos selecionados não resultaram na inclusão de mais estudos nesta *umbrella review*. Após a remoção de duplicatas (n = 33), 99 artigos foram submetidos à análise de títulos e resumos e na sequência 31 estudos foram selecionados para a aplicação dos critérios de elegibilidade na leitura de texto completo, dos quais 19 foram excluídos por: não relacionar periodontite e obesidade (n = 5), obesidade como desfecho secundário (n = 5), critérios de diagnóstico clínico periodontal e de obesidade não reportados (n = 2), tipo de estudo (n = 5) [carta ao editor (n = 2) e overview (n = 3)], gestação como fator de confusão para o objetivo/desfecho pretendido (n = 1), implante dentário como objeto de associação com a obesidade (n = 1), deficiência das informações reportadas sobre a heterogeneidade estatística (n = 1), e inconsistência entre as medidas sumário das meta-análises e as conclusões dos autores (n = 1). Assim, 12 revisões sistemáticas com meta-análises foram incluídas (Figura 1).


Identificação de estudos via bases de dados e registros de protocolo
Identificação de estudos via outros métodos
Identificação
Seleção dos estudos
Incluídos
Registros recuperados de:
Bases de dados (n = 132)
Registros de protocolo (n = 0)
Registros removidos na leitura de título e resumo (Fase 1) por:
Duplicidade (n = 33)
Não relacionados ao tema ou questões metodológicas (n = 68)
Registros recuperados por:
Outras fontes (literatura cinza) (n = 0)
Busca manual (n = 0)
Registros recuperados (n = 99)
Registros excluídos na Fase 1 (n = 68)
Contato com autores dos estudos primários (n = 0)
Contatos não respondidos (n = 0)
Registros selecionados para leitura de texto completo e aplicação dos critérios de exclusão (Fase 2) (n = 31)
Motivos de exclusão:
• Não relacionar periodontite e obesidade (n = 5)
• Obesidade como desfecho secundário (n = 5)
• Critérios de diagnóstico clínico periodontal e de obesidade não reportados (n = 2)
• Tipo de estudo (n = 5) [carta ao editor (n = 2) e overview (n = 3)]
• Gestação como fator de confusão para o objetivo/desfecho pretendido (n = 1)
• Implante dentário como objeto de associação com a obesidade (n = 1)
• Deficiência das informações reportadas sobre a heterogeneidade estatística (n = 1)
• Inconsistência entre as medidas sumário das meta-análises e as conclusões dos autores (n = 1)
Estudos incluídos (n = 12 revisões sistemáticas com meta-análise)

Fonte (adaptado de): Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ 2021;372:n71. doi: 10.1136/bmj.n71. For more information, visit: http://www.prisma-statement.org/

FIGURA 1. Fluxograma PRISMA das etapas de busca e seleção de estudos primários

Características dos estudos. Doze meta-análises foram selecionadas para análise de seus dados gerais e específicos incluindo nome do estudo e base de dados registrada; objetivo do estudo; guia ou roteiro de estrutura do artigo; PI/ECO; buscas, número e desenho dos estudos incluídos; ferramenta de avaliação de qualidade/risco de viés, qualidade geral/risco de viés; descrição da meta-análise; certeza da evidência; conclusão dos autores; conflito de interesse e apoio financeiro; controlado por tabagismo; diagnóstico de periodontite/obesidade; tipos de intervenções periodontais ou abordagem da obesidade; grupo controle; cuidados periodontais de suporte; evidências da eficácia do tratamento periodontal/da associação periodontite-obesidade; acompanhamento; principais resultados e dados de meta-análises (Tabelas 1, 2 e 3).

Cinco das 12 revisões sistemáticas com meta-análises incluídas (41,7%) consideraram estudos observacionais e observaram a associação, razão de chances ou de risco entre periodontite e obesidade.[12,13,15,16,19] A maioria das revisões incluídas se basearam em estudos de intervenção, sendo três (25%) de tratamento da periodontite[14,17,18] e quatro (33,3%) sobre os efeitos da cirurgia bariátrica nos parâmetros periodontais locais ou resposta ao tratamento da periodontite.[20-23] Cinco dos 12 estudos incluídos (41,7%) controlaram seus resultados para tabagismo,[12,18,20,22,23] enquanto seis estudos (50%) não reportaram esta variável em nenhuma seção do artigo[13-15,17,19,21] e um estudo (8,3%) não controlou seus dados/resultados para este fator de confusão.[16] O período de acompanhamento longitudinal variou entre os estudos de 6 a 12 meses, exceto para a revisão de Nascimento et al. (2015) que reportou a síntese de dados observacionais de 4 a 20 anos de acompanhamento. Os critérios de diagnóstico clínico periodontal e de obesidade variaram entre os estudos incluídos, porém, é possível identificar um perfil crônico da periodontite compatível com os estágios 1-3, e a obesidade caracterizada pelos valores de referência para IMC, CC, RCQ e gordura corporal (Tabela 2).

Resultados de estudos individuais

Associação entre obesidade e periodontite. Três estudos indicaram evidências de associação positiva entre sobrepeso/obesidade e prevalência de doença periodontal.[12,13,19] É sugerido aumento de aproximadamente um terço nas chances de prevalência de obesidade entre os indivíduos com doença periodontal, uma maior NCI média entre pacientes com obesidade, um IMC mais alto entre os indivíduos com doença periodontal e um aumento linear leve, mas não estatisticamente significativo, nas chances de doença periodontal com o aumento do IMC.[12] Várias hipóteses para interações biológicas entre obesidade e doenças periodontais têm sido propostas, como alterações na resposta pró-inflamatória e imunológica, tolerância à glicose prejudicada, perturbações nos perfis lipídicos, alterações na imunidade do hospedeiro, aumento da ativação de macrófagos, função microvascular prejudicada, respostas fisiológicas ao estresse psicossocial e secreção de substâncias pró-inflamatórias do tecido adiposo, incluindo fator de necrose tumoral alfa (TNF-α), interleucina 6 (IL-6) e proteína C-reativa (PCR).[19]

Por outro lado, também foi mostrada uma associação negativa entre IMC e secreção salivar e associações positivas entre IMC e sangramento gengival, cálculo subgengival, aumento de hormônios celulares e bactérias no fluído crevicular gengival (FCG), o que corrobora com revisões anteriores de estudos em adultos.[13] No total, esses achados são altamente improváveis devido ao acaso e persistem ao longo de estudos usando uma infinidade de estratégias de medição para avaliar essas duas condições de saúde. Mecanismos moleculares e celulares específicos ainda não estão claros e mais estudos são necessários para desvendar os mecanismos, que podem fornecer alvos para prevenção ou tratamento.[12,19]

Resposta ao tratamento periodontal em pacientes com obesidade. O tratamento periodontal em pacientes com sobrepeso/obesidade sistemicamente saudáveis foi associado à maior diminuição nos níveis de TNF-α e maior diminuição nos níveis de HbA1c em comparação com pacientes com peso normal sistemicamente saudáveis.[14] A meta-análise de profundidade de sondagem (PS) e perda de inserção clínica (NCI) entre pacientes com obesidade e sem obesidade mostrou resultados comparáveis [PS (p = 0,91), I^2 = 67,36%; NCI (p = 0,87), I^2 = 77,16%]. No entanto, por outro lado, em três estudos, o TPNC resultou em um resultado clínico periodontal significativamente melhor entre indivíduos sem obesidade do que indivíduos com obesidade. A diferença nos níveis séricos de citocinas pró-inflamatórias [interleucina 1 beta (IL-1β), IL-6, TNF-α, interferon-gama (IFN-γ), leptina, adiponectina e PCR] entre pacientes com obesidade e sem obesidade após tratamento para periodontite crônica foi inconsistente.[18]

A análise estatística demonstrou que a terapia periodontal em indivíduos obesos foi eficaz para melhorar os resultados clínicos. Não foram observadas diferenças clínicas entre os resultados pós-terapia de obesos e não obesos. Os efeitos da terapia periodontal em marcadores inflamatórios permanecem obscuros.[17]

Efeitos da obesidade na incidência da periodontite. A meta-análise, considerando os efeitos do ganho de peso na incidência de periodontite, mostrou que os indivíduos que ficaram acima do peso tinham maior risco de desenvolver novos casos de periodontite [RR = 1,13 (IC95%: 1,06–1,20)], bem como aqueles que se tornaram obesos [RR = 1,33 (IC95%: 1,21–1,47)] em comparação com colegas que permaneceram com peso normal pelo mesmo período. Esses achados suportam a hipótese de que o acúmulo de gordura pode desempenhar um papel no desenvolvimento da periodontite em adultos, sugerindo que a incidência de doença periodontal aumenta com o aumento do acúmulo de gordura corporal. Uma associação positiva entre doença periodontal e obesidade foi demonstrada em muitos relatórios.[15]

Nível das citocinas do FCG em pacientes com periodontite e obesidade. A diferença média geral nos níveis de TNF-α entre pacientes com PC e obesidade e pacientes com periodontite crônica sem obesidade foi significativa [diferença média padronizada [SMD = 0,58, Z = 1,94 (p = 0,004)]. A

variabilidade nas diferenças nos níveis de TNF-α também foi significativa [Q-valor = 21,55 (p < 0,001), I^2 = 81,44%]. IL-6 não mostrou diferença significativa no FCG dos grupos com obesidade e sem obesidade com periodontite crônica em todos os quatro estudos [SMD = 0,018, Z = 0,12 (p = 0,903)]. Participantes obesos com periodontite crônica apresentaram níveis de resistina significativamente mais altos do que indivíduos com periodontite crônica não obesos [SMD = 0,32, Z = 2,28 (p = 0,02)]. Por outro lado, os níveis de adiponectina não mostraram diferença significativa na diferença média geral [SMD = 0,14, Z = 1,20 (p = 0,23); Q-valor = 3,75 (p = 0,43), e I^2 = 0%] entre os estudos. A diferença média geral nos níveis de IL-8 entre pacientes obesos e não obesos com PC não mostrou diferença significativa [SMD = 0,74, Z = 1,22 (p = 0,22)]. A heterogeneidade nos níveis de FCG de interleucina 8 (IL-8) entre os estudos foi, no entanto, significativa [valor Q = 12,42 (p = 0,0004), I^2 = 91,95%]. Os participantes com obesidade e com PC apresentaram níveis de FCG significativamente mais altos de IL1-β do que os com PC e sem obesidade [SMD = 0,628, Z = 3,895 (p < 0,001)]. No entanto, a heterogeneidade para IL1-β entre os estudos não foi significativa [Q- valor = 0,81 (p = 0,36), I^2 = 0%).[16]

Efeito da cirurgia bariátrica no estado periodontal. Os estudos apontaram que os pacientes com obesidade apresentaram pior condição periodontal após a cirurgia bariátrica.[20] Aos 6 meses de acompanhamento observou-se aumento da inflamação periodontal (p = 0,03) e destruição periodontal.[17] Não foram observadas mudanças significativas em relação à destruição periodontal atual e cumulativa [profundidade de sondagem (PS) e nível clínico de inserção (NCI), respectivamente] antes e após a cirurgia bariátrica. Com relação à porcentagem de locais com PS de 4-5 mm (ou seja, destruição periodontal moderada), um aumento estatisticamente significativo foi observado no grupo de cirurgia bariátrica aos 6 meses após a cirurgia (p = 0,04). Os resultados não foram significativos para sítios periodontais com PS de 6 mm ou mais.[21] Acredita-se que a redução da PS e o restabelecimento do NCI só são possíveis pela terapia periodontal. Um estudo observou uma melhora no estado periodontal após a cirurgia bariátrica, que eles atribuíram às mudanças impostas na dieta e nas instruções de higiene bucal dadas aos pacientes em preparação para a cirurgia, que parecem contribuir para uma melhora na saúde periodontal e na prevenção da progressão da doença.[22]

Alguns resultados mostram consistentemente uma piora significativa (p < 0,05) do sangramento à sondagem (SS) [4,21% (IC95%: 0,32–8,11)], NCI [0,16 mm (IC95%: 0,05–0,27)], PS [0,14 mm (95%CI: 0,06–0,23)] e %PS 4-5 mm [1,72% (95%CI: 0,11–3,34)] 6 meses após a cirurgia bariátrica, mas nenhuma alteração após 12 meses. Uma mudança estatisticamente significativa 6 meses após a cirurgia bariátrica foi observada como a piora em alguns parâmetros periodontais, ou seja, SS, NCI, PS e %PS 4-5 mm, e como uma diminuição (ou seja, melhora) nos parâmetros relacionados à obesidade, ou seja, IMC e glicose em jejum.[23]

Alguns estudos apontaram que pacientes submetidos à cirurgia bariátrica apresentam melhor

resposta à terapia periodontal do que aqueles que apresentam obesidade. Segundo os mesmos autores, ainda é difícil afirmar se isso ocorre devido a uma mudança no estilo de vida, alteração hormonal e sistêmica, ou uma combinação desses fatores. A análise quantitativa mostrou que o NCI [diferença média (MD): 0,07 (IC95%: -0,17–0,31)], o índice gengival (IG) [MD: -0,28 (IC95%: -1,68–1,11)], a %SS [MD: -0,21 (IC95%: -0,77–0,35)] e PS [MD: 0,08 (IC95%: -0,14–0,31)] não foram diferentes antes e após a cirurgia bariátrica. No entanto, o índice de placa (IP) foi menor após a cirurgia bariátrica [MD: -1,29 (IC95%: -2,34– -0,24)].[20]

TABELA 1

Caracterização metodológica e variáveis de tendenciosidade das revisões sistemáticas com meta-análise incluídas										
Estudo | Base de dados registrada	**Objetivo do estudo**	**Guia ou roteiro de estrutura do artigo**	**PICO ou PECO**	**Consulta da literatura**	**Número e desenho dos estudos incluídos**	**Ferramenta de avaliação de qualidade/risco de viés | Qualidade geral/risco de viés**	**Certeza das evidências (GRADE)**	**Conclusão dos autores**	**Conflito de interesses**	**Apoio financeiro**
Chaffee; Weston, 2010 NR	"Esta revisão visa compilar sistematicamente as evidências de uma relação obesidade-doença periodontal a partir de estudos epidemiológicos e derivar um resumo quantitativo da associação entre esses estados de doença"	NR	NR	Base de dados: MEDLINE, Scopus, LILACS, Cochrane Library e BIOSIS Outras fontes: BIOSIS e Brazilian Bibliography of Dentistry Restrições: NO Data das publicações: NO	70 estudos (sendo 2 estudos de coortes e 68 estudos transversais) que representavam 57 populações de estudo únicas foram incluídas para revisão sistemática 28 estudos transversais foram incluídos na meta-análise	FI	NR	"Esta associação positiva foi consistente e coerente com um papel biologicamente plausível para a obesidade no desenvolvimento da doença periodontal. No entanto, com poucos estudos longitudinais de qualidade, há uma incapacidade de distinguir a ordenação temporal dos eventos, limitando assim a evidência de que a obesidade é um fator de risco para doença periodontal ou que a periodontite pode aumentar o risco de ganho de peso. Na prática clínica, uma maior prevalência de doença periodontal deve ser esperada entre adultos obesos"	NE	Bolsa (DE007306) dos Institutos Nacionais de Saúde, Bethesda, Maryland.
Li et al., 2015 NR	"O objetivo desta revisão sistemática foi identificar e resumir evidências da associação entre medidas antropométricas e estado periodontal	PRISMA statement[33]	NR	Base de dados: PubMed, Cochrane Library e British Nursing Index	16 estudos (10 artigos de caso-controle, 5 estudos transversais e 1 estudo de coorte) foram incluídos na	FI	NR	"Em conclusão, a obesidade está associada a alguns sinais de doença periodontal em crianças e adolescentes. Mais estudos com um desenho de coorte prospectivo abrangente e mais variáveis potenciais são recomendados."	NE	Apoiado pelo Conselho de Bolsas de Pesquisa da Região Administrativa

	em crianças e adolescentes.”			Outras fontes: Institute for Scientific Information Web of Knowledge, ProQuest Medical Library, ProQuest Research Library, ComDisDome, Gender Watch, e ProQuest Deep Indexing: Medical and Health & Safety Science Abstracts (via ProQuest) Restrições: NR Data das publicações: Até Dezembro de 2014	revisão sistemática 5 estudos de caso-controle foram incluídos na meta-análise					Especial de Hong Kong, China (Projeto No. 781112).
Papageorgiou et al., 2015 PROSPERO (CRD4201300479 2)	“O objetivo desta revisão sistemática foi investigar se a resposta ao tratamento periodontal, avaliada com medidas periodontais, inflamatórias, metabólicas ou antropométricas, difere entre pacientes obesos,	Cochrane Handbook[34] PRISMA statement[33]	(P) Pacientes de qualquer idade ou sexo com doença periodontal (I) Pacientes recebendo qualquer tipo de tratamento periodontal (restaurador, regenerativo ou qualquer outro (C) Comparação de pacientes tratados obesos ou com sobrepeso com pacientes tratados com peso normal. (O) Qualquer resultado em relação a (a) saúde periodontal,	Base de dados: MEDLINE/PubMed, Cochrane Library, Embase, Scielo, Lilacs and Scopus Outras fontes: IndMed, Cambridge Scientific Abstracts,	15 estudos foram incluídos na revisão sistemática e metanálise (sendo 2 ECR paralelamente controlados por placebo, duplo-cego; 2 ECR paralelamente controlados por placebo,	O risco de viés dos ECRs foi avaliado com a ferramenta Cochrane Handbook[34] O risco de viés dos não-ECRs foi avaliado com uma ferramenta inapropriada	Abordagem GRADE[35]	“De acordo com as evidências existentes sobre a resposta ao tratamento da periodontite crônica, as seguintes conclusões podem ser tiradas: Nenhuma diferença clara pode ser identificada para pacientes sistemicamente saudáveis ou diabéticos na resposta ao tratamento periodontal entre pacientes com sobrepeso/obesidade e pacientes com peso normal na maioria dos parâmetros clínicos	NE	Este estudo foi apoiado pela Unidade de Pesquisa Clínica 208 (Fundaçã o Alemã de Pesquisa e

	com sobrepeso ou eutróficos.”		(b) marcadores inflamatórios, (c) marcadores metabólicos ou (d) medidas antropométricas	UMI/ProQuest, German National Library of Medicine, ISI Web of Knowledge, metaRegister of Controlled Trials, OpenSIGLE and Scirus Restrições: NO Data das publicações: Até Julho de 2013	único-cego; 10 estudos prospectivos não-ECRs, 1 análise retrospectiva de 3 ECRs e 1 não-ECR.)			periodontais, inflamatórios, metabólicos ou antropométricos investigados. Em pacientes sistemicamente saudáveis, pode ser encontrada uma maior diminuição nos níveis de TNF- α e HbA1c em pacientes com sobrepeso/obesidade em comparação com pacientes com peso normal, embora as evidências existentes sejam fracas e derivam de um único estudo. Em pacientes diabéticos, um aumento nos níveis de adiponectina e uma diminuição nos níveis de leptina foram encontrados em pacientes com sobrepeso/obesidade, em contraste com pacientes com peso normal, embora as evidências existentes sejam fracas e derivem de dois estudos. Com base nas evidências existentes, nenhuma associação significativa pode ser encontrada entre o peso do paciente e a resposta ao tratamento periodontal de pacientes sistemicamente saudáveis ou diabéticos.”		Faculdade de Medicina, Universidade de Bonn)
Nascimento et al., 2015 NR	“Este estudo teve como objetivo realizar uma revisão sistemática avaliando os efeitos do ganho de peso na incidência de periodontite em adultos.”	PRISMA statement[33]	NR	Base de dados: MEDLINE/PubMed, Scopus e Embase Outras fontes: Web of Knowledge Restrições: NA	5 estudos de coorte preencheram os critérios para serem incluídos na revisão sistemática e meta-análise	A versão específica da escala de Newcastle–Ottawa para estudos de coorte foi utilizada para avaliar a qualidade dos estudos incluídos. [36]	Abordagem GRADE[35]	“Uma clara associação positiva entre ganho de peso e novos casos de periodontite foi encontrada. No entanto, esses resultados são originados de evidências limitadas. Assim, mais estudos com desenho prospectivo longitudinal são necessários.”	NE	O estudo foi autofinanciado pelos autores e suas instituiçõ es.

				Data das publicações: Até e incluindo Fevereiro de 2015						
Akram et al., 2016a PROSPERO (CRD42015029928)	"O objetivo deste estudo foi revisar sistematicamente o perfil de citocinas do fluido crevicular gengival em pacientes com periodontite crônica com e sem obesidade."	PRISMA statement[33]	NR	Base de dados: M MEDLINE/PubMed, Scopus, ScienceDirect and Embase Outras fontes: ISI Web of Knowledge Restrições: NR Data das publicações: De 1977 até Maio de 2016	11 estudos (8 estudos transversais e 3 estudos prospectivos não-ECR) foram incluídos na revisão sistemática 6 estudos (4 estudos transversais e 2 estudos prospectivos não-ECR) foram incluídos na meta-análise	A qualidade dos estudos incluídos foi avaliada usando a escala Newcastle-Ottawa Quality Assessment for Observational Studies[36]	NR	"A presente revisão sugere que o nível de inflamação periodontal localizada pode ter uma influência maior nos níveis de biomarcadores pró-inflamatórios FCG em comparação com a obesidade sistêmica. Se os pacientes com periodontite crônica com obesidade têm níveis elevados de biomarcadores pró-inflamatórios FCG em comparação com indivíduos não obesos permanece discutível."	NE	Decanato de Pesquisa Científica na Universidade King Saud (PRG-1437-38).
Akram et al., 2016b NR	"O objetivo da presente revisão sistemática foi avaliar a eficácia da TPNC no manejo da periodontite crônica em pacientes obesos e não obesos."	PRISMA statement[33]	(P) Pacientes obesos e com periodontite crônica; (I) Tratamento periodontal não cirúrgico (TPNC) (C) TPNC em pacientes não-obesos com periodontite; (O) Desfechos primários— Alterações no NIC e PBS desde a medição da linha de base até o acompanhamento. Desfechos secundários— (i) índice de placa; (ii) índice de sangramento gengival; (iii) sangramento à sondagem (SS); (iv) níveis séricos de citocinas pró-inflamatórias; (v) perda óssea, (vi) contagem de	Base de dados: MEDLINE, EMBASE, Cochrane Central Register of Controlled Trials (CENTRAL) e Scopus Outras fontes: Web of Knowledge e Scholar Google Restrições: NR	5 estudos não-ECR foram incluídos na revisão sistemática 3 estudos foram incluídos na meta-análise	FI	NR	"Ainda não está claro se a TPNC tem um impacto significativamente maior nos resultados clínicos periodontais em pacientes obesos do que em pacientes não obesos com periodontite crônica, uma vez que o número de estudos selecionados foi relativamente baixo e os achados relatados foram inconsistentes."	NE	O trabalho foi apoiado pela Universidade da Malásia [Grant No. PG140-2013A] e RG303/11HTM, Departamento de Periodontologia, Kuala

			bacteriana; (vii) dor e desconforto e (viii) estética.	Data das publicações: De 1977 até Dezembro de 2014.						Lumpur, Malásia.
Nascimento et al., 2016 NR	"O objetivo deste estudo foi revisar sistematicamente a literatura para responder às questões: (i) "O tratamento periodontal é eficaz para melhorar as condições clínicas e imunológicas em sujeitos obesos?"; (ii) "Os sujeitos obesos apresentam resposta clínica e imunológica após terapia periodontal quando comparado a indivíduos não obesos?""	NR	NR	Base de dados: MEDLINE/PubMed, Scopus, Embase, Latin American and Caribbean Center on Health Sciences Information (LILACS) e Scientific Electronic Library Online (SciELO) Outras fontes: Web of Knowledge Restrições: NA Data das publicações: NR	5 estudos foram incluídos na revisão sistemática 3 estudos (1 ECR e 2 não-ECR) foram incluídos na meta-análise	FI	NR	"O tratamento periodontal parece ser eficaz para melhorar a cicatrização em indivíduos obesos. Nenhuma diferença foi observada na cicatrização periodontal entre indivíduos obesos e não obesos; no entanto, apenas uma base de evidências limitada e frágil estava disponível para análise."	NE	NR
Martens et al., 2017 NR	"Fornecer uma revisão sistemática e meta-análises investigando a associação entre sobrepeso/obesidade conforme definido pelo índice de massa corporal (IMC) e doença periodontal em termos de	NR	NR	Base de dados: MEDLINE/PubMed, Scopus, LILACS e SciELO Outras fontes: Web of Science (ISI) e SIGLE	12 estudos (7 estudos transversais, 3 estudos de caso-controle, 1 estudo de coorte e 1 estudo observacional comparativo) foram incluídos na	FI	NR	"As evidências disponíveis sugerem uma associação significativamente positiva entre doença periodontal e obesidade em crianças. Os odontopediatras devem estar cientes das alterações periodontais como um risco potencial associado à obesidade."	NE	NR

	resultados clínicos periodontais”			Restrições: Língua inglesa Data das publicações: Até Setembro de 2015	revisão sistemática 7 estudos (5 estudos transversais, 1 estudo de caso-controle e 1 estudo observacional comparativo) foram incluídos na meta-análise					
de Souza et al., 2018 PROSPERO (CRD42017071288)	“O objetivo da presente revisão sistemática foi investigar o efeito da cirurgia bariátrica (CB) no estado periodontal.”	MOOSE statement[37]	NR	Base de dados: MEDLINE/PubMed, Biblioteca Virtual em Saúde, Science Direct, Scopus e Cochrane Library Outras fontes: Web of Science, Google Acadêmico e ClinicalTrials.gov Restrições: NO Data das publicações: Até Maio de 2017	9 estudos (6 estudos de coorte e 3 estudos transversais) foram incluídos na revisão sistemática 5 estudos (4 estudos de coorte e 1 estudo transversal) foram incluídos na meta-análise	O risco de viés foi estimado para cada estudo selecionado com base na escala de Newcastle–Ottawa (NOS) para estudos longitudinais[36] e uma FI para estudos transversais	NR	“Pode-se concluir que a CB pode melhorar a condição periodontal de pacientes com obesidade, principalmente o índice de placa, provavelmente por promover alterações comportamentais, controle metabólico do nível glicêmico e redução de mediadores inflamatórios. No entanto, não está claro a maneira exata como isso ocorre.”	NE	NR
Fontanille et al., 2018 PROSPERO	“O objetivo da presente revisão sistemática e meta-análise foi avaliar a literatura atual sobre	PRISMA statement[33]	NR	Base de dados: MEDLINE/PubMed, Embase e	10 estudos (6 estudos de coorte e 4 estudos transversais)	A Escala de Newcastle-Ottawa foi usada para avaliar a	NR	“A presente revisão sistemática e meta-análise sugere que a deterioração do estado periodontal pode ser observada nos primeiros 6 meses após a	NE	NR

(CRD42018087338)	o impacto da CB no estado periodontal.”			Cochrane Library Outras fontes: OpenGrey e ClinicalTrials.gov Restrições: NR Data das publicações: Até Setembro de 2017	foram incluídos na revisão sistemática 4 estudos de coorte foram incluídos na meta-análise	qualidade dos estudos de coorte[36]		cirurgia. Consequentemente, a triagem periodontal e o manejo da solicitação do paciente para CB devem ser recomendados para evitar maior deterioração do estado periodontal após a CB.”		
dos Santos et al., 2019 PROSPERO (CRD42018099313)	“O objetivo do presente estudo foi realizar uma revisão sistemática e metanálise para avaliar se a CB tem alguma influência nas condições clínicas periodontais em pacientes obesos. A hipótese nula foi de que não há alteração na condição clínica periodontal em pacientes após CB.”	PRISMA statement[33]	(P) Pacientes com obesidade (I) CB (C) Pacientes com obesidade não submetidos à CB (O) Impacto da CB no estado periodontal	Base de dados: MEDLINE/PubMed e Cochrane Library Outras fontes: Web of Science Restrições: NO Data das publicações: Até Maio de 2018	6 estudos (4 estudos de coorte e 2 estudos prospectivos, com períodos de avaliação pré e pós-operatórios de 3, 6 e 12 meses) foram incluídos na revisão sistemática 4 estudos (2 estudos de coorte e 1 estudo prospectivo) foram incluídos na meta-análise	FI	NR	“Os pacientes submetidos à CB apresentaram maior risco de perda de inserção clínica. Em contraste, a intervenção cirúrgica não teve influência estatisticamente significativa no SS ou PBS em curtos períodos de acompanhamento.”	NE	NR
Čolak et al., 2021 PROSPERO (CRD42016503 1)	“Determinar se a saúde periodontal se deteriora após a CB.”	PRISMA statement[33]	(P) Pacientes obesos submetidos à CB, maiores de 18 anos, de ambos os sexos, que consentiram voluntariamente em fazer parte do estudo e que receberam exames clínicos periodontais antes da cirurgia e no seguimento	Base de dados: MEDLINE e EMBASE Outras fontes: NR	4 estudos de coorte foram incluídos na revisão sistemática e meta-análise	FI	NR	“Dentro dos limites deste estudo, podemos concluir que a CB pode levar a uma piora do estado periodontal a curto prazo 6 meses após a CB, que não está presente 12 meses após a CB. No entanto, estudos observacionais futuros com coleta adequada dos dados são	NE	NR

			(E) Estudos de coorte prospectivos sobre a influência da CB no estado periodontal (C) Medidas antes da CB (O) Os resultados primários foram focados na mudança nos parâmetros clínicos periodontais (SS, nível clínico de inserção (NCI), profundidade de sondagem (PS), porcentagem de sítios periodontais com PS > 4-5 mm, porcentagem de sítios periodontais com placa, porcentagem de sítios periodontais com cálculo, alteração nos índices periodontais e gengivais, índices de higiene bucal e análise radiológica) e a prevalência de periodontite e gengivite. Os desfechos secundários foram focados na alteração dos parâmetros antropométricos, IMC, circunferência da cintura, análise sanguínea para glicemia de jejum, proteína C-reativa (PCR), perfil lipídico e presença de comorbidades.	Restrições: Língua inglesa Data das publicações:Entre 2000 e 2019				necessários para explorar ainda mais esse achado, pois os estudos até agora não apresentam dados periodontais e sistêmicos suficientes. No entanto, os dados apresentados em nossa revisão nos fornecem uma base razoável para aconselhar que um dentista deve monitorar os pacientes antes e após a CB, porque eles correm um risco potencial de ruptura periodontal adicional.”		

Legenda: PROSPERO, international prospective register of systematic reviews; PRISMA, preferred reporting items for systematic reviews and meta-analyses; PICO, população-intervenção-controle-desfecho; PECO, população-exposição-controle-desfecho; NR, não relatado; FI, ferramenta inapropriada; ECR, ensaio clínico randomizado; NE, não existe; TPNC, tratamento periodontal não cirúrgico; CB, cirurgia bariátrica; IMC, índice de massa corpórea; PS/PBS, profundidade de sondagem; NCI/NIC/PIC, nível clínico de inserção ou perda de inserção periodontal; SS, sangramento à sondagem., PCR, proteína C-reativa.

Referências: [1], Moher D, Liberati A, Tetzlaff J, Altman DG; PRISMA Group. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. PLoS Med. 2009 Jul 21;6(7):e1000097. doi: 10.1371/journal.pmed.1000097; [2], Higgins JPT, Green S (editors). Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0 [uPBSated March 2011]. The Cochrane Collaboration, 2011. AvailPOAe from www.handbook.cochrane.org; [3], Guyatt GH, Oxman AD, Vist GE, Kunz R, Falck-Ytter Y, Alonso-Coello P, Schünemann HJ; GRADE Working Group. GRADE: an emerging consensus on rating quality of evidence and strength of recommendations. BMJ. 2008 Apr 26;336(7650):924-6. doi: 10.1136/bmj.39489.470347.AD; [4], Wells, GA, Shea, B, O’Connell, D, Peterson, J, Welch, V, Losos, M, Tugwell, P. The Newcastle-Ottawa Scale (NOS) for assessing the quality of non randomised studies in meta-analyses. Ottawa. University of Ottawa. 2001. http://www.ohri.ca/programs/clinical_epidemiology/oxford.htm; e [5], Stroup DF, Berlin JA, Morton SC, et al. Meta-analysis of observational studies in epidemiology: a proposal for reporting. Meta-analysis Of Observational Studies in Epidemiology (MOOSE) group. JAMA 2000; 283: 2008–12.

TABELA 2

Dados descritivos relacionados à população estudada, intervenção/exposição investigada, grupo comparativo e principais resultados

Estudo	(P/E) Critérios de diagnóstico clínico periodontal (P) ou de obesidade [E (exposição)]	(P) Controlado para tabagismo	(I) Tipos de intervenções periodontais ou abordagem da obesidade	Acompanhamento	Principais resultados
Chaffee; Weston, 2010	Obesidade: Índice de Massa Corporal (IMC) ≥ 25 kg/m²; Relação cintura-quadril (RCQ) > 0,8 para homens e > 0,9 para mulheres Periodontite: ≥ 1 sítio periodontal ou ≥ 1 dente com nível clínico de inserção (NCI) ≥ 3 mm somado ou não à profundidade de sondagem (PS) ≥ 4 mm; NCI médio > 2,41 mm; Reabsorção da crista alveolar > 3 mm observada em radiografia periapical	Sim	NA	NR	Associação positiva entre prevalência de obesidade A meta-análise dos resultados sistematicamente identificados de 57 populações de estudos independentes sugeriu um aumento de aproximadamente um terço na chance de obesidade entre os indivíduos com periodontite, uma maior perda de inserção (NCI) média entre indivíduos com obesidade, um IMC mais alto entre indivíduos com periodontite e um aumento linear leve, mas não estatisticamente significativo, na chance de ocorrência de periodontite com o aumento do IMC
Li et al., 2015	Obesidade: IMC > 30 kg/m² (ajustado para idade e sexo)	NR	NA	NR	Associação negativa entre IMC e secreção salivar e associação positiva entre IMC e sangramento gengival, cálculo subgengival e bactérias no fluido crevicular gengival Não houve um único consenso sobre a relação entre medidas antropométricas e índice de placa visível, cálculo supragengival, PS ou NCI A obesidade pode estar relacionada a alguns sinais de periodontite em crianças e adolescentes, de acordo com as meta-análises, principalmente no que diz respeito à inflamação gengival
Papageorgiou et al., 2015	Periodontite: ≥ 1 sítio periodontal ou ≥ 1 dente com NCI ≥ 3 mm somado ou não à PS ≥	NR	Raspagem e alisamento radicular (RAR) de boca toda com instrumento ultrassônico ou manual, associado ou não a antibióticos asjuvantes (10 mg de minociclina local, 400 mg metronidazol	1–6 meses	Não houve diferença significativa na maioria dos parâmetros clínicos periodontais, inflamatórios, metabólicos ou antropométricos após o tratamento periodontal entre pacientes com sobrepeso/obesidade e peso normal

	4 mm NCI médio > 2,41 mm Periodontite grave generalizada (> 2 dentes com PS > 5 mm; perda óssea alveolar marginal > 30%; > 50% dos dentes afetados)		por 10 dias, 250 mg de metronidazol e 500 mg de amoxicilina a cada 8 horas por 7 dias) ou a 10 mg alendronato 2x/dia, ou Protocolo de *full mouth desinfection*		As evidências existentes são fracas e nenhuma relação forte de causa e efeito pode ser estabelecida
Nascimento et al., 2015	Obesidade: IMC ≥ 30 kg/m² (ajustado para idade e sexo); Circunferência da cintura (CC) > 40 e RCQ > 0,95 Periodontite: Bolsa periodontal autorreferida; PS ≥ 4 mm ou NCI ≥ 5 mm; Perda óssea alveolar (POA) ≥ 40%	NR	NA	4–20 anos	Indivíduos com sobrepeso ou obesidade apresentaram maior risco de desenvolver novos casos de periodontite do que aqueles que permaneceram com peso normal no mesmo período, sugerindo que a incidência de doença periodontal aumenta com o aumento do acúmulo de gordura corporal Uma associação positiva entre periodontite e obesidade foi demonstrada em muitos estudos
Akram et al., 2016a	Periodontite: IG > 1 associado a PS ≥ 4 mm e NCI > 2 mm em ≥ 20% dos sítios periodontais; Sangramento à sondagem (SS) em ≥ 50% dos sítios periodontais; Evidência radiográfica de perda óssea alveolar (≥ 2 mm)	Não	NA	NR	A gravidade da inflamação periodontal localizada nos níveis de citocinas do fluido crevidular gengival em indivíduos sem obesidade pode exceder o impacto da obesidade nestes parâmetros em pacientes com obesidade e periodontite Quase metade dos estudos não relataram a exclusão de pacientes com doenças sistêmicas, representando um potencial viés/fator de confusão Os autores propõem que o equilíbrio entre mediadores pró-inflamatórios e anti-inflamatórios nos tecidos periodontais de indivíduos não obesos pode ser deslocado para um estado hiperinflamatório que poderia prejudicar a resposta do hospedeiro contra patógenos e favorecer a destruição periodontal
Akram et al., 2016b	Obesidade: IMC > 30 kg/m² (ajustado para idade e sexo), CC >102 cm para homens e >88 cm para mulheres, RCQ ≥0.8 para mulheres e ≥0.9 para homens e gordura corporal ≥33 % para mulheres e ≥25 % para homens. Periodontite: NCI médio de 2.5–4.4 mm e PS > 4mm	Sim	Tratamento periodontal não cirúrgico (TPNC)	Até 12–24 semanas	Todos os estudos relataram redução significativa dos parâmetros clínicos periodontais inflamatórios em indivíduos com e sem obesidade após TPNC

Nascimento et al., 2016	Obesidade: Obesidade ≥ 30 kg/m²: Classe I- 30–34,930 kg/m²; Classe II, 35–39,9; Classe III, ≥40 30 kg/m²; CC > 102 para homens e > 88 para mulheres; RCQ ≥ 0,9 para homens e ≥ 0,8 para mulheres; Gordura corporal ≥ 25% para homens e ≥ 33% para mulheres Periodontite: PS ≥ 4 mm e NCI > 2 mm em ≥ 30% dos sítios periodontais ou ≥ 5 dentes associado ou não a Sangramento à sondagem (SS)	NR	TPNC com ou sem bochecho de clorexidina 0,12% por 14 dias	2–6 meses	O tratamento da periodontite pode melhorar os parâmetros clínicos periodontais inflamatórios em indivíduos com obesidade A obesidade parece não influenciar a cicatrização periodontal, quando comparados os resultados pós-tratamento deste grupo com indivíduos não obesos
Martens et al., 2017	Obesidade: IMC ≥ 30 kg/m² (ajustado para idade e sexo); Periodontite: Presença de ≥1 sítio com perda inserção ≥3 mm e PS ≥3 mm, IPV >25%, SS > 25% e PBS> 4 mm	NR	NA	NR	Evidências de associação positiva entre sobrepeso/obesidade e prevalência de periodontite
de Souza et al., 2018	Obesidade: IMC ≥ 30 kg/m² Periodontite: NR	Sim	Sleeve Bypass Gástrico em Y de Roux	4 semanas a 12 meses	Alguns estudos primários reportaram melhor resposta ao tratamento periodontal após cirurgia bariátrica—este resultado pode estar relacionado a uma mudança no estilo de vida, alteração hormonal e sistêmica, ou uma combinação destes fatores Em contrapartida, outros estudos apontaram que os pacientes com obesidade apresentaram pior condição periodontal após a cirurgia bariátrica
Fontanille et al., 2018	Obesidade: IMC ≥ 30 kg/m² (ajustado para idade e sexo); Periodontite: NR	NR	Sleeve Bypass Gástrico em Y de Roux	6–12 meses	Nas análises de dados agrupados, um aumento estatisticamente significativo na inflamação periodontal foi observado 6 meses após a cirurgia bariátrica em comparação com os dados basais (p = 0,03) Não houve mudanças significativas em relação à destruição periodontal atual e cumulativa (PS e NCI, respectivamente) antes e após a cirurgia bariátrica Houve um aumento estatisticamente significativo da porcentagem de sítios periodontais com PS 4–5 mm (destruição periodontal moderada) no grupo

					submetido à cirurgia bariátrica 6 meses após a cirurgia (p = 0,04). Os resultados não foram significativos para sítios periodontais com PS ≥ 6 mm Entre os estudos que reportaram dados de 6 meses, apenas três estudos reportaram dados em 12 meses de acompanhamento: não foi observada diferença significativa antes e após a cirurgia bariátrica em relação à destruição periodontal atual e cumulativa, inflamação periodontal e porcentagem de sítios periodontais com PS ≥ 4 mm
dos Santos et al., 2019	Obesidade: IMC ≥ 30 kg/m² (ajustado para idade e sexo); Periodontite: Periodontite leve: PIC 1–2 mm, periodontite moderada: PIC 3–4 mm; Periodontite grave: PIC >5 mm; bolsas de 4–5 (% de sítios), bolsas ≥6 mm bolsas (% de sítios)	Sim	Sleeve Bypass Gástrico em Y de Roux	6–12 meses	A meta-análise revelou piora de NCI entre os pacientes submetidos à cirurgia bariátrica, entretanto não houve diferenças estatisticamente significativas em SS ou PS
Čolak et al., 2021	Obesidade: IMC ≥ 30 kg/m² (ajustado para idade e sexo); Periodontite: PS >4–5 mm (%PS >4–5 mm)	Sim	Sleeve Bypass Gástrico em Y de Roux	6–12 meses	Piora estatisticamente significativa dos parâmetros clínicos periodontais SS, NCI, PS e % PS 4–5 mm 6 meses após cirurgia bariátrica, mesmo na melhora de parâmetros relacionados à obesidade (IMC e glicemia em jejum) Não houve mudança estatisticamente significativa 6 meses após a CG para a presença de cálculo dentário Melhora estatisticamente significativa dos parâmetros relacionados à obesidade (IMC e glicemia e jejum) 12 meses após cirurgia bariátrica; não houve mudança estatisticamente significativa dos parâmetros clínicos periodontais12 meses após a cirurgia bariátrica

Legenda: PS, profundidade de sondagem; NCI/PIC, nível clínico de inserção ou perda de inserção periodontal; SS, sangramento à sondagem, IMC, índice de massa corportal; CC, circunferência da cintura; RCQ, relação cintura-quadril.

References: [1], Arnett FC, Edworthy SM, Bloch DA, McShane DJ, Fries JF, Cooper NS, Healey LA, Kaplan SR, Liang MH, Luthra HS, et al. The American Rheumatism Association 1987 revised criteria for the classification of rheumatoid arthritis. Arthritis Rheum. 1988 Mar;31(3):315-24. doi: 10.1002/art.1780310302; [2], Armitage GC. Development of a classification system for periodontal diseases and conditions. Ann Periodontol. 1999 Dec;4(1):1-6. doi: 10.1902/annals.1999.4.1.1; [3], Löe H, Silness J. Periodontal disease in pregnancy. I. Prevalence and severity. Acta Odontol Scand. 1963;21:533–51; [4], Machtei EE, Christersson LA, Grossi SG, Dunford R, Zambon JJ, Genco RJ. Clinical criteria for the definition of "estPOAished periodontitis". J Periodontol. 1992 Mar;63(3):206-14. doi: 10.1902/jop.1992.63.3.206; [5], Okada M, Kobayashi T, Ito S, Yokoyama T, Abe A, Murasawa A, Yoshie H. Periodontal treatment decreases levels of antibodies to Porphyromonas gingivalis and citrulline in patients with rheumatoid arthritis and periodontitis. J Periodontol. 2013 Dec;84(12):e74-84. doi: 10.1902/jop.2013.130079; [6], World Health Organization - WHO. Definition and diagnosis of diabetes mellitus and intermediate hyperglycaemia [Internet]. Geneva: WHO; 2016. AvailPOAe from: http://whqlibdoc. who.int/publications/2006/9241594934_eng.PBSf; [7], Eke PI, Page RC, Wei L, Thornton-Evans G, Genco RJ. UPBSate of the case definitions for population-based surveillance of periodontitis. J Periodontol. 2012 Dec;83(12):1449-54. doi: 10.1902/jop.2012.110664.

Síntese dos resultados. Os resultados das meta-análises transcritos na Tabela 3 sugerem maior chance de desenvolver periodontite e ocorrer piora de parâmetros clínicos periodontais e biomarcadores de inflamação no fluido crevicular gengival como resistina e IL-1β na obesidade, e maior índice de massa corporal (IMC) entre indivíduos com periodontite, com base em cinco revisões sistemáticas de estudos observacionais.[12,13,15,16,19] A adiponectina, leptina, TNF-α, IL-6 e IL-8 não foram influenciadas de forma significativa pela obesidade em indivíduos com periodontite.[16]

A obesidade parece não exercer efeito significativo sobre a resposta ao tratamento periodontal e parâmetros locais.[14,17,18] No contexto da intervenção para tratamento da obesidade, a cirurgia bariátrica não resultou em benefício significativo para a saúde periodontal, tendo sido reportadas pioras nos parâmetros clínicos após a bariátrica por alguns autores, especialmente no longo prazo—12 meses de seguimento (Tabela 3).[20-23]

À síntese qualitativa dos dados apresentados na Tabela 2, 41,7% das revisões sistemáticas com meta-análise incluídas controlaram seus dados/resultados para tabagismo, das quais 1:5 (20%) foi baseada em estudos observacionais, 1:5 (20%) em estudos de tratamento periodontal, e 4:4 (75%) em estudos de cirurgia bariátrica. Sendo assim, os resultados das meta-análises de estudos que avaliaram os efeitos da cirurgia bariátrica podem ser interpretados sem interferência significativa deste fator de confusão, enquanto as demais meta-análises devem ser consideradas com atenção a esta limitação (Tabela 2).

Risco de viés. Todos os estudos incluídos nesta *umbrella review* foram classificados como baixo risco de viés. Dos domínios e critérios de avaliação da ferramenta ROBIS, cinco estudos apresentaram limitações metodológicas relacionadas ao domínio 3 (Coleta de dados e avaliação do estudo). Dois critérios do domínio 4 (Síntese e descobertas) não foram plenamente contemplados por alguns estudos: A) "Os resultados foram robustos como demonstrado por meio de gráfico de funil ou análises de sensibilidade?",[13,14,16-18,20-23] e B) "Os vieses nos estudos primários foram mínimos ou abordados na síntese?" (Tabela 4).[12,13,16,17,19]

TABELA 3

Resultados de meta-análises reportadas nos estudos incluídos

Estudo	Análises	Meta-análises							Significância estatística
		Modelo de efeito	*n*	Subgrupos	Chi² | df (*p*-valor)	I²	Magnitude do efeito [diferença média[a], desvio padrão da diferença[b], razão de chances[c], e risco relativo[d]	Teste para efeito geral: Z (*p*-valor)	
Chaffee e Weston, 2010	Associação entre prevalência de periodontite e obesidade	MEF	28	-	81,7 com 27 graus de liberdade ($p < 0,005$)	-	1,35 (1,23 – 1.47)[c]	-	Sim
		MER	28	-		-	1,48 (1,32 – 1,66)	-	Sim
		MER	28	Exclusão de um estudo (Wang et al., 2009) que apresentou peso de 39% para o cálculo de razão de chances		-	1,40 (1,25 – 1,57)	-	Sim
Li et al., 2015	Diferenças nas razões de chance para parâmetros clínicos periodontais em crianças e adolescentes com obesidade em comparação com eutróficas (peso normal)	MER	3	Índice de placa visível >25%	0,2, df = 2 ($p = 0,906$)	0%	4,75 (2,42 – 9,34)[c]	$p < 0,001$	Sim
		MER	3	Índice de sangramento à sondagem >25%	$p = 0,75$	0%	5,41 (2,42 – 9,34)[c]	$p < 0,001$	Sim
		MER	2	Presença de cálculo subgengival	$p = 0,7$	0%	3,07 (1,10 – 8,62)[c]	-	Sim
		MER	2	Presença de cálculo supragengival	$p = 0,55$	0%	1,08 (0,60 – 1,94)[c]	-	Sim
		MER	2	Profundidade de sondagem > 4 mm	$p = 0,66$	0%	14,15 (5,10 – 39,25)[c]	-	Sim
	Diferenças na secreção salivar estimulada média para crianças e	MER	3	-	4,9, df = 2 ($p = 0,086$)	59,1%	-0,89 mL/min (-1,18 – -0,61)[c]	$p < 0,001$	Sim

	adolescentes com obesidade em comparação com eutróficas (peso normal)								
Nascimento et al., 2015	Efeito combinado do excesso de peso na incidência de periodontite	MEF	6	-	$p = 0,128$	41,6%	1,13 (1,06 – 1,20)[d]	-	Sim
	Efeito combinado da obesidade na incidência de periodontite	MEF	6	-	$p = 0,399$	2,7%	1,34 (1,21 – 1,47)[d]	-	Sim
Papageorgiou et al., 2015	Alterações clínicas do nível clínico de inserção após o tratamento periodontal em pacientes com sobrepeso/obesidade em comparação com pacientes com peso normal	MER	5	Pacientes sistemicamente saudáveis	$p = 0,672$	0%	-0,04 (-0,25 – 0,16)[a]	-	Não
		MER	2	Pacientes com diabetes mellitus	$p = 0,544$	0%	-0,05 (-0,21 – 0,11)[a]	-	Não
	Alterações clínicas da profundidade de sondagem após o tratamento periodontal em pacientes com sobrepeso/obesidade em comparação com pacientes com peso normal	MER	6	Pacientes sistemicamente saudáveis	$p = 0,135$	0%	-0,07 (-0,16 – 0,02)[a]	-	Não
		MER	2	Pacientes com diabetes mellitus	Omitido	84%	Omitido	-	Não
Akram et al., 2016a	Diferença média padrão dos níveis de citocinas no fluido crevicular gengival entre periodontite crônica com e sem obesidade	MER	4	Resistina	1,05, df = 3 ($p = 0,78$)	0%	0,32 (0.04 – 0,60)[a]	2,28 ($p = 0,02$)	Sim
		MER	5	Adiponectina	3,75, df = 4 ($p = 0,43$)	0%	0,14 (-0.09 – 0,38)[a]	1,20 ($p = 0,23$)	Não
		MER	3	Leptina	1,38, df = 2 ($p = 0,49$)	0%	0,027 (-0.308 – 0,36)[a]	0,16 ($p = 0,87$)	Não
		MER	5	TNF-α	21,55, df = 4 ($p < 0,001$)	81,44%	0,58 (-0.0084 – 1,18)[a]	1,94 ($p = 0,004$)	Não
		MER	4	IL-6	1,77, df = 3 ($p = 0,62$)	0%	0,018 (-0.28 – 0,32)[a]	0,123 ($p = 0,903$)	Não

		MER	2	IL-8	12,42, df = 1 (p = 0,0004)	91,95%	0,74 (-0.45 – 1,93)[a]	1,22 (p = 0,22)	Não
		MER	2	IL-1β	0,81, df = 1 (p = 0,36)	0%	0,62 (0.309 – 0,94)[a]	3,89 (p < 0,001)	Sim
Akram et al., 2016b	Diferença da redução de profundidade de sondagem pós-tratamento periodontal entre pacientes com e sem obesidade	MER	3	-	6,12, df = 2 (p = 0,046)	67,36%	0,032 (-0,584 – 0,65)[a]	0,105 (p = 0,916)	Não
	Diferença de ganho de nível clínico de inserção pós-tratamento periodontal entre pacientes com e sem obesidade	MER	3	-	8,75, df = 2 (p = 0,012)	77,16%	-0,05 (-0,8 – 0,68)[a]	0,157 (p = 0,87)	Não
Nascimento et al., 2016	Resultados clínicos antes e após o tratamento periodontal em indivíduos com obesidade	MEF	3	Sangramento à sondagem (%)	0,28, df = 2 (p = 0,87)	0%	-32,34 (-33,92 – -30,76)[a]	40,19 (p < 0,00001)	Sim
		MEF	2	Profundidade de sondagem (mm)	0,36, df = 1 (p = 0,55)	0%	-0,69 (-0,91 – -0,46)[a]	6,05 (p < 0,00001)	Sim
		MEF	2	Nível clínico de inserção (mm)	0,33, df = 1 (p = 0,56)	0%	-0,68 (-1,00 – -0,35)[a]	4,07 (p < 0,0001)	Sim
	Resultados clínicos pós-tratamento periodontal em indivíduos com e sem obesidade	MEF	3	Sangramento à sondagem (%)	0,09, df = 2 (p = 0,96)	0%	-0,74 (-1,85 – 0,36)[a]	1,32 (p = 0,19)	Não
		MEF	2	Profundidade de sondagem (mm)	5,97, df = 1 (p = 0,01)	83%	0,02 (-0,48 – 0,53)[a]	0,09 (p = 0,93)	Não
		MEF	2	Nível clínico de inserção (mm)	7,72, df = 1 (p = 0,005)	87%	-0,05 (-1,08 – 0,98)[a]	0,10 (p = 0,92)	Não
Martens et al., 2017	Associação entre prevalência de periodontite e obesidade em crianças	MEF	7	-	33,4 com 6 graus de liberdade	-	1,46 (1,20 – 1,77)[c]	p < 0,005	Sim
		MER					1,07 (0,40 – 1,73)		Sim
de Souza et al., 2018	Diferença de parâmetros clínicos periodontais antes e após cirurgia bariátrica	MER	3	Índice de placa	p < 0,0001	93,3%	-1,29 (-2,34 – -0,24)[a]	-	Sim
			2	Índice gengival	p < 0,0001	99,1%	-0,28 (-1,68 – 1,11)[a]	-	Não
			5	Sítios sangrantes (*não está claro se é sangramento da*	p < 0,0001	99,1%	-0,21 (-0,77 – 0,35)[a]	-	Não

				margem gengival ou sangramento à sondagem)					
			4	Profundidade de sondagem	$p = 0,0015$	80,5%	0,08 (-0,14 – 0,31)[a]	-	Não
			4	Nível clínico de inserção	$p = 0,0099$	73,6%	0,07 (-0,17 – 0,31)[a]	-	Não
Fontanille et al., 2018	Mudanças nos parâmetros clínicos periodontais 6 meses após cirurgia bariátrica	MEF	4	Sangramento à sondagem	2,85, df = 3 ($p = 0,42$)	0%	-4,14 (-7,90 – -0,38)[a]	2,16 ($p = 0,03$)	Sim
		MER	4	Nível médio de inserção periodontal (destruição periodontal cumulativa)	6,47, df = 3 ($p = 0,09$)	54%	-0,09 (-0,23 – 0,05)[a]	1,26 ($p = 0,21$)	Não
		MER	4	Nível médio de profundidade de sondagem (*status* periodontal atual)	12,55, df = 3 ($p = 0,006$)	76%	-0,10 (-0,27 – 0,06)[a]	1,21 ($p = 0,23$)	Não
		MEF	3	Porcentagem de sítios com destruição moderada (profundidade de sondagem 4–5 mm)	0,78, df = 2 ($p = 0,68$)	0%	-1,34 (-2,62 – -0,06)[a]	2,06 ($p = 0,04$)	Sim
		MEF	3	Porcentagem de sítios com destruição grave (profundidade de sondagem ≥ 6 mm)	1,03, df = 2 ($p = 0,60$)	0%	-0,07 (-0,55 – 0,42)[a]	0,27 ($p = 0,79$)	Não
	Mudanças nos parâmetros clínicos periodontais 12 meses após cirurgia bariátrica	MER	3	Sangramento à sondagem	4,27, df = 2 ($p = 0,12$)	53%	-0,62 (-7,40 – 6,16)[a]	0,18 ($p = 0,86$)	Não
		MEF	3	Nível médio de inserção periodontal (destruição periodontal cumulativa)	2,47, df = 2 ($p = 0,29$)	19%	-0,05 (-0,16 – 0,06)[a]	0,90 ($p = 0,37$)	Não
		MER	4	Nível médio de profundidade de sondagem (*status* periodontal atual)	16,01, df = 2 ($p = 0,0003$)	88%	-0,06 (-0,31 – 0,18)[a]	0,51 ($p = 0,61$)	Não
		MER	2	Porcentagem de sítios com destruição moderada (profundidade de sondagem 4–5 mm)	1,71, df = 1 ($p = 0,19$)	41%	-0,06 (-2,17 – 2,04)[a]	0,06 ($p = 0,95$)	Não
		MEF	2	Porcentagem de sítios com destruição grave (profundidade de sondagem ≥ 6 mm)	0,85, df = 1 ($p = 0,36$)	0%	0,23 (-0,39 – 0,85)[a]	0,72 ($p = 0,47$)	Não

dos Santos et al., 2019	Mudanças nos parâmetros clínicos periodontais comparando antes e após cirurgia bariátrica	MER	3	Sangramento à sondagem	19,72, df = 2 (p < 0,0001)	90%	-0,70 (-11,43 – 10,04)[a]	0,13 (p = 0,90)	Não
		MER	4	Profundidade de sondagem	512,54, df = 3 (p < 0,00001)	99%	-0,46 (-1,55 – 0,63)[a]	0,83 (p = 0,41)	Não
		MEF	3	Nível clínico de inserção	4,01, df = 2 (p = 0,13)	50%	0,18 (0,07 – 0,30)[a]	3,11 (p = 0,002)	Sim
Čolak et al., 2021	Mudanças nos parâmetros clínicos periodontais 6 meses após cirurgia bariátrica	MEF	3	Sangramento à sondagem	1,47, df = 2 (p = 0,48)	0%	4,21 (0,32 – 8,11)[a]	2,12 (p = 0,03)	Sim
		MEF	2	Índice de cálculo	0,73, df = 1 (p = 0,39)	0%	0,57 (-1,77 – 2,91)[a]	0,48 (p = 0,63)	Não
		MEF	4	Nível clínico de inserção	4,00, df = 2 (p = 0,14)	50%	0,16 (0,05 – 0,27)[a]	2,77 (p = 0,006)	Sim
		MEF	3	Profundidade de sondagem	11,94, df = 2 (p = 0,003)	83%	0,14 (0,06 – 0,23)[a]	3,31 (p = 0,0009)	Sim
		MER	2	Porcentagem de sítios periodontais com profundidade de sondagem 4–5 mm)	0,02, df = 1 (p = 0,89)	0%	1,72 (0,11 – 3,34)[a]	2,09 (p = 0,04)	Sim
	Mudanças nos parâmetros clínicos periodontais 12 meses após cirurgia bariátrica	MEF	3	Sangramento à sondagem	3,60, df = 2 (p = 0,17)	44%	2,78 (-1,68 – 7,24)[a]	1,22 (p = 0,22)	Não
		MEF	2	Índice de cálculo	0,08, df = 1 (p = 0,77)	0%	-0,29 (-2,70 – 2,12)[a]	0,24 (p = 0,81)	Não
		MEF	2	Nível clínico de inserção	1,49, df = 1 (p = 0,22)	33%	0,08 (-0,05 – 0,21)[a]	1,17 (p = 0,24)	Não
		MEF	3	Profundidade de sondagem	7,86, df = 2 (p = 0,02)	75%	0,02 (-0,08 – 0,12)[a]	0,40 (p = 0,69)	Não

Legenda: MEF, modelo de efeito fixo; MER, modelo de efeito randômico; *n*, número de estudos incluídos nas meta-análises; Chi^2, teste Qui-quadrado; I^2, teste de Inconsistência de Higgs; -, "não se aplica" e "dado não reportado".

TABELA 4

Análise de risco de viés utilizando a ferramenta ROBIS (Tabela em inglês, por não haver uma versão validada desta ferramenta na língua portuguesa)

	Chaffee e Weston, 2010	Li et al., 2015	Nascimento et al., 2015	Papageorgiou et al., 2015	Akram et al., 2016a	Akram et al., 2016b	Nascimento et al., 2016	Martens et al., 2017	de Souza et al., 2018	Fontanille et al., 2018	dos Santos et al., 2019	Čolak et al., 2021
Domain 1: Study eligibility criteria												
1.1 Did the review adhere to pre-defined objectives and eligibility criteria?	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
1.2 Were the eligibility criteria appropriate for the review question?	PY	PY	PY	PY	PY	PY	PY	PY	PY	PY	PY	PY
1.3 Were eligibility criteria unambiguous?	PY	PY	PY	PY	PY	PN	PY	PY	PY	PY	PY	PY
1.4 Were any restrictions in eligibility criteria based on study characteristics appropriate (e.g. study design, date, sample size, study quality, outcomes measured)?	PY	PY	PY	PY	PY	PY	PY	PY	PY	PY	PY	PY
1.5 Were any restrictions in eligibility criteria based on sources of information appropriate (e.g. publication status or format, language, availability of data)?	PY	PY	PY	PY	PY	PY	PY	PY	PY	PY	PY	PY
Low concern - High concern - Unclear concern	Low concern	Low concern	Low concern	Low concern	Low concern	Low concern	Low concern	Low concern	Low concern	Low concern	Low concern	Low concern
Domain 2: Identification and selection of studies												

2.1 Did the search include an appropriate range of databases/electronic sources for published and unpublished reports?	PY	PY	PY	PY	PY	PY	PY	PY	PY	PY	PY	PY
2.2 Were methods additional to database searching used to identify relevant reports?	PY	PY	PY	PY	PY	PY	PY	PY	PY	PY	PY	PY
2.3 Were the terms and structure of the search strategy likely to retrieve as many eligible studies as possible?	PY	PY	PY	PY	PY	PY	PY	PY	PY	PY	PY	PY
2.4 Were restrictions based on date, publication format, or language appropriate?	Y	Y	Y	Y	Y	Y	Y	PY	Y	Y	Y	PY
2.5 Were efforts made to minimise error in selection of studies?	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
Low concern - High concern - Unclear concern	Low concern	Low concern	Low concern	Low concern	Low concern	Low concern	Low concern	Low concern	Low concern	Low concern	Low concern	Low concern
Domain 3: Data collection and study appraisal												
3.1 Were efforts made to minimise error in data collection?	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
3.2 Were sufficient study characteristics available for both review authors and readers to be able to interpret the results?	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
3.3 Were all relevant study results collected for use in the synthesis?	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y

3.4 Was risk of bias (or methodological quality) formally assessed using appropriate criteria?	N	N	Y	Y	Y	N	N	N	Y	Y	N	N
3.5 Were efforts made to minimise error in risk of bias assessment?	N	N	Y	Y	Y	N	N	N	Y	Y	N	N
Low concern - High concern - Unclear concern	Unclear concern	Unclear concern	Low concern	Low concern	Low concern	Unclear concern	Unclear concern	Unclear concern	Low concern	Low concern	Unclear concern	Unclear concern
Domain 4: Synthesis and findings												
4.1 Did the synthesis include all studies that it should?	PY	PY	PY	PY	PY	PY	PY	PY	PY	PY	PY	PY
4.2 Were all pre-defined analyses reported or departures explained?	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
4.3 Was the synthesis appropriate given the nature and similarity in the research questions, study designs and outcomes across included studies?	PY	PY	PY	PY	PY	PY	PY	PY	PY	PY	PY	PY
4.4 Was between-study variation (heterogeneity) minimal or addressed in the synthesis?	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
4.5 Were the findings robust, e.g. as demonstrated through funnel plot or sensitivity analyses?	Y	NI	Y	NI	NI	NI	NI	Y	NI	NI	NI	NI
4.6 Were biases in primary studies minimal or addressed in the synthesis?	N	N	Y	Y	Y	N	N	N	Y	Y	N	N
Low concern - High concern - Unclear concern	Low concern	Low concern	Low concern	Low concern	Low concern	Low concern	Low concern	Low concern	Low concern	Low concern	Low concern	Low concern

Overall risk of bias	**LOW RISK OF BIAS**	**LOW RISK OF BIAS**	**LOW RISK OF BIAS**	**LOW RISK OF BIAS**	**LOW RISK OF BIAS**	**LOW RISK OF BIAS**	**LOW RISK OF BIAS**	**LOW RISK OF BIAS**	**LOW RISK OF BIAS**	**LOW RISK OF BIAS**	**LOW RISK OF BIAS**	**LOW RISK OF BIAS**

DISCUSSÃO

O aumento da expectativa média de vida tem sido relacionado com a ocorrência de doenças crônicas não transmissíveis (DCNT), condições de saúde que se desenvolvem ao longo da vida e interagem ou interferem umas nas outras de forma cumulativa ou sinérgica, a necessidade de novas abordagens preventivas e terapêuticas, e seus impactos socioeconômicos e na qualidade de vida dos indivíduos.[39] A patogênese das DCNTs segue um curso inflamatório crônico de baixa intensidade e longa duração, diagnosticadas muitas vezes em estágios avançados da doença, e de difícil tratamento no curto prazo. A obesidade e a periodontite se enquadram neste contexto, em que ambas compartilham fatores de risco e mecanismos biológicos relacionados com a exaustão da capacidade adaptativa de tecidos e órgãos e o comprometimento da homeostasia de diferentes sistemas do corpo humano. As DCNTs representam uma epidemia global de alta complexidade, morbidade e limitante, que impacta de forma significativa a vida das pessoas e a economia frente à demanda elevada por cuidados médicos e mais investimentos em pesquisa nessa área. Hoje, a periodontite também é considerada uma DCNT e uma comorbidade do diabetes, fortemente associado à obesidade.[40-45]

Indivíduos com obesidade apresentam um estado hiperinflamatório[46] decorrente das adipocinas produzidas e liberadas no tecido adiposo, bem como pela interação destas adipocinas, de parâmetros clínicos e biomarcadores sistêmicos alterados na obesidade, e dos fatores de risco associados a esta condição e suas comorbidades. Ocorre um desequilíbrio entre os níveis e proporções de mediadores pró-inflamatórios e anti-inflamatórias em favor da inflamação,[47,48] e duas a três vezes mais chance de desenvolver periodontite independente de outros fatores de risco como idade, sexo e tabagismo.[49-55]

A literatura mais recente define a periodontite como uma doença inflamatória multifatorial crônica associada a biofilme disbiótico e caracterizada pela destruição progressiva do aparelho de suporte dentário.[56] A reação inflamatória na bolsa periodontal e sua repercussão sistêmica decorrente da translocação de citocinas, bactérias (bacteremia) e seus fatores de virulência (endotoxemia) participam do mecanismo biológico da relação bidirecional entre a periodontite e as DCNTs, como o diabetes, a obesidade e as doenças cardiovasculares, dentre outras condições/doenças.[57-62] O tratamento periodontal está associado à redução da inflamação periodontal e sistêmica em pacientes com periodontite associada a outras doenças inflamatórias crônicas[63] e, portanto, com a menor ocorrência e complicações de suas comorbidades. A importância sistêmica da periodontia e as manifestações periodontais de condições/doenças sistêmicas reforçam o questionamento dos termos “saúde bucal” e “saúde sistêmica”, haja vista que saúde é saúde e os diferentes órgãos e sistemas estão permanentente interligados.

Em uma revisão recente, Azevedo et al. (2020) descreveram a relação entre a obesidade e a periodontite como um processo pro- ou hiperinflamatório associado com o comprometimento do metabolismo da glicose, níveis elevados de IL-1β, IL-6 e TNF-α, perda da homeostasia de leptina e adiponectina, aumento dos níveis de ácidos graxos livres e de espécies reativas de oxigênio, acúmulo de produtos finais da glicação avançada (AGEs), aumento da colagenólise e complicações vasculares decorrentes da hiperglicemia, do estresse oxidativo, dos níveis elevados de PCR e angiotensinogênio.[64] Segundo Martens et al. (2017), várias hipóteses para interações biológicas entre obesidade e doenças periodontais têm sido propostas, como alterações na resposta pró-inflamatória e imunológica, tolerância à glicose prejudicada, perturbações nos perfis lipídicos, alterações na imunidade do hospedeiro, aumento da ativação de macrófagos, função microvascular prejudicada, respostas fisiológicas ao estresse psicossocial e secreção de substâncias pró-inflamatórias do tecido adiposo, incluindo IL-6, TNF-α e PCR.[19] No entanto, os mecanismos moleculares e celulares específicos ainda não estão claros e mais estudos são necessários para desvendar os mecanismos, que podem fornecer alvos para prevenção ou tratamento. Os resultados das meta-análises apresentados na Tabela 3 sugerem maior chance de desenvolver periodontite e ocorrer piora de parâmetros clínicos periodontais, níveis de resistina e IL-1β no FCG na obesidade, e maior IMC entre indivíduos com periodontite.[12,13,15,16,19] Apesar dos mecanismos biológicos propostos, os resultados das meta-análises reportadas por Akram et al. (2006a) apontaram que adiponectina, leptina, TNF-α, IL-6 e IL-8 não são influenciadas de forma significativa pela obesidade em indivíduos com periodontite.[16]

Nossos resultados indicam a existência de evidência científica para uma maior chance de desenvolver periodontite e ocorrer piora dos parâmetros clínicos periodontais e biomarcadores de inflamação no FCG como resistina e IL-1β na obesidade, e maior índice de massa corporal (IMC) entre indivíduos com periodontite.[12,13,15,16,19] A adiponectina, leptina, TNF-α, IL-6 e IL-8 medidas no FCG não foram influenciadas de forma significativa pela obesidade em indivíduos com periodontite.[16] Uma associação positiva foi repetidamente demonstrada entre a periodontite e a obesidade em vários estudos. Observou-se aumento de aproximadamente um terço na prevalência de obesidade entre indivíduos com periodontite, maior perda de inserção periodontal média entre indivíduos com obesidade,[12] associações positivas entre IMC e sangramento gengival, cálculo subgengival e aumento de biomarcadores inflamatórios e de bactérias no FCG.[13] Em geral, os parâmetros periodontais se mostraram significativamente pobres em indivíduos com obesidade em comparação com indivíduos não obesos nos períodos de acompanhamento.[16,18]

Apesar dos resultados positivos para a associação entre obesidade e periodontite em revisões sistemáticas com meta-análise que se basearam em estudos observacionais, as revisões de estudos intervencionais sugerem o oposto. A obesidade parece não exercer efeito significativo

sobre a resposta ao tratamento periodontal e parâmetros locais,[14,17,18] e a cirurgia bariátrica não resultou em benefício significativo para a saúde periodontal, tendo sido reportadas pioras nos parâmetros clínicos após a bariátrica por alguns autores, especialmente 12 meses após a cirurgia.[20-23] A inclusão de fumantes nas amostras estudadas deve ser considerada um importante fator de confusão em estudos clínicos em periodontia tanto por ser um fator modificador desta condição, quanto por prejudicar a resposta ao tratamento periodontal.[16,65-67] Neste contexto, 41,7% das revisões sistemáticas com meta-análise incluídas controlaram seus dados/resultados para tabagismo, das quais 20% foram baseadas em estudos observacionais, 20% em estudos de tratamento periodontal e 75% em estudos de cirurgia bariátrica. Sendo assim, os resultados dos estudos que avaliaram os efeitos da cirurgia bariátrica podem ser interpretados sem interferência significativa deste fator de confusão, enquanto as demais meta-análises devem ser consideradas com atenção a esta limitação.

Para dos Santos et al. (2019), os efeitos negativos da cirurgia bariátrica no periodonto podem ser explicados pelo estado periodontal insatisfatório antes da cirurgia e pelo fato de nenhum tratamento periodontal ter sido realizado em nenhum dos estudos primários analisados, incluindo cuidados de saúde bucal adequados.[22] A redução da PS e o ganho de NIC só são possíveis pelo tratamento periodontal. Segundo os autores, um estudo observou melhora no estado periodontal após a cirurgia bariátrica, que eles atribuíram às mudanças impostas na dieta e nas instruções de higiene bucal dadas aos pacientes em preparação para a cirurgia, que parecem contribuir para uma melhora na saúde periodontal e na prevenção da progressão da doença. de Souza et al. (2018) também reportaram a ausência de benefícios significativos da cirurgia bariátrica nos parâmetros clínicos periodontais inflamatórios, com discreta piora de PS e NCI.[20] A maioria dos estudos primários incluídos nas meta-análises apresentaram metodologias semelhantes aos estudos com resultados positivos, portanto, diferenças metodológicas não explicam os achados contraditórios. Os autores sugerem que a alteração metabólica pós-cirúrgica pode levar a distúrbios metabólicos que resultam em menor absorção de vitamina B12 e cálcio, o que influenciaria o metabolismo ósseo e resultaria em piores índices periodontais, como a PS.

Segundo de Souza et al. (2018), as pessoas que reduzem o IMC ficam mais motivadas e são mais propensas a adotar comportamentos que melhoram a saúde, como melhoria da dieta e exercícios físicos.[20] Para os autores, isto pode representar um viés na interpretação dos efeitos da redução de IMC sobre os parâmetros clínicos periodontais, na resposta ao tratamento da periodontite e nos efeitos sistêmicos da condição periodontal. Além disso, a atividade física também é responsável por reduzir a inflamação sistêmica geral, com efeitos positivos em outras condições, como as doenças cardiovasculares. A divergência de resultados observada entre as meta-análises de dados observacionais e de dados intervencionais pode estar relacionada com a

progressão das DCNTs ao longo do tempo, onde seus efeitos negativos em diferentes tecidos e órgãos, acumulados e potencializados a longo prazo, podem representar sequelas parcial ou totalmente irreversíveis. Nesse sentido, o tratamento da periodontite ou da obesidade em pacientes com estas condições descompensadas ou sem tratamento adequado por anos pode ser insuficiente para gerar benefícios estatisticamente significativos e de magnitude de efeito clínico (*effect size*) relevante. Outro ponto considerado um desafio nos estudos clínicos e epidemiológicos em periodontite e obesidade é a etiologia multifatorial destas doenças.

Os resultados desta *umbrela review* refletem o melhor nível de evidência sobre o tema e dá luz às lacunas da literatura e à necessidade de novos estudos, bem delineados, para a investigação dos efeitos mútuos da obesidade e da periodontite. Ainda assim, se faz necessário reconhecer as limitações metodológicas existentes nos estudos primários e secundários que subsidiaram esta síntese, uma vez que fatores de confusão como tabagismo, parâmetros e condições sistêmicas, tempo de evolução e gravidade de ambas as doenças devem ser mais bem consideradas nas meta-análises e interpretações dos resultados. Independente destas observações, o presente estudo contribui para a tomada de decisão clínica em periodontia na abordagem de indivíduos com obesidade, e chama a atenção para a importância da prevenção e do diagnóstico e tratamento precoces destas condições.

CONCLUSÕES

A síntese dos dados desta *umbrella review* revela a existência de evidência científica para a associação entre obesidade e parâmetros clínicos peridontais, resistina e IL-1β no fluido crevicular gengival, mas não para a adiponectina, leptina, TNF-α, IL-6 e IL-8, e a ausência de evidência para efeitos da obesidade sobre a resposta ao tratamento da periodontite e para benefícios da cirurgia bariátrica para os tecidos periodontais, tomando como unidades de análise revisões sistemáticas com meta-análises classificadas como baixo risco de viés.

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Conflito de interesses

Nenhum dos autores possui qualquer tipo de conflito de interesse relacionado ao estudo, bem como relacionado ao processo de revisão por pares do manuscrito. Nenhuma das universidades e órgãos públicos de apoio à pesquisa no Brasil representa conflito de interesse neste estudo.

Declaração de contribuição

Todos os autores fizeram contribuições substanciais para o estudo e foram igualmente responsáveis por sua concepção, execução e conteúdo, e concordaram com sua submissão para publicação.

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CAPÍTULO 4

Cardiometabolic, inflammatory, oxidative and microbiological benefits of periodontal therapy in patients with obesity and periodontitis: A systematic review

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ABSTRACT

Backgroung. Although the relationship between obesity and periodontitis has been investigated in recent years, evidence on the systemic effects of periodontitis-therapy in patients with obesity remains unclear. This systematic review aimed to answer the focused question: "What are the benefits of subgingival periodontal therapy on blood hematological and biochemical index, biomarkers of inflammation and oxidative stress, quality of life and periodontopathogen counts in patients with obesity and periodontitis?"

Methods. A systematic literature search was performed in PubMed, Scopus, Embase, Web of Science, Cochrane Library, LILACS and BBO electronic databases, complemented by other sources, manual search and contact of experts until January 2022. Inclusion criteria were randomized and non-randomized controlled clinical trials and before-and-after studies on patients with obesity and periodontitis comparing periodontitis-therapy with the absence of subgingival instrumentation. This study was conducted according to PRISMA 2021. The synthesis of qualitative results followed the SWiM reporting guideline. Risk of bias within studies were

assessed using RoB 2 and ROBINS-I tools. The certainty of evidence was evaluated following the GRADE approach, adapting all the judgments to qualify the evidence in a narrative way.

Results. A total of three RCT and 15 clinical trials with pre-post data from patients with obesity and periodontitis were included. Non-surgical periodontal therapy (NSP) plus azithromycin, chlorhexidine and cetylpyridinium chloride reduced systolic and diastolic blood pressure, decreased serum levels of HbA1c, hsCRP, IL-1β and TNF-α. Salivary resistin level also reduced in patients with obesity and periodontitis after NSPT and mouth rinse with chlorhexidine adjunct to therapy. Before-and-after data suggest a potential improvement in total cholesterol, LDL, triglycerides, insulin resistance and C3, GCF levels of TNF-α, chemerin, vaspin, omentin-1, visfatin and 8-OHdG, and *Pg*, *Pi*, *Aa*, *Tf* and *Td* counts after NSPT and full-mouth disinfection. Smoking and diabetes mellitus were not confirmed as confounding factors in the included studies.

Conclusions and practical implications. Periodontitis-therapy has the potential to improve blood pressure, serum levels of total cholesterol, LDL, triglycerides, HbA1c, insulin resistance, hsCRP, IL-1β, TNF-α and C3, GCF levels of TNF-α, chemerin, vaspin, omentin-1, visfatin and 8-OHdG, and *Pg*, *Pi*, *Aa*, *Tf* and *Td* counts of patients with obesity and periodontitis. It is suggested that periodontitis-therapy has the potential to improve cardiometabolic parameters, inflammatory biomarkers and periodontopathogen counts patients with obesity. However, further well-designed clinical trials are recommended to confirm these findings.

Protocol record. PROSPERO [CRD42021241653].

Keywords. Periodontal diseases; periodontitis; obesity; dental scaling; root planning.

INTRODUCTION

Obesity is the excessive accumulation of fat in the body, which can cause systemic changes in humans health. It has a high degree of morbidity and is a risk factor for several types of diseases such as type 2 Diabetes Mellitus (DM), heart disease and cancer (Akran et al., 2016). According to the World Health Organization (WHO), obesity is identified by body mass index (BMI) ≥ 30.0 kg/m^2. Person with obesity have high levels of inflammatory biomarkers, secreted by adipocytes, that modulate inflammatory, immune, and metabolic responses, leading to a hyper inflammatory state, and a greater susceptibility to infections and difficulty in healing (Akran et al., 2016). In addition, other metabolic levels can also be altered due to obesity, such as glucose, triglycerides, total cholesterol, high-density lipoprotein cholesterol (HDL), low-density lipoprotein cholesterol (LDL), C-reactive protein (CRP), among others, which influence the

individual's general health. Adipose tissue, as a metabolically active endocrine organ (Suresh, 2014), can be considered a risk factor for several chronic diseases such as hypertension, type 2 DM, dyslipidemia and cardiovascular diseases.

Periodontitis is a chronic inflammatory condition, characterized by the loss of periodontal tissue and alveolar bone support, induced by the accumulation of bacterial biofilm on the gingival margin, gingival sulcus, and periodontal pockets (Papapanou et al., 2018). The interaction between bacterial load and host response links periodontitis to several chronic inflammatory diseases such as DM, cardiovascular (Sanz et al., 2018; Licardo et al., 2019), and kidney diseases (Kapellas et al., 2019), preterm birth and low birth weight newborn (Moliner-Sanchés et al., 2020), representing a public health problem.

Although its pathophysiological mechanism is unknown, studies suggested that obesity may be a risk factor for periodontitis (Al-Zahrani & Alghamdi, 2012; Martinez-Herrera et al., 2017), as first proposed by Perlstein & Bissada (1977). Some studies propose that the high levels of circulating pro inflammatory cytokines such as interleukyne-1β (IL-1β), IL-6, tumor necrosis factor-α (TNF-α) in patients with obesity may increase periodontal destruction (Zuza et al., 2011; Kose et al., 2015). Systematic reviews have demonstrated the effect of obesity on non-surgical periodontal therapy (Papageorgiou et al., 2015) and in periodontal and immunological parameters in patients with obesity, compared to non-obesity (Gerber et al., 2015; Nascimento et al., 2015; Akram et al., 2016). Despite periodontal therapy being associated with reduced periodontal and systemic inflammation in patients with periodontitis and non-communicable diseases of chronic inflammatory course (Artese et al., 2015), one question remains: Is there evidence that subgingival periodontal therapy offers systemic benefits for patients with obesity? In this context, this review aims to answer the focused question: “What are the benefits of subgingival periodontal therapy on blood hematological and biochemical index, biomarkers of inflammation and oxidative stress, quality of life and periodontopathogen counts in patients with obesity and periodontitis?”

METHODS

Protocol and Registration. This study was conducted according to The Enhancing the QUAlity and Transparency Of health Research (EQUATOR network) recommendations, including the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA [Page et al., 2021]). The review protocol was registered in the PROSPERO database (http://www.crd.york.ac.uk/PROSPERO) under the number [CRD42021241653].

Focused question. Based on the PICO principle—the Population: patients with obesity and periodontitis, regardless of age, sex and race; the Intervention: periodontal therapy with subgingival approach*; the appropriate Control (or comparator): no periodontal treatment with subgingival approach, included non-periodontal treatment or supragingival periodontal treatment (without subgingival approach); the Outcomes of interest: blood hematological and biochemical index, biomarkers of inflammation and oxidative stress on serum, saliva and gingival crevicular fluid (GCF), quality of life, periodontopathogen counts and adverse effects.

*We did not restrict the search by type of periodontal therapy. Periodontal interventions were based on scaling and root planing sections [SRP (e.g, non-surgical periodontal therapy)], one-stage/intensive full mouth SRP, full-mouth disinfection and surgical procedures (e.g, periodontal flap surgery), for supra- and subgingival biofilm and calculus removal [Intervention (I)]. Mechanical therapy plus local or systemic drug use (e.g, antimicrobial, anti-inflammatory or others), or associated with photodynamic therapy/laser therapy, were also included.

Study selection criteria

- Inclusion criteria: i- randomized controlled trials (RCT), non-randomized controlled clinical trials (CCT) and before-and-after (pre-post) data from groups of patients with obesity and periodontitis from clinical trials (BAS); ii- studies that evaluated the systemic effect (on serum, saliva and/or gingival crevicular fluid) of therapeutic interventions for periodontitis in patients with obesity, with at least 3-months follow-up; and iii- primary outcomes of interest: blood hematological and biomarkers index, cytokines, chemokines, adipokines and oxidative stress biomarkers in serum, GCF and/or saliva, and quality of life with at least 4-weeks follow-up. Secondary outcomes of interest: periodontopathogen counts and adverse effects.
- Exclusion criteria: i- pilot studies; ii- participants with congenital syndrome (i.e., Down syndrome, Ehlers-Danlos syndrome, Marfan syndrome, Stickler syndrome, Osteogenesis imperfecta, Papillon-Lefevre syndrome or others.); iii- trials in which no confirmation or diagnosis criteria for obesity and/or periodontitis were reported and could not be retrieved after contacting the original authors; iv- trials in which outcomes of interest were not available for analysis and the original values could not be retrieved after contacting the original authors; and v- unavailability of full paper copy.
- No data or language restrictions were applied.

Information sources. Searches were performed in the MEDLINE using the PubMed search engine (http://www.ncbi.nlm.nih.gov/sites/pubmed), Scopus (http://www.scopus.com) and Embase (https://www.embase.com) through Elsevier (https://www.elsevier.com), Web of Science – WOS (https://www.webofknowledge.com) accessed through the Clarivate Analytics (https://clarivate.com), Cochrane Library (https://www.cochranelibrary.com), LILACS and BBO

(https://bvsalud.org). Other sources were consulted through Google Scholar (https://scholar.google.com.br) and System for Information on Grey Literature in Europe (SIGLE) through OpenGrey (www.opengrey.eu) databases. The protocol registration databases included ClinicalTrials.gov and ReBEC (*Registro Brasileiro de Ensaios Clínicos*). Hand-searches were also performed in specialized periodicals (Step 1): *Journal of Periodontology; Journal of Clinical Periodontology; Journal of Periodontal Research; Periodontology 2000; Journal of Periodontal & Implant Science; The International Journal of Periodontics & Restorative Dentistry; The Journal of American Dental Association; Journal of Oral Pathology & Medicine; Oral Surgery, Oral Medicine, Oral Pathology and Oral Radiology*; and in reference lists of selected articles (step 2). Experts were identified using expertscape.com (https://expertscape.com) and contacted for other data sources.

Search strategy. The search strategy was created using MeSH terms, DeCS/MeSH terms, Emtree terms and other free terms, combined by the Boolean operators "OR" and "AND". The electronic search was performed on March 5, 2021. Databases alerts were created to identify studies published after the time of the search, until January 2022.

Database	Search strategy
PubMed	(((obesity[Mesh] OR obesity [TiAb]) AND (periodontal diseases[Mesh] OR periodontal diseases[TiAb] OR disease, periodontal[TiAb] OR diseases, periodontal[TiAb] OR periodontal disease[TiAb] OR periodontitis[TiAb])) AND (root planing [Mesh] OR periodontal therapy[TiAb] OR periodontal treatment[TiAb] OR scaling and root planing[TiAb]))
Scopus	TITLE-ABS-KEY ((obesity) AND ("periodontal disease*" OR "disease*, periodontal" OR periodontitis)) AND ("periodontal therapy" OR "periodontal treatment" OR "scaling and root planing") AND (LIMIT-TO (DOCTYPE , "ar"))
Embase	#1 AND #2 AND #3 AND 'article'/it #3 'periodontal therapy' OR (periodontal AND treatment) OR (scaling AND 'root planing') #2 'periodontal disease' OR 'periodontitis' #1 'obesity'
Web of Science	((obesity AND ("periodontal disease*" OR "disease*, periodontal" OR periodontitis)) AND ("periodontal therapy" OR "periodontal treatment" OR "scaling and root planing")) Filter: Type of Document: (ARTICLE)
Cochrane Library	ID Search #1 MeSH descriptor: [obesity] explode all trees #2 obesity #3 MeSH descriptor: [periodontal diseases] explode all trees #4 periodontal diseases OR periodontitis #5 MeSH descriptor: [root planing] explode all trees #6 periodontal therapy OR periodontal treatment OR scaling and root planing #7 #1 OR #2 #8 #3 OR #4 #9 #5 OR #6 #10 #7 AND #8 #11 #10 AND #9

LILACS	((mh:obesidade OR mh:obesity OR mh:obesidad OR mh:obésité) AND (mh:doenças periodontais OR mh:periodontal diseases OR mh:enfermedades periodontales OR mh:maladies pariodontales OR mh:periodontite OR mh:periodontitis OR mh:parodontite)) AND (tratamento periodontal OR periodontal therapy OR periodontal treatment OR tratamiento periodontal OR traitement parodontal OR mh:root planning OR mh: aplainamento radicular OR mh: aplanamiento de la raíz OR mh: surfaçage radiculaire OR scaling AND root planning OR raspagem e aplainamento radicular OR détartrage et surfaçage radiculaire OR raspado y aplanamiento de la raiz)
Other sources	(obesity) AND (periodontal diseases OR periodontitis) AND (root planning OR periodontal therapy OR periodontal treatment OR scaling and root planning)

Selection process. The retrieved articles were exported to Endnote® Web (www.myendnoteweb.com) and duplicates were removed by the program and manually. Authors of studies that were not retrieved in full text were contacted by e-mail up to five attempts. If two studies had sample overlapping, and the same methodology criteria assessed, the least complete study was excluded. The selection process was conducted in two phases: Phase 1, two researchers (CCM and DSB) independently examined the titles and abstracts of all identified references, applying the including process (blind process); and Phase 2, the same two reviewers independently applied the exclusion criteria to the other studies, based on reading the full text (blind process). Inter-reviewer reliability in the study selection process was determined by the Cohen κ test, assuming an acceptable threshold value of 0.80 (Landis and Koch, 1977). The disagreement at any stage was resolved by discussion and mutual decision (consensus meeting) with a third reviewer (MCMB). The final decision/selection was always based on the full text of the publication. The reasons for studies exclusion were reported (Figure 1).

Data collection process. The full texts were evaluated and judged in the entire document. Authors were contacted through electronic mail, during five consecutive weeks, when necessary to obtain details on study design and data clarification. Data were extracted by two independent reviewers (CCM and DSB) from the included studies and described in the paper at a consensus meeting with the third reviewer (MCMB). When there were unclear or missed information, lack of data or when the full text was not available, weekly attempts were made for up to 5 weeks to contact the authors. In case there were no return from the authors to identify data in graphs, it was used the digital program WebPlotDigitizer® online (https://automeris.io/WebPlotDigitizer/). The accuracy of extracted data was confirmed by another author (MCMB). Google translator program was used in case of studies in a foreign language not provided by the researchers (https://translate.google.com.br/?hl=pt-BR).

Data items and synthesis. Data were independently extracted by the two reviewers (C.C.M. and D.S.B. [blinded process]) using a standardized sheet, as recommended by the Cochrane Collaboration's handbook for systematic review (Higgins et al., 2021). From the

selected articles the following data were extracted: Author, country and year; participants profile (i.e., demographic variables); smoking; alcohol consumption; systemic conditions/diseases, periodontal diagnosis + periodontal diagnosis criteria; obesity diagnosis + obesity diagnosis criteria; periods of data collection; characteristics of periodontal intervention; comparison groups; blood hematological and biochemical index; biomarkers of inflammation and oxidative stress; quality of life; study duration (follow-up); periodontal pathogens count and adverse effects. The synthesis of qualitative results followed the SWiM reporting guideline (Campbell et al. 2020).

The primary outcomes were: blood hematological and biochemical index [white blood cells; fasting blood glucose; glycated hemoglobin (HbA1c); insulin; total cholesterol; HDL; LDL; triglycerides; creatinine; α-1 antitrypsin; Homeostatic Model Assessment (HOMA) 2 β-cell function; HOMA2 insulin sensitivity; HOMA2 insulin resistance; HOMA IR; RBP4; lipoprotein-a, fibrinogen, CRP and hsCRP], biomarkers of inflammation in blood, saliva or GCF (IL-1β; IL-6; IL-8; TNF-α; C3; leptin; adiponectin; chemerin; vaspin; and omentin-1), biomarkers of oxidative stress [8-OHdG (8-hydroxy-2' -deoxyguanosine) in blood serum, saliva and GCF]; quality of life [OHIP-14 (Oral Health Impact Profile-14)] and periodontal pathogens count [*Porphyromonas gingivalis* (*Pg*); *Prevotella intermedia* (*Pi*); *Aggregatibacter actinomycetemcomitans* (*Aa*); *Tannerella forsythia* (*Tf*); *Treponema denticola* (*Td*); *Parvimonas micra*; *Fusobacterium nucleatum* (*Fn*); *Campylobacter rectus*; *Eikenella corrodens* (*Ec*); *Capnocytophaga* spp.]. Descriptive results were presented in the form of text, figure and tables in the order of the PICO strategy (Table 1, 2 and 3).

Risk of bias within studies. The evaluation of quality and risk of bias in clinical studies was performed by two authors independently (C.C.M. and D.S.B.), using specific risk of bias and methodological quality assessment tools for Randomized controlled trials ["Revised Cochrane risk-of-bias tool for randomized trials" (RoB 2)], and Non-randomized studies of intervention ["Risk Of Bias In Non-randomized Studies - of Interventions" (ROBINS-I) tool for (uncontrolled) before-after studies] – Figure 4A and 4B. The authors of reports were contacted to retrieve any possible bias of missing data. The contact was done by e-mail up to five attempts.

Certainty assessment. The certainty of evidence was evaluated following the GRADE approach (Schünemann et al., 2013; GRADEpro GDT, 2020), adapting all the judgments to qualify the evidence in a narrative way (Murad et al., 2017). The risk of bias, inconsistency, indirectness, imprecision, and other information (suspicion of publication bias, presence of large effect, dose-response gradient and plausible confounders) were the items considered to rate the overall certainty of evidence. The Classification of Assessment, Development and Assessment Recommendations (GRADE) was used to assess the quality of responses in this systematic review, based on the study design, risk of bias, inconsistency, indirect evidence, imprecision, and

publication bias. Thus, the evidence quality index is defined in four categories: high, moderate, low, and very low applied to each of the evaluated outcomes (Guyatt et al., 2008, 2011; Santesso et al., 2020).

RESULTS

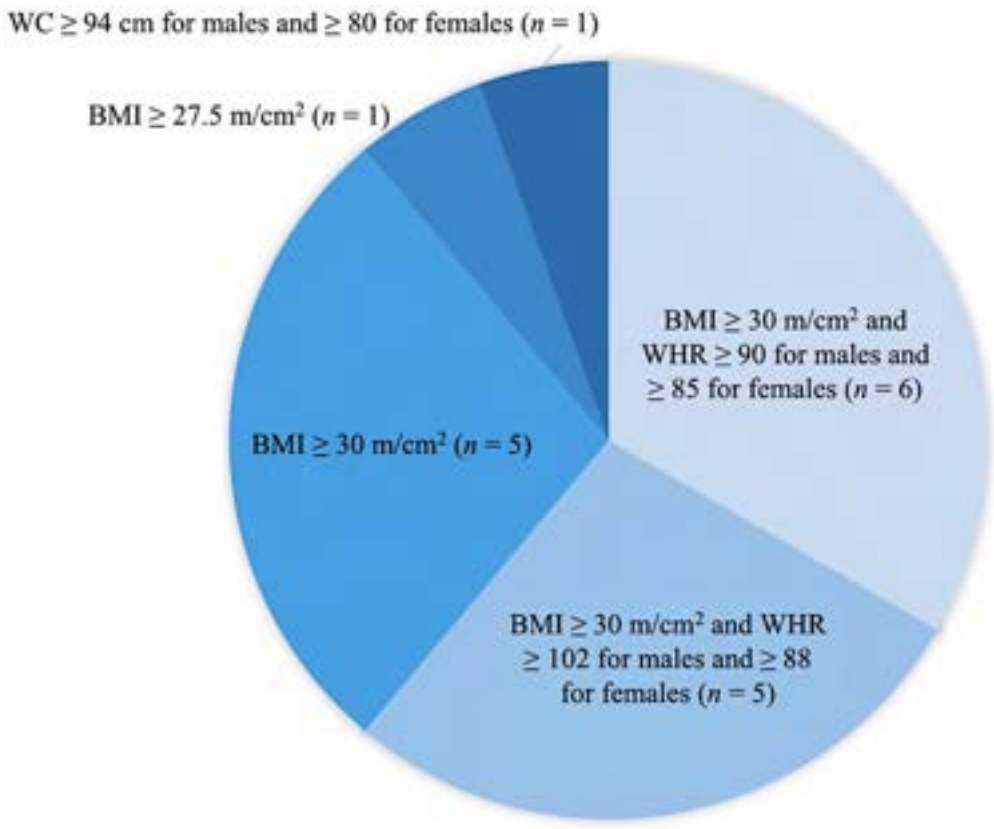
Study selection. There were identified 763 records from the following databases: PubMed (*n* = 86), Scopus (*n* = 341), Embase (*n* = 193), Web of Science (*n* = 101), Cochrane Library (*n* = 31) and LILACS and BBO (*n* = 10). After removing 390 duplicates, 345 reports were excluded by eligibility criteria, and 28 were selected for full-text reading. Four reports were excluded by study design (Ongoz-Dede et al., 2016; Vohra et al., 2017; Varghese et al., 2018; Zúñiga Curz et al., 2019), five because obesity group included non-obesity (Lopez et al., 2012; Bunjaku et al., 2017; Al-Hamoud et al., 2018; Suresh et al., 2018; Wanichkittikul et al., 2021), and one because periodontitis diagnosis criteria was not reported (Eldin et al., 2013) (Figure 1). No records were included from the other sources because of subject or duplicity.

Study characteristics. A total of 18 reports were included in this systematic review: three RCT (Akram et al., 2016; Basher et al., 2017; Montero et al., 2020), and 15 BAS (Al-Zaharani et al., 2012; Altay et al., 2013; Gonçalves et al., 2015a and 2015b; Balli et al., 2016a and 2016b; Öngoz-Dede et al., 2016; Taşdemir et al., 2016; Zuza et al., 2016; Çetiner et al., 2018; Martinez-Herrera et al., 2018a and 2018b; Peralta et al., 2019; MdTahir et al., 2020; Cortelli et al., 2021) (Table 1). 634 patients with obesity and periodontitis were considered for analysis, of which 187 from RCT and 447 from BAS. The diagnostic criteria for obesity and periodontitis varied between studies, as reported in Table 1 and Figure 2 and 3. The distribution of smokers in the CG and IG did not differ between the three RCT studies (Akram et al., 2016; Basher et al., 2017; Montero et al., 2020). Akram et al. (2016) controlled statistical analyzes for smoking and Montero et al. (2020) reported adjusted *p*-values for this variable.

The clinical approach performed in RCT studies were nonsurgical SRP (NSPT) with adjunctive systemic antibiotic administration (azithromycin 500 mg q.d. for three days) in the IG and supragingival plaque removal plus administration of placebo in the CG (Montero et al., 2020), and NSPT in the IG and no-periodontal therapy in the CG (Akram et al., 2016; Basher et al., 2017). Akram et al. (2016) and Basher et al. (2017) used 0.12 % chlorhexidine, and Montero et al. (2020) used 0.12 % chlorhexidine and 0.05 % cetylpyridinium chloride twice daily for 14 days post-therapy.

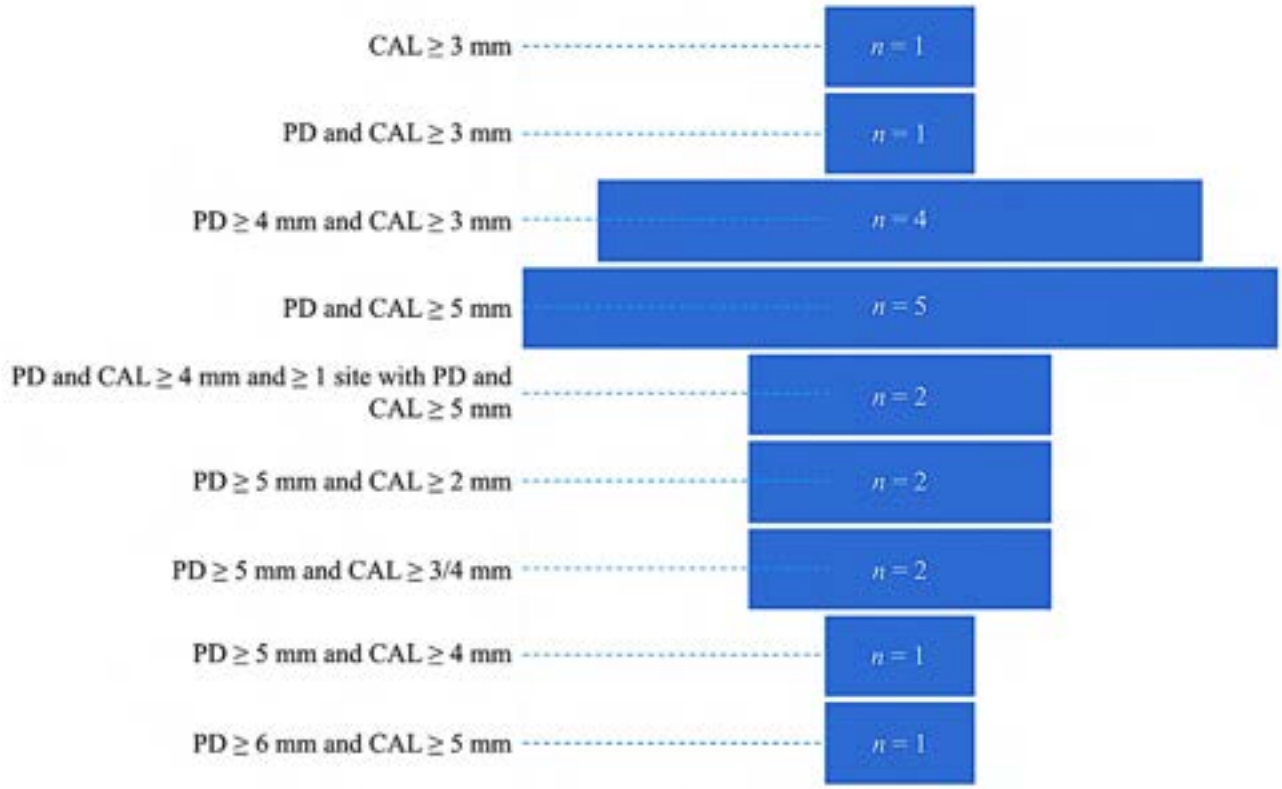
Among BAS studies, all participants were diagnosed with obesity and periodontitis, and were evaluated before and after periodontal therapy: seven studies performed NSPT in more than one session (Al-Zaharani et al., 2012; Gonçalves et al., 2015a, 2015b; Balli et al., 2016a, 2016b; Zuza et al., 2016); six studies performed intensive full-mouth NSPT (Öngoz Dede et al., 2016; Taşdemir et al., 2016; Martínez-Herrera et al., 2018a, 2018b; Çetiner et al., 2019; Md Tahir et al., 2020), and three studies adopted full-mouth disinfection protocol proposed by Quirynen et al.(1995) (Altay et al., 2012; Peralta et al., 2019; Cortelli et al., 2021). Chlorhexidine protocols as adjuvant to periodontal therapy and in the periodontal maintenance phase varied between studies (Table 1). BAS data from Altay et al. (2013), Martinez-Herrera et al. (2018a, 2018b), Peralta et al. (2019) and Md Tahir et al. (2020) included smokers.

FIGURE 2. Descriptive pie charts of diagnostic criteria for obesity reported in the studies



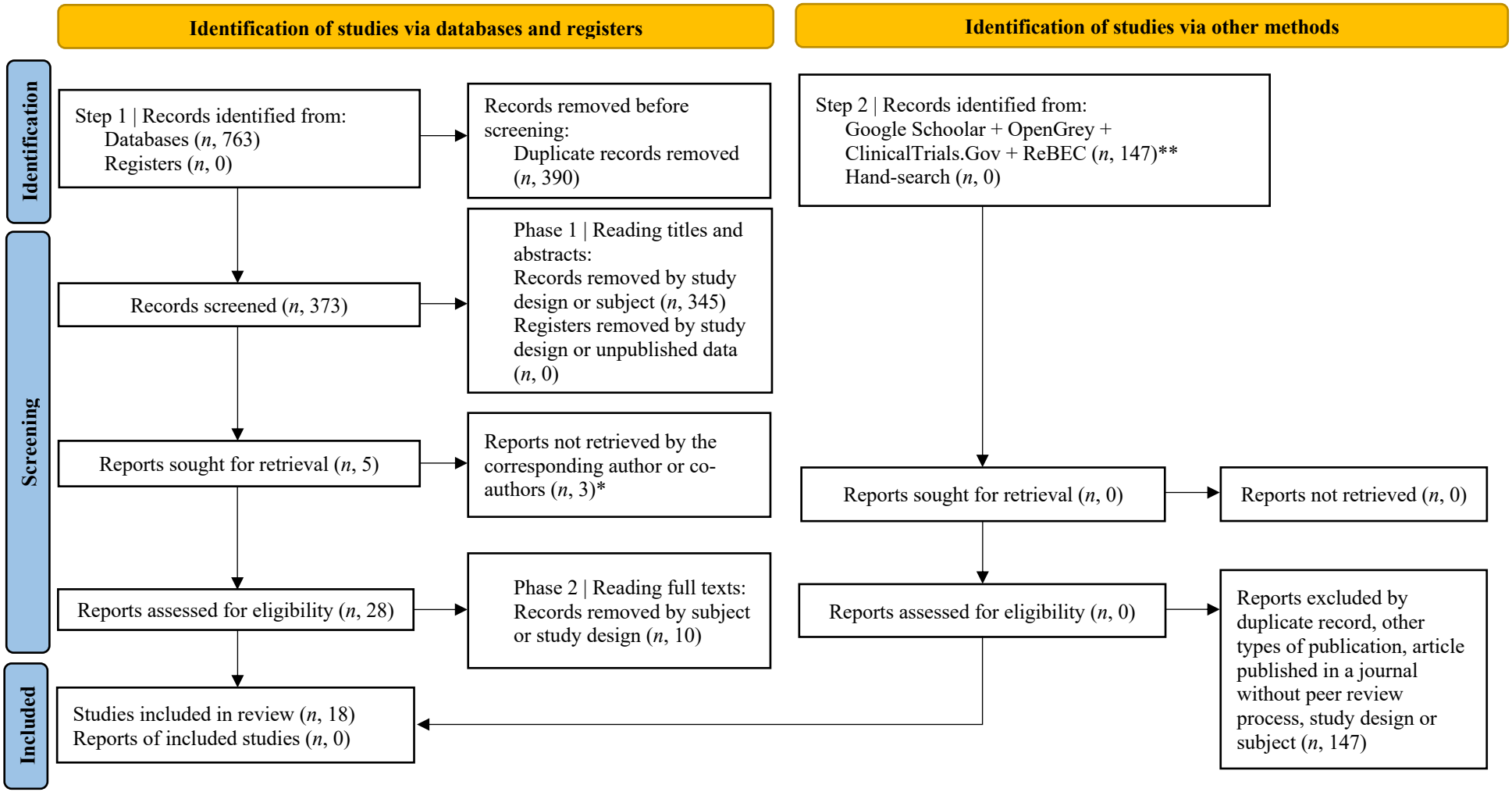
Legend: BMI, bone mass index (m/cm^2); WC, waist circumference (cm); WHR, waist-to-hip ratio. Six studies used body mass index (BMI) ≥ 30 m/cm^2 and waist-hip ratio (WHR) ≥ 0.9 for males ≥ 0.85 for females (Gonçalves et al., 2015a and 2015b; Akram et al., 2016; Balli et al., 2016a and 2016b; and Zuza et al., 2016); five studies used BMI ≥ 30m/cm^2 and waist circumference (WC) > 102 cm for males and > 88 cm for females (Altay et al., 2013; Taşdemir et al., 2016; Çetiner et al., 2019; Peralta et al., 2019; Cortelli et al., 2021); five reports used BMI ≥ 30 m/cm^2 (Al-Zaharani et al., 2012; Öngoz-Dede et al., 2016; Martinez-Herrera et al., 2018a and 2018b; MdTahir et al., 2020), one study used BMI ≥ 27.5m/cm^2 (Basher et al., 2017), and one study used WC ≥ 94 cm in males and ≥ 80 cm in females (Montero et al., 2020).

FIGURE 3. Descriptive funnel chart of diagnostic criteria for periodontitis reported in the studies.



Legend: *n*, absolute frequency of studies per criteria; CAL, clinical attachment level (mm); PD, probing depth (mm). The limit score of clinical attachment level (CAL) and probing depth (PD) varied between studies. Four studies used PD ≥ 4 mm and CAL ≥ 3 mm (Martinez-Herrera et al., 2015a, 2015b; Basher et al., 2017; MdTahir et al., 2020); four studies used PD and CAL ≥ 5 mm (Balli et al., 2016a, 2016b; Öngoz-Dede et al., 2016; Çetiner et al., 2019); two studies used PD and CAL ≥ 4 mm and ≥ 1 site with PD and CAL ≥ 5 mm (Gonçalves et al., 2015a, 2015b); two studies used PD ≥ 5 mm and CAL ≥ 3/4 mm (Zuza et al., 2016; Peralta et al., 2019); and two studies used PD ≥ 5 mm and CAL ≥ 2 mm (Altay et al., 2013; Taşdemir et al., 2016). Other scores were used by one report only: CAL ≥ 3 mm (Al-Zaharani et al., 2012); PD ≥ 5 mm and CAL ≥ 4 mm (Akram et al., 2016); PD ≥ 6 mm and CAL ≥ 5 mm (Montero et al., 2020); and PD and CAL ≥ 3mm (Cortelli et al., 2021).

FIGURE 1. Article screening process depicted in the PRISMA Flow Diagram



From: Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ 2021;372:n71. doi: 10.1136/bmj.n71. For more information, visit: http://www.prisma-statement.org/

Footnote: *, Only Montero et al. (2020) and MdTahir et al. (2020) returned the contact. The other three studies were not excluded, as data available only in graphics were extracted by the WebPlotDigitizer® version 4.4 program; **, the first 100 results of Google Schoolar search results were accessed for the eligibility criteria.

TABELE 1

Descriptive data on medical and periodontal condition

Study	Elegibility Criteria	Participants	Obesity	Periodontitis	Intervention	Control group	Periodontal maintenance phase | Follow-up
Al-Zahrani et al., 2012 Kingdon of Saudi Arabia BAS	IC: female, ≥ 35 years old, generalized moderate/severe chronic periodontitis and at least 20 remaining teeth EC: systemic diseases or infection, periodontal therapy in the previous 12 months, systemic antibiotic in the previous 3 months, pregnancy or lactation, smokers, antibiotic prophylaxis before periodontal treatment	*n* = 20 Mean age: 44. ± 8.4 years	BMI ≥ 30 kg/m^2	≥ 30 % of the sites with CAL ≥ 3 mm	NSPT and OHI	Before NSPT	NA 2-months follow-up
Altay et al., 2013 Turkey BAS	IC: > 25 years old, and ≥ 15 natural remaining teeth EC: antibiotic therapy within the previous 6 months and anti-inflammatory drugs within the previous 3 months, pregnancy or use of contraceptives or any other hormone therapy, periodontal treatment within the previous 24 months, and any systemic problem or treatment during the evaluation period of 3 months before and after periodontal treatment	*n* = 22 Males: 5 (22.7 %) Females: 17 (77.3 %) Mean age: 45.6 ± 23.8 years; and Age range: 35–68 years	BMI ≥ 30 kg/m^2 WC > 102 cm (males) and > 88 cm (females)	≥ 5 teeth with ≥ 1 sites with PD ≥ 5 mm and CAL ≥ 2 mm	FMD	Before NSPT	0.12 % chlorhexidine mouth rinse, b.i.d., for 14 days after NSPT Plaque control and OHR at days 1, 7, 14, and 30 3-months follow-up
Gonçalves et al., 2015a Brazil BAS	IC: > 30 years old, and ≥ 15 remaining teeth excluding third molars and teeth with advanced decay indicated for exodontia, generalized chronic periodontitis, HbA1c < 6.5 %, FPG 70-99 mg/dL, and CRP < 6 mg/L EC: pregnancy, lactation, current smoking and smoking within the past 10 years, prophylactic antibiotic coverage before	*n* = 18 Males: 72.2 % Females: 27.8 % Mean age: 48.8 ± 5.9 years	BMI ≥ 30 and < 40 kg/m^2 WHR ≥ 0.9 (males) and ≥ 0.85 (females)	> 30 % of the sites with PD and CAL ≥ 4 mm or ≥ 6 teeth with ≥ 1 site with PD and CAL ≥ 5 mm and BOP	NSPT	Before NSPT	Professional plaque control, OHR and SRP of deep sites presenting BOP 3- and 6-months post-therapy

	dental treatment, subgingival periodontal therapy in the previous 12 months, antimicrobial, anti-inflammatory, immunosuppressive, and lipid-lowering therapies in the previous 6 months, regular use of mouth rinses containing antimicrobials, orthodontic appliances, and presence of systemic conditions that could affect the progression of periodontitis and/or gain/loss of weight						6-months follow-up
Gonçalves et al., 2015b Brazil BAS	IC: > 30 years old, and ≥ 15 remaining teeth excluding third molars and teeth with advanced decay indicated for exodontia, generalized chronic periodontitis, HbA1c < 6.5 %, FPG 70-99 mg/dL, and CRP < 6 mg/L EC: pregnancy, lactation, current smoking and smoking within the past 10 years, prophylactic antibiotic coverage before dental treatment, subgingival periodontal therapy in the previous 12 months, antimicrobial, anti-inflammatory, immunosuppressive, and lipid-lowering therapies in the previous 6 months, regular use of mouth rinses containing antimicrobials, orthodontic appliances, and presence of systemic conditions that could affect the progression of periodontitis and/or gain/loss of weight	*n* = 20 Males: 11 (55 %) Females: 9 (45 %) Mean age: 50 ± 4.5 years	BMI ≥ 30 and < 40 kg/m^2 WHR ≥ 0.9 (males) and ≥ 0.85 (females)	> 30 % of the sites with PD and CAL ≥ 4 mm or ≥ 6 teeth with ≥ 1 site with PD and CAL ≥ 5 mm and BOP	NSPT	Before NSPT	Periodontal maintenance (non-specified) every 3 months post-therapy 12-months follow-up
Balli et al., 2016a Turkey BAS	IC: 30–49 years old, > 20 remaining teeth HbA1c < 6.5 %, and FPG < 100 mg/dL EC: aggressive periodontitis, periapical pathologies, exposure to mechanical force as a result of occlusion/orthodontics, systemic diseases such as cancer, HIV, diabetes mellitus or additional diseases which may interfere with adipokines levels and the periodontal conditions high-grade steroid therapies, radiation/immuno-suppressive therapies, pregnancy, lactation,	*n* = 20 Males: 9 (45 %) Females: 11 (55 %) Mean age: 40.56 ± 4.11 years	BMI ≥ 30 and < 40 kg/m^2 WHR ≥ 0.9 (males) and ≥ 0.85 (females)	PD and CAL ≥ 5mm with bone loss affecting > 30 % of existing teeth on clinical/radiographic examination	NSPT	Before NSPT	NA 6-weeks follow-up

	smoking over the past five years, allergic reaction to any kind of drug, no history of either periodontal or drug therapies within the preceding six months, namely anti-inflammatory treatments, and antibiotic courses or other pharmacological treatments						
Balli et al., 2016b Turkey BAS	IC: 30–49 years old, > 20 remaining teeth HbA1c < 6.5 %, and FPG < 100 mg/dL EC: aggressive periodontitis, periapical pathologies, exposure to mechanical force as a result of occlusion/orthodontics, systemic diseases such as cancer, HIV, diabetes mellitus or additional diseases which may interfere with adipokines levels and the periodontal conditions high-grade steroid therapies, radiation/immuno-suppressive therapies, pregnancy, lactation, smoking over the past five years, allergic reaction to any kind of drug, no history of either periodontal or drug therapies within the preceding six months, namely anti-inflammatory treatments, and antibiotic courses or other pharmacological treatments	*n* = 20 Males: 9 (45 %) Females: 11 (55 %) Age: 42 (36–46) years	BMI ≥ 30 and < 40 kg/m^2 WHR ≥ 0.9 (males) and ≥ 0.85 (females)	PD and CAL ≥ 5mm with bone loss affecting > 30 % of existing teeth on clinical/radiographic examination	NSPT	Before NSPT	NA 6-weeks follow-up
Öngöz Dede et al., 2016 Turkey BAS	IC: ≥ 20 remaining teeth excluding third molars, non-smokers who had never smoked, no history of systemic disease, had not undergone periodontal therapy or taken medicine for at least 6 months before the study, no pregnancy or lactation, and no alcohol or antioxidant vitamin consumption	*n* = 15 Males: 8 (53.3 %) Females: 7 (46.7 %) Mean age: 47.13 ± 7.17 years; and Age range: 34–60 years	BMI ≥ 30 kg/m^2	PD and CAL ≥ 5mm with bone loss affecting > 30 % of existing teeth on clinical/radiographic examination	Intensive hygiene phase and full-mouth NSPT, and the maintenance and monitoring of oral hygiene	Before NSPT	Periodontal maintenance and monitoring of oral hygiene (non-specified) 4-weeks follow-up
Taşdemir et al., 2016 Turkey	IC: > 25 years old, chronic periodontitis, obesity, ≥ 15 remaining teeth, and type 2 diabetes mellitus (in diabetes group)	*n* = 14 Males: 9 (64.3 %) Females: 5 (35.7 %)	BMI ≥ 30 kg/m^2 WC > 102 cm (males) and > 88 cm (females)	≥ 5 teeth with ≥ 1 sites with PD ≥ 5 mm and CAL ≥ 2 mm	Intensive full-mouth NSPT	Before FMT	NA 6-months follow-up

BAS	EC: antibiotic or anti-inflammatory drug use within the previous 6 months, pregnancy or lactation, periodontal therapy within the previous 6 months, smoking or history of smoking, alcohol consumption, and lipid lowering medications	Mean age: 49.2 ± 9.2; and Age range: 30–62 years					
Zuza et al., 2016 Brazil BAS	IC: 35–55 years old, both sexes, chronic periodontitis, and ≥ 20 remaining teeth EC: smokers or former smokers, antibiotics or anti-inflammatory in prior 3 months, diabetes, or other systemic diseases, pregnant or lactating women, use of hormones, mental or physical limitations, and periodontal therapy in the previous 12 months	*n* = 28 Males: 6 (21.4 %) Females: 22 (78.6 %) Mean age: 45.7 ± 8.4 years	BMI ≥ 30 and < 40 kg/m^2 WHR ≥ 0.9 (males) and ≥ 0.85 (females) WC >102 cm (male) and >88 cm (female) % of body fat ≥25% (male) ≥35% (female)	≥ 6 teeth with PD ≥5 mm and CAL ≥ 3 mm and BOP	NSPT and OHI and motivation	Before NSPT	3-months follow-up
Akram et al., 2017 Malaysia RCT	IC: 30–66 years old, chronic periodontitis, and ≥ 12 remaining teeth excluding third molars EC: pregnant or lactating mothers medical condition requiring prophylactic antibiotic administration before dental treatment, periodontal treatment during the previous 6 months, intellectual disability that might interfere with oral hygiene procedures, not Malaysian, presence of systemic conditions that could affect progression of periodontitis, or weight gain/loss or other inflammatory conditions	*n* = 62 CG = 31 and IG = 31 Males: 17 (27.4 %); CG = 9 (32.3 %) and IG = 8 (25.8 %) Females: 45 (72.6 %); CG = 22 (67.7 %) and IG = 23 (74.2 %) Mean age: CG = 44.84 ± 9.02 years and IG = 44.68 ± 10.63 years	BMI ≥ 27.5 kg/m^2 WHR ≥ 0.9 (males) and ≥ 0.85 (females)	≥ 2 interproximal sites with PD ≥ 5 mm (different teeth) or ≥ 2 interproximal sites with CAL ≥ 4 mm (different teeth)	NSPT, OHI and 0.12 % chlorhexidine mouth rinse	No periodontal therapy or oral hygiene instruction	Professional prophylaxis, re-motivation and OHR 6-weeks and 3-months follow-up

Basher et al., 2017 Malaysia RCT	IC: malaysians, ≥ 30 years old, chronic periodontitis, obesity, and ≥ 12 remaining teeth EC: periodontal treatment within the past 6 months, antibiotic treatment within the past 4 months, require prophylactic antibiotic coverage, use of systemic or topical NSAIDs for the past 4 months, pregnant or intend to and lactating mothers, mentally handicapped, rheumatic heart disease, and valve replacement	*n* = 62 CG = 31 and IG = 31 Males: 18 (29 %); CG = 10 (32.25 %) and IG = 8 (25.8 %) Females: 44 (71 %); CG = 21 (67.75 %) and IG = 23 (74.20 %) Mean age: CG = 44.85 ± 9.02 years and IG = 45.03 ± 10.72 years	BMI ≥ 27.5 kg/m^2	≥ 2 interproximal sites with PD ≥ 4 mm and ≥ 2 interproximal sites with CAL ≥ 3 mm (different teeth) or one site with PD ≥ 5 mm	NSPT, OHI and 0.12 % chlorhexidine mouth rinse	No periodontal therapy or oral hygiene instruction	Professional prophylaxis, re-motivation and OHR 3-months follow-up
Martínez-Herrera et al., 2018a Spain BAS	EC: aggressive periodontitis, < 14 remaining teeth, infectious or other inflammatory diseases, periodontal therapy in the last 6 months or antibiotics in the last 3 months, treatment with systemic anti-inflammatory drugs, pregnancy or lactation, secondary obesity, antibiotic treatment before the dental intervention, and diabetes mellitus	At baseline, *n* = 96 Males: 29 % Females: 71 % Mean age: 42.7 ± 10.2 years After 3 months, *n* = 74	BMI ≥ 30 kg/m^2	≥ 4 teeth with ≥1 sites with PD ≥ 4 mm and CAL ≥ 3 mm	Intensive full-mouth NSPT, OHI and 0.12 % chlorhexidine mouth rinse	Before NSPT	Periodontal examinations at 3 months post-therapy 3-months follow-up
Martínez-Herrera et al., 2018b Spain BAS	EC: aggressive periodontitis, < 14 remaining teeth, infectious or other inflammatory diseases, periodontal therapy in the last 6 months or antibiotics in the last 3 months, treatment with systemic anti-inflammatory drugs, pregnancy or lactation, secondary obesity, antibiotic treatment before the dental intervention, and diabetes mellitus	*n* = 47 Males: 31.9 % Females: 68.1 % Mean age: 44.4 ± 10.4 years	BMI ≥ 30 kg/m^2	≥ 4 teeth with ≥ 1 sites with PD ≥ 4 mm and CAL ≥ 3 mm	Intensive full-mouth NSPT, OHI and 0.12 % chlorhexidine mouth rinse	Before NSPT	Periodontal examinations at 3-months post-therapy 3-months follow-up
Çetiner et al., 2019	IC: > 20 years old, > 22 remaining teeth, and no systemic diseases	*n* = 21 Females: 100 %	BMI ≥ 30 kg/m^2	≥ 30 % of the sites with bone loss and ≥ 2 non-adjacent teeth with ≥ 1 sites with	Intensive full-mouth NSPT	Before FMT	NA

Turkey BAS	EC: localized chronic periodontitis, receiving periodontal therapy/surgery in the last 6 months, pregnancy or use of any hormone therapy, antibiotic or anti-inflammatory drug therapy within the last 6 months, smoker, lactating, aggressive periodontitis, and periapical pathologies	Mean age: 44.67 ± 10.87 years	WC > 102 cm (males) and > 88 cm (females)	PD ≥ 5 mm and CAL ≥ 5 mm in each quadrant and BOP			3-months follow-up
Peralta et al., 2019 Brazil BAS	IC: ≥ 45 years old, both sexes, moderate, severe, and advanced periodontitis, and ≥ 12 remaining teeth EC: orthodontic devices, pregnancy or breast-feeding, systemic diseases or other conditions that could influence the periodontal status (other than diabetes), alcohol abuse, prophylactic antibiotic coverage, systemic antibiotics and/or anti-inflammatory drugs six months prior to the study, and periodontal therapy within six months prior to the study	*n* = 55 Males: 19 (34.5 %) Females: 36 (65.5 %) Mean age: 48.9 ± 7.8 years	BMI ≥ 30 kg/m^2 WC > 102 cm (males) and > 88 cm (females)	Stage II: interdental PD ≤ 5 mm, CAL 3 to 4 mm, and radiographic bone loss at coronal third between 15 % to 33 % Stage III and IV: PD ≥ 6 mm, interdental CAL ≥ 5 mm, and radiographic bone loss extending to mild-third of the root	FMD	Before NSPT	0.12 % chlorhexidine mouth rinse for 14 days post-therapy Every 3-months, OHR, supragingival dental scaling and professional prophylaxis
Md Tahir et al., 2020 Malaysia BAS	IC: > 30 years old, obesity and normal weight, and ≥ 12 remaining teeth EC: history of periodontal therapy in last 6 months, on antibiotics and topical/systemic steroid treatment in last 4 months, pregnancy, lactating mothers, mentally handicapped, and valve replacement and rheumatic heart disease which require antibiotic coverage	*n* = 18 Males: 6 (33.3 %) Females: 12 (66.7 %) Mean age: 44.7 ± 2.4 years	BMI ≥ 30 kg/m^2	≥ 2 interproximal sites with PD ≥ 4 mm and ≥ 2 interproximal sites with CAL ≥ 3 mm (different teeth) or one site with PD ≥ 5 mm	Intensive full-mouth NSPT and OHI Root surface debridement at sites with PD ≥ 5mm Periodontal pockets irrigated with 0.12 % chlorhexidine 0.12 % chlorhexidine mouth rinse	Before NSPT	15 mL 0.12 % chlorhexidine mouth rinse, t.i.d., for 14 days post-therapy 3-months follow-up

Montero et al., 2020 Spain RCT	IC: 35–65 years old, metabolic syndrome [MetS (at least, 3 risk factors: WC ≥ 94 cm in men and ≥ 80 cm in women, triglycerides ≥150 mg/dL, HDL < 40 mg/dL in males and < 50 mg/dL in females, BP systolic ≥ 130 and/or diastolic ≥ 85 mm Hg, FPG ≥ 100 mg/dL)], stages III-IV generalized periodontitis, and ≥ 16 remaining teeth EC: uncontrolled systemic diseases other than diabetes or hypertension, surgical treatment in the previous 3 months, alcoholism or psychiatric disorders, systemic antibiotic in the previous 3 months, NSPT in the previous 6 months, or surgical periodontal treatment over the previous 12 months	*n* = 63 CG = 31 and IG = 32 Males: 44 (69.8 %); CG = 22 (70.9 %) and IG = 22 (68.8 %) Females: 19 (30.2 %); CG = 9 (29.1 %) and IG = 10 (31.2 %) Mean age: CG = 58.3 ± 5.8 years and IG = 56.7 ± 6.5 years	WC ≥ 94 cm (males) and ≥ 80 cm (females)	≥ 8 sites with PD ≥ 6 mm and 4 sites with CAL ≥ 5 mm in ≥ 2 different quadrants	NSPT, OHI and administration of a systemic antibiotic (azithromycin 500 mg, q.d., for 3 days), administered at the last session of SRP	Minimal periodontal therapy (supragingival professional mechanical plaque and calculus removal) + administration of placebo medication for 3 days + OHI	0.12 % chlorhexidine and 0.05 % cetylpyridinium chloride mouth rinse for 14 days post-therapy professional prophylaxis in both groups at the 3- and 6-months post-therapy 6-months follow-up
Cortelli et al., 2021 Brazil BAS	IC: ≥ 45 years old, both genders, moderate to advanced generalized periodontitis (Stage II-IV), and ≥ 12 remaining teeth EC: chronic renal failure, stroke history, not controlled diabetes, rheumatism, osteoporosis, HIV, acute myocardial infarction 6 months before the study, pregnant and lactating, and periodontal treatment in last year	*n* = 55 Males: 19 (34.5 %) Females: 36 (65.5 %) Mean age: 48.9 ± 7.8 years	BMI ≥ 30 kg/m^2 WC > 102 cm (males) and > 88 cm (females)	Interproximal CAL detectable in ≥ 2 teeth (non-adjacent) or PD > 3 mm and CAL ≥ 3 mm in ≥ 2 teeth	FMD	Before NSPT	0.12 % chlorhexidine mouth rinse for 14 days post-therapy Every 3 months, OHR, professional prophylaxis and supragingival debridement 6-months follow-up

Legend: RCT, randomized controlled trial; BAS, before and after (pre-post) study; IC, inclusion criteria; EC, exclusion criteria; CG, control group; IG, intervention group; NSAID, non-steroidal anti-inflammatory drugs; PD, probing depth; CAL, clinical attachment level/loss; BOP, bleeding on probing; HDL, high density lipoprotein cholesterol; BP, blood pressure; FPG, fasting plasma glucose; HbA1c, glycated hemoglobin; FPG, fasting plasma glucose; CRP, C-reactive protein; *n*, sample size; Age, mean (standard deviation) or median (percentile 25–75); BMI, body mass index; WC, waist circumference; WHR, waist-hip ratio; NSPT, non-surgical periodontal therapy (supragingival plaque and calculus removal and subgingival scaling and root planning); FMD, full-mouth disinfection protocol adapted from Quirynen et al. (1995); OHI, oral hygiene instructions; OHR, oral hygiene reinstructions; NA, data not available.

Results of individual studies. Individual descriptive data from included studies are presented in Table 2 for RCT's outcomes, and Table 3 for BAS's outcomes.

Result of syntheses

RCT studies

Blood pressure. Systolic blood pressure was significantly reduced at 3-months follow-up in the IG compared with the CG, after adjustment for covariates (7.3 mmHg; 95 % CI = 1.9 to 12.6; $p = 0.008$). The reduction for diastolic blood pressure in favor to the IG lasted for six months after NSPT: i- 3-months follow-up: 7.8 mmHg, 95 % CI = 1.3 to 14.4 ($p = 0.019$); and ii- 6-months follow-up: 11 mmHg, 95 % CI = 2.9 to 19.1 ($p = 0.009$) (Montero et al., 2020). According to the authors, no other metabolic, vascular and renal parameters showed any significant difference.

Blood hematological and biochemical index. Three months after NSPT, HbA1c decreased in the IG compared with the CG—difference adjusted for covariates = 0.3 % (95 % CI = 0.1 to 0.6; $p = 0.013$). The proportion of patients with HbA1c ≥ 7 % decreased significantly in the IG, from 31.25 % at baseline to 18.8 % at 3-months follow-up ($p = 0.028$), with no changes in the CG (Post hoc analyses); no differences between both groups were observed six months after NSPT. The multilevel linear regression determined that the variance in HbA1c was only predicted by being in the IG ($p = 0.013$) and by the baseline HbA1c percentage ($p < 0.001$), without any significant additional effect in the model for age, sex, BMI or smoking status. In addition, no differences between the CG and the IG were observed for white blood cells count, fibrinogen and α-1 antitrypsin at any time point after therapy (Montero et al., 2020).

Montero et al. (2020) reported a decrease in the mean hsCRP concentration after three and six months in the IG, but not in the CG. The difference between groups, adjusted for age, sex, smoking, baseline BMI, and hsCRP was 1.4 mg/L (95 % CI = 0.5 to 2.2; $p = 0.001$) at three months and 1.2 mg/L (95 % CI = 0.4 to 2.0; $p = 0.004$) at 6-months follow-up. The odds ratio for GI versus GC going from an hsCRP value ≥ 3 to < 3 mg/L was 5.4 (95 % CI = 1.0 to 31.6; $p = 0.040$). 68.8 % of patients in the IG experienced a reduction in hsCRP levels within 6-months follow-up, while this percentage was 29 % in the CG ($p < 0.001$). The NSPT led to a 30.8 % reduction in hsCRP from baseline and a difference of 1.2 mg/L at 6-months follow-up compared to the GC. Improvements in periodontal health, despite actively following strict cardiovascular risk reduction protocols, significantly improved hsCRP levels and therefore their cardiovascular risk. In multilevel linear regression, baseline hsCRP levels ($p < 0.001$) and being a smoker ($p =$

0.014) significantly and independently predicted the variance of hsCRP decline over six months in the IG.

Cytokines and chemokine. Montero et al. (2020) reported a significant decrease in IL-1β and TNF-α at 3-months follow-up in the IG compared with the CG. However, no differences between the groups were observed for these biomarkers at 6-months follow-up, or for IL-6 and IL-8 at any time point after therapy.

Adipokines. In the study by Akram et al. (2016), the mean resistin level differed between the CG and IG (14.25 ± 4.58 ng/mL and 12.26 ± 1.24 ng/mL, respectively; $p < 0.05$). There was a significant reduction in resistin after periodontal therapy ($p < 0.05$) in the IG but not in the CG (mean difference 0.65 ± 1.24 ng/mL and 0.78 ± 4.08 ng/mL, respectively)—logistic regression analysis revealed that change in salivary resistin level was not significantly associated with improvement in PD or CAL, even after smoking control ($p > 0.05$). According to the authors, resistin level did not differ between the CG and IG at 12-weeks follow-up.

Microbiological evaluation. Montero et al. (2020) also reported counts of anaerobic bacteria and high proportions and counts of *Porphyromonas gingivalis* (*Pg*) in all patients at baseline. The NSPT significantly reduced both the counts of anaerobic bacteria and *Pg*, and this microbiological impact was associated with significant reductions in hsCRP.

Quality of life. Regarding quality of life, Basher et al. (2017) reported a decrease in OHIP-14 PI and OHIP-14 EI and an increase in OHIP-14 SS over time in both groups ($p < 0.05$). The mean OHIP-14 EI at 12 weeks post-NSPT decreased in both CG and IG at 0.65 (1.02 %) and 0.47 (0.91 %), respectively, suggesting a significant improvement at the subject's self-perception level of OHRQoL (Oral Health-Related Quality of Life). A detailed comparison of the OHIP-14 items revealed that only "bad breath" (functional limitation domain) and "food impaction" (psychological discomfort domain) were significantly reduced ($p < 0.05$) (Basher et al., 2017). According to the authors, quality of life did not differ between the CG and IG.

Table 2

Primary outcome measures for RCT studies							
		Akram et al., 2017		Basher et al., 2017		Montero et al., 2020	
Object of investigation	**Follow-up**	**CG** (*n*=31)	**IG** (*n*=31)	**CG** (*n*=31)	**IG** (*n*=31)	**CG** (*n*=31)	**IG** (*n*=32)
Blood hematological and biochemical index							
High-sensitivity C-reactive protein (hsCRP) - mg/L	Baseline	-	-	-	-	3.9 ± 3.4^{A}	3.9 ± 2.9^{A}
	3 months	-	-	-	-	3.9 ± 0.6^{B}	2.7 ± 0.4^{B}
	6 months	-	-	-	-	4 ± 0.8^{B}	2.9 ± 0.4^{B}
Fibrinogen - mg/dL	Baseline	-	-	-	-	398.5 ± 89.1^{A}	419.7 ± 108.7^{A}
	3 months	-	-	-	-	398.3 ± 17.9^{B}	421.8 ± 20.4^{B}
	6 months	-	-	-	-	400.5 ± 16.1^{B}	419.6 ± 21.8^{B}
White blood cells count - K/µL	Before	-	-	-	-	7.5 ± 1.7^{A}	7.8 ± 1.9^{A}
	3 months	-	-	-	-	7.8 ± 0.3^{B}	7.5 ± 0.4^{B}
	6 months	-	-	-	-	7.6 ± 0.2^{B}	7.9 ± 0.7^{B}
Glycated hemoglobin (Hba1c) - %	Before	-	-	-	-	6 ± 1^{A}	6.3 ± 1.2^{A}
	3 months	-	-	-	-	6.1 ± 0.2^{A}	5.9 ± 0.1^{A}
	6 months	-	-	-	-	6.1 ± 0.2^{A}	6 ± 0.1^{A}
Fasting plasma glucose - mg/dL	Before	-	-	-	-	133 ± 51.7^{A}	128.6 ± 30.3^{A}

	3 months	-	-	-	-	130 ± 8.8[B]	123.3 ± 7.9[B]
	6 months	-	-	-	-	130.5 ± 9.7[B]	121 ± 6.3[B]
Fasting insulin - mIU/L	Before	-	-	-	-	14.5 ± 9.3[A]	19.3 ± 10.8[A]
	3 months	-	-	-	-	14.1 ± 1.4[B]	17.2 ± 2.9[B]
	6 months	-	-	-	-	14.4 ± 1.7[B]	14.3 ± 2.1[B]
Total cholesterol - mg/dL	Before	-	-	-	-	189.4 ± 48.4[A]	174.8 ± 34.7[A]
	3 months	-	-	-	-	180.6 ± 8.1[B]	184 ± 8.4[B]
	6 months	-	-	-	-	189.9 ± 9.2[B]	183.5 ± 7.5[B]
High density lipoprotein cholesterol (HDL) - mg/dL	Before	-	-	-	-	46.9 ± 12.4[A]	46.1 ± 13.3[A]
	3 months	-	-	-	-	47.1 ± 3.1[B]	46.2 ± 3.8[B]
	6 months	-	-	-	-	48.4 ± 2.7[B]	47.2 ± 2.7[B]
Low density lipoprotein cholesterol (LDL) - mg/dL	Before	-	-	-	-	105.7 ± 44.9[A]	114.3 ± 34.7[A]
	3 months	-	-	-	-	103.5 ± 7[B]	109.6 ± 8.5[B]
	6 months	-	-	-	-	107.5 ± 8.3[B]	107.6 ± 6.6[B]
Triglycerides - mg/dL	Before	-	-	-	-	136.6 ± 42.5[A]	129.5 ± 52.3[A]
	3 months	-	-	-	-	155.4 ± 17.5[B]	136.5 ± 9.7[B]
	6 months	-	-	-	-	131.7 ± 8.3[B]	125.6 ± 9.7[B]
Creatinine - mg/dL	Before	-	-	-	-	0.9 ± 0.3[A]	0.9 ± 0.5[A]
	3 months	-	-	-	-	0.9 ± 0.1[B]	1.0 ± 0.1[B]

	6 months	-	-	-	-	1 ± 0.1^{B}	1.0 ± 0.1^{B}
α-1 antitrypsin - mg/dL	Before	-	-	-	-	138.5 ± 28.1^{A}	145.6 ± 29.7^{A}
	3 months	-	-	-	-	130 ± 5^{B}	138.4 ± 6.2^{B}
	6 months	-	-	-	-	127.6 ± 5.2^{B}	137.5 ± 5.7^{B}
Homeostatic model assessment 2 (HOMA2) β-cell function	Before	-	-	-	-	92.7 ± 50.6^{A}	104.8 ± 69^{A}
	3 months	-	-	-	-	87.2 ± 10.6^{B}	106 ± 14.8^{B}
	6 months	-	-	-	-	100.4 ± 11.9^{B}	106.1 ± 14^{B}
Homeostatic model assessment 2 (HOMA2) insulin sensitivity	Before	-	-	-	-	62.6 ± 28^{A}	59 ± 55.3^{A}
	3 months	-	-	-	-	57.9 ± 5.4^{B}	67 ± 13.6^{B}
	6 months	-	-	-	-	59.7 ± 5.3^{B}	65.8 ± 11.6^{B}
Homeostatic model assessment 2 (HOMA2) insulin resistance	Before	-	-	-	-	2 ± 1.2^{A}	2.6 ± 1.4^{A}
	3 months	-	-	-	-	2 ± 0.2^{B}	2.3 ± 0.4^{B}
	6 months	-	-	-	-	2 ± 0.2^{B}	2.2 ± 0.3^{B}
Systemic biomarkers of inflammation							
Resistin - ng/mL (blood serum)	Baseline	14.25 ± 4.58^{A}	12.26 ± 1.24^{A}	-	-	-	-
	3 months	13.47 ± 5.20^{A}	11.62 ± 0.90^{A}	-	-	-	-
Interlukin-1β (IL-1β) - pg/mL (blood serum)	Baseline	-	-	-	-	1.9 ± 1.2^{A}	1.5 ± 0.9^{A}
	3 months	-	-	-	-	2.3 ± 0.5^{B}	0.9 ± 0.1^{B}

	6 months	-	-	-	-	1.5 ± 0.2[B]	1.5 ± 0.2[B]
Interleukin-6 (IL-6) - pg/mL (blood serum)	Baseline	-	-	-	-	2.8 ± 1.9[A]	2.2 ± 1.8[A]
	3 months	-	-	-	-	2.6 ± 0.4[B]	1.9 ± 0.4[B]
	6 months	-	-	-	-	2.5 ± 0.4[B]	2.0 ± 0.4[B]
Interleukin-8 (IL-8) - pg/mL (blood serum)	Baseline	-	-	-	-	5.4 ± 3[A]	6.9 ± 9.7[A]
	3 months	-	-	-	-	5.4 ± 0.8[B]	4.6 ± 1.1[B]
	6 months	-	-	-	-	6 ± 1.2[B]	5 ± 1.2[B]
Tumor necrosis factor-α (TNF-α) - pg/mL (blood serum)	Baseline	-	-	-	-	8.7 ± 8.6[A]	7.9 ± 6.2[A]
	3 months	-	-	-	-	10 ± 2.3[B]	6.4 ± 0.8[B]
	6 months	-	-	-	-	8.2 ± 1.4[B]	6.3 ± 0.8[B]
Quality of Life							
Oral Health Impact Profile (OHIP PI)	Baseline	-	-	19 ± 61.29[A]	21 ± 67.74[A]	-	-
	3 months	-	-	12 ± 38.71[A]	10 ± 32.26[A]	-	-
Oral Health Impact Profile (OHIP SS)	Baseline	-	-	58.29 ± 6.12[A]	57.2 ± 8.61[A]	-	-
	3 months	-	-	60.95 ± 6.64[A]	61.89 ± 7.04[A]	-	-
Oral Health Impact Profile (OHIP EI)	Baseline	-	-	1.5 ± 1.53[A]	1.62 ± 1.84[A]	-	-
	3 months	-	-	0.65 ± 1.02[A]	0.47 ± 0.91[A]	-	-
Periodontal pathogens count/group							

Porphyromonas gingivalis (log of CFU)	Baseline	-	-	-	-	13.3 ± 2.1[A]	11.3 ± 5.7[A]
	3 months	-	-	-	-	11.8 ± 1[B]	3.8 ± 0.9[B]
	6 months	-	-	-	-	11.8 ± 1.1[B]	4.5 ± 1[B]
Prevotella intermedia (log of CFU)	Baseline	-	-	-	-	11.2 ± 3.7[A]	10.3 ± 5.1[A]
	3 months	-	-	-	-	10.3 ± 1[B]	4.2 ± 1[B]
	6 months	-	-	-	-	9.9 ± 1[B]	6.2 ± 1[B]
Aggregatibacter actinomycetemcomitans (log of CFU)	Baseline	-	-	-	-	0	0.9 ± 2.8[A]
	3 months	-	-	-	-	0.4 ± 0.4[B]	0
	6 months	-	-	-	-	0	0.1 ± 0.1[B]
Tannerella forsythia (log of CFU)	Baseline	-	-	-	-	6.3 ± 6.1[A]	6.7 ± 6.3[A]
	3 months	-	-	-	-	6.1 ± 1.3[B]	0.3 ± 0.3[B]
	6 months	-	-	-	-	5.2 ± 1.3[B]	2.4 ± 0.8[B]
Parvimonas micra (log of CFU)	Baseline	-	-	-	-	1.3 ± 3.4[A]	2 ± 4.6[A]
	3 months	-	-	-	-	1.8 ± 0.9[B]	1.4 ± 0.7[B]
	6 months	-	-	-	-	0.7 ± 0.5[B]	0.3 ± 0.3[B]
Fusobacterium nucleatum (log of CFU)	Baseline	-	-	-	-	10 ± 4.1[A]	8 ± 5.6[A]
	3 months	-	-	-	-	9.4 ± 1.1[B]	6.4 ± 0.9[B]
	6 months	-	-	-	-	8.3 ± 1.2[B]	6.1 ± 0.9[B]
Campylobacter rectus (log of CFU)	Baseline	-	-	-	-	NA	1.1 ± 3.4[A]

	3 months	-	-	-	-	0.9 ± 0.6[B]	0.7 ± 0.5[B]
	6 months	-	-	-	-	0	1.0 ± 0[B]
Eikenella corrodens (log of CFU)	Baseline	-	-	-	-	2.4 ± 4.7[A]	1.9 ± 4.2[A]
	3 months	-	-	-	-	2.4 ± 0.9[B]	1.2 ± 0.6[B]
	6 months	-	-	-	-	3.3 ± 1[B]	1.2 ± 0.6[B]
Capnocytophaga spp. (log of CFU)	Baseline	-	-	-	-	1.7 ± 4.1[A]	1.3 ± 3.5[A]
	3 months	-	-	-	-	2 ± 0.8[B]	1 ± 0.6[B]
	6 months	-	-	-	-	0.4 ± 0.4[B]	1.2 ± 0.6[B]

Legend: CG, control group; IG, intervention group; *n*, sample size; OHIP-14 (Oral Health Impact Profile-14): PI_ prevalence of impact, SS_ severity score, and EI_ extent of impact; CFU, colony-forming units; [A], mean ± standard deviation; [B], mean ± standard error; -, variable not assessed by the authors; NA, data not available.

BAS studies

Blood hematological and biochemical index. Although the slight improvement in metabolic parameters after periodontal therapy, Altay et al. (2013) reported a significant reduction in serum levels of HOMA-IR score and Martínez-Herrera et al. (2018a) reported a significant decrease in RBP4 three months after NSPT. There was also a significant improvement in anthropometric and metabolic parameters and C3 (immunity) 12 weeks after NSPT in the obesity diet group ($p < 0.05$) (Martinez-Herrera et al., 2018a). Al Zahrani et al., 2012 reported a mean difference in hsCRP of 0.19 ± 0.32 (pre- post-treatment, $p = 0.015$). According to Zuza et al. (2016), patients with obesity and periodontitis who received basic periodontal therapy exhibited significant reduction in the serological levels of total cholesterol, low-density lipoprotein, triglycerides and hsCRP 90 days after NSPT. In contrast, Altay et al. (2013), Taşdemir et al. (2016) and Martínez-Herrera et al. (2018a, 2018b) reported a non-significant reduction in hsCRP after NSPT.

Cytokines. Altay et al. (2013), Taşdemir et al. (2016) and Martínez-Herrera et al. (2018a, 2018b) reported a decrease in serum TNF-α levels after NSPT. Balli et al. (2016b) reported the same result in GCF. According to Gonçalves et al. (2015b), concentrations of TNF-α and leptin increased in shallow and deep sites of patients with obesity at 6- and 12-months follow-up compared to baseline ($p < 0.05$). There were no statistically significant changes in the GCF levels of IL-6 and resistin, and in the serum levels of any adipokines at any time-point after therapy. In contrast, Çetiner et al. (2018) did not observe a significant decrease in TNF-α in the GCF after NSPT. Furthermore, serum PTX-3 levels were not significantly reduced after NSPT (Taşdemir et al., 2016).Seven studies evaluated the concentration of IL-6 in serum (Altay et al., 2013; Taşdemir et al., 2016; Çetiner et al., 2018; Martínez-Herrera et al., 2018a, 2018b) and in the GCF (Gonçalves et al., 2015a, 2015b; Balli et al., 2016a). Only two studies (2:5 ratio, 28.57 %) reported significant reductions in serum and GCF IL-6 (Altay et al., 2013 and Balli et al., 2016a, respectively).

Adipokines. Altay et al. (2013) reported a reduction in serum leptin levels after NSPT, although Gonçalves et al. (2015a) reported no changes in serum leptin levels three and six months after NSPT. Periodontal therapy reduced the GCF levels of chemerin, vaspin, omentin-1 and visfatin in the GCF (Balli et al., 2016a, 2016b; Çetiner et al., 2018) and increased leptin levels in the shallow and deep sites 12 months after therapy, compared to baseline (Gonçalves et al., 2015b) ($p < 0.05$). There were no statistically significant changes in the serum and GCF levels of resistin and adiponectin at any time-point after NSPT (3-, 6- and 12-months follow-up) (Gonçalves et al., 2015a, 2015b; Md Tahir et al., 2020).

Oxidative stress. Levels of 8-OHdG in plasma, saliva and GCF significantly decreased after NSPT ($p < 0.01$) (Öngöz Dede et al., 2016).

Microbiological evaluation. In the study by Peralta et al. (2019), within nine months, *Pg* and *Aggregatibacter actinomycetemcomitans* (*Aa*) significantly decreased ($p < 0.05$). Small counts of *Tannerella forsythia* (*Tf*) were observed only at 3-months follow-up; however, the reductions *Tf* count at were not maintained at 9-months follow-up. NSPT also reduced *Treponema denticola* (*Td*) count ($p < 0.05$). In contrast, Md Tahir et al. (2020) reported no significant changes in mean *Pg* and *Tf* counts at 12-weeks follow-up. According to the authors, the mean *Prevotella intermedia* (*Pi*) count decreased by almost half after 12 weeks after the NSPT.

Quality of life. OHQoL (Oral Health-Related Quality of Life) increased and OIDP (Oral Impact on Daily Performance) decreased six months after NSPT ($p < 0.05$). Regarding OIDP, pain, discomfort and functional limitation significantly improved at six months follow-up. The prevalence of oral impacts on daily activities, such as eating and enjoying food and cleaning teeth, significantly decreased six months after NSPT (Cortelli et al., 2021).

Risk of bias in studies. All RCT included in this review were considered high methodological quality (Akram et al., 2017; Basher et al., 2017; Montero et al., 2020), as evidenced by the low risk of (Figure 4A). Nine of 15 BAS studies were classified as low risk of bias (Al-Zaharani et al., 2012; Gonçalves et al., 2015a, 2015b; Balli et al., 2016a, 2016b; öngoz-Dede et al., 2016; Taşdemir et al., 2016; Zuza et al., 2016; Çetiner et al., 2018). Bias due to confounding and bias due to missing data domains accounted for the low methodological quality of the BAS studies [serious risk of bias: Altay et al., 2013, Martinez-Herrera et al., 2018a, 2018b; and Cortelli et al., 2021; and critical risk of bias: Peralta et al., 2019; MdTahir et al., 2020; and MdTahir et al., 2020 (Figure 4B)].

Certainty of evidence. Regardless of the variation in the approach of the applied intervention, outcome assessed, type of sample, and evaluation time, the overall certainty of the evidence ranged from moderate (evidence from RCT) to low or very low (evidence from BAS studies). The evidence from RCT was seriously affected for the imprecision item due to the small number of individuals included in the syntheses. It is important to mention that some aspects such as the precision of the estimates and consistency of the results could not be evaluated because meta-analysis was not performed and the syntheses for all outcomes always included a single RCT, respectively. On the other hand, the evidence from BAS studies was seriously or very seriously affected for the risk of bias item, seriously affected for the inconsistency item in most of the syntheses that included more than one study, and seriously affected for the imprecision item due to the insufficient number of subjects evaluated.

Table 3. Descriptive data on primary outcomes for BAS.

Descriptive data on primary outcomes for BAS								
Object of investigation	**Follow-up**	**Al-Zahrani et al., 2012** (*n* = 20)	**Altay et al., 2013** (*n* = 22)	**Gonçalves et al., 2015a** (*n* = 18)	**Gonçalves et al., 2015b** (*n* = 20)	**Balli et al., 2016a** (*n* = 20)	**Balli et al., 2016b** (*n* = 20)	**Óngoz-Dede et al., 2016** (*n* = 15)
Blood hematological and biochemical index								
High-sensitivity C-reactive protein (hsCRP) - mg/L	Baseline	0.96 ± 0.41[A]	3.3 (3.2 to 6)[C]	-	-	-	-	-
	2 months	Δ = 0.19 ± 0.32[A]	-	-	-	-	-	-
	3 months	-	3 (3.1 to 4.1)[C]	-	-	-	-	-
Fasting blood glucose - mg/dL	Before	-	104 (93 to 115)[C]	-	-	-	-	-
	3 months	-	97 (83 to 109)[C]	-	-	-	-	-
Insulin - μU/mL	Before	-	16.8 (11.5 to 24.8)[C]	-	-	-	-	-
	3 months	-	15.1 (7.1 to 17.8)[C]	-	-	-	-	-
Homeostasis model assessment of insulin resistance (HOMA-IR)	Before	-	4.9 (1.1 to 11.8)[C]	-	-	-	-	-
	3 months	-	3.6 (0.79 to 7.8)[C]	-	-	-	-	-
Total cholesterol - mg/dL	Before	-	194 ± 37[A]	-	-	-	-	-

	3 months	-	188 ± 31[A]	-	-	-	-	-
High density lipoprotein cholesterol (HDL) - mg/dL	Before	-	41 ± 9[A]	-	-	-	-	-
	3 months	-	41 ± 7[A]	-	-	-	-	-
Low density lipoprotein cholesterol (LDL) - mg/dL	Before	-	107 (96 to 134)[C]	-	-	-	-	-
	3 months	-	103 (91 to 128)[C]	-	-	-	-	-
Triglycerides - mg/dL	Before	-	167 (135 to 224)[C]	-	-	-	-	-
	3 months	-	162 (113 to 202)[C]	-	-	-	-	-
Lipoprotein-a - g/L	Baseline	-	0.15 (0.1 to 0.22)[C]	-	-	-	-	-
	3 months	-	0.14 (0.1 to 0.2)[C]	-	-	-	-	-
Systemic biomarkers of inflammation								
Tumor necrosis factor-α (TNF-α) - mg/L[¢] or pg/mL[¥] (blood serum)	Before	-	5.4 (3 to 9.1)[C¢]	-	3 ± 0.8[A¥]	-	-	-
	3 months	-	3.3 (2.8 to 5.5)[C¢]	-	3.1 ± 1.4[A¥]	-	-	-
	6 months	-	-	-	3.1 ± 1[A¥]	-	-	-
	12 months	-	-	-	2.9 ± 1[A¥]	-	-	-

Tumor necrosis factor-α (TNF-α) - pg/mL (gingival crevicular fluid)	Baseline	-	-	-	-	-	10.8 (6.2 up to 14.2)[D]	-
	6 weeks	-	-	-	-	-	3.8 (3.1 up to 4.8)[D]	-
Interleukin-6 (IL-6) - ng/L[£] or pg/mL[¥] (blood serum)	Before	-	1.1 (0.8 to 1.9)[C£]	-	2.7 ± 1.6[A¥]		-	-
	3 months	-	0.6 (0.3 to 1.4)[C£]	-	2.9 ± 0.9[A¥]	-	-	-
	6 months	-	-	-	2.3 ± 0.8[A¥]	-	-	-
	12 months	-	-	-	2.3 ± 0.8[A¥]	-	-	-
Interleukin-6 (IL-6) - pg/mL (gingival crevicular fluid)	Baseline	-	-	-	-	2.3 (2 up to 2.7)[D]	-	-
	6 weeks	-	-	-	-	0.7 (0.3 up to 1.2)[D]	-	-
Resistin - ng/mL x 5 (blood serum)	Before	-	-	-	2.9 ± 1.7[A]	-	-	-
	3 months	-	-	-	3.3 ± 1.7[A]	-	-	-
	6 months	-	-	-	3.3 ± 2[A]	-	-	-
	12 months	-	-	-	3.2 ± 2.3[A]	-	-	-
Leptin - ng/L[£] or pg/mL[¥] x 100 (blood serum)	Baseline	-	17.5 (4.3 to 43.9)[C£]	441.8 ± 213.7[A¥]	481.8 ± 415.5[A¥]	-	-	-
	3 months	-	14.4 (3.2 to 35.4)[C£]	475.7 ±194.8[A¥]	381 ± 301.8[A¥]	-	-	-
	6 months	-	-	421.8 ± 266.7[A¥]	319.3 ± 141.7[A¥]	-	-	-

	12 months	-	-	-	400.9 ± 391[A¥]	-	-	-
Adiponectin - ng/mL x 100 (blood serum)	Baseline	-	-	52.5 ± 36[A]	62.2 ± 43.2[A]	-	-	-
	3 months	-	-	49.1 ± 25.6[A]	70.7 ± 47.8[A]	-	-	-
	6 months	-	-	47.4 ± 34.3[A]	56.3 ± 34.6[A]	-	-	-
	12 months	-	-	-	71.1 ± 57.1[A]	-	-	-
Chemerin (gingival crevicular fluid)	Baseline	-	-	-	-	112.2 (107.9 up to 125.0)[D]	-	-
	6 weeks	-	-	-	-	47.6 (36.9 up to 53.8)[D]	-	-
Vaspin (gingival crevicular fluid)	Baseline	-	-	-	-	-	1.1 (0.8 up to 1.3)[D]	-
	6 weeks	-	-	-	-	-	0.5 (0.4 up to 0.6)[D]	-
Omentin-1 (gingival crevicular fluid)	Baseline	-	-	-	-	-	16.8 (15 up to 18.6)[D]	-
	6 weeks	-	-	-	-	-	25.7 (21.1 up to 31.9)[D]	-
Systemic biomarkers of oxidative stress								
8-hydroxy-deoxyguanosine (8-OHdG) - Pg/µg DNA (blood serum)	Before	-	-	-	-	-	-	1.9 ± 0.35[A]
	30 days	-	-	-	-	-	-	0.54 ± 0.23[A]

8-hydroxy-deoxyguanosine (8-OHdG) - pg/mL (saliva)	Before	-	-	-	-	-	-	927.94 ± 116.66[A]
	30 days	-	-	-	-	-	-	652.58 ± 139.51[A]
8-hydroxy-deoxyguanosine (8-OHdG) - pg/mL (gingival crevicular fluid)	Before	-	-	-	-	-	-	1178.44 ± 97.34[A]
	30 days	-	-	-	-	-	-	1003.66 ± 157.85[A]

TABLE 3

Descriptive data on primary outcomes for BAS (*Cont*…)									
Object of investigation	**Follow-up**	**Taşdemir et al., 2016** (*n* = 14)	**Zuza et al., 2016** (*n* = 28)	**Martínez-Herrera et al., 2018a** (*n* = 74)	**Martínez-Herrera et al., 2018b** (*n* = 46)	**Çetiner et al., 2019** (*n* = 21)	**Peralta et al., 2019** (*n* = 55)	**Md Tahir et al., 2020** (*n* = 18)	**Cortelli et al., 2021** (*n* = 55)
Blood hematological and biochemical index									
Retinol-binding protein 4 (RBP4) - mg/L	Baseline	-	-	3.84 ± 1.06[A]	3.78 ± 1.11[A]	-	-	-	-
	3 months	-	-	3.46 ± 1.01[A]	3.44 ± 1.05[A]	-	-	-	-
Glucose - mg/L	Before	86.5 (80.5 to 92.2)[D]	99.8 ± 13.4[A]	95 ± 12[A]	95.2 ± 11.2[A]	-	-	-	-

	3 months	91.5 (78.5 to 96.5)[D]	102 ± 15.9[A]	94.8 ± 12[A]	95.7 ± 11.4[A]	-	-	-	-
	6 months	90.5 (78.5 to 97.5)[D]	-	-	-	-	-	-	-
Glycated hemoglobin (Hba1c) - %	Before	5.3 (5.2 to 5.6)[D]	5.4 ± 1[A]	-	-	-	-	-	-
	3 months	5.2 (5.1 to 5.4)[D]	4.4 ± 0.8[A]	-	-	-	-	-	-
	6 months	5.2 (5.1 to 5.5)[D]	-	-	-	-	-	-	-
Insulin - µU/mL	Before	18.3 (10.7 to 22.6)[D]	-	20 ± 14.6[A]	19.5 ± 10.9[A]	-	-	-	-
	3 months	14.7 (7.8 to 18.6)[D]	-	19.2 ± 11.3[A]	20.9 ± 11.9[A]	-	-	-	-
	6 months	17.1 (8.5 to 23.4)[D]	-	-	-	-	-	-	-
Homeostasis model assessment of insulin resistance (HOMA-IR)	Before	3.93 (2.25 to 5.06)[D]	-	4.73 ± 3.8[A]	4.58 ± 2.86[A]	-	-	-	-
	3 months	3 (1.8 to 4.18)[D]	-	4.61 ± 3.17[A]	5.04 ± 3.39[A]	-	-	-	-
	6 months	3.87 (2.05 to 5.37)[D]	-	-	-	-	-	-	-
Total cholesterol - mg/dL	Before	192.5 ± 31.4[A]	250 ± 14.1[A]	182 ± 34[A]	184 ± 33[A]	208 ± 34.6[A]	-	-	-
	3 months	200.2 ± 35.2[A]	210.6 ± 16.3[A]	185 ± 40[A]	188 ± 37[A]	200.3 ± 38.3[A]	-	-	-

	6 months	192.7 ± 37.6[A]	-	-	-	-	-	-	-
High density lipoprotein cholesterol (HDL) - mg/dL	Before	49.4 ± 15.6[A]	51.1 ± 3.5[A]	42 ± 11[A]	43.1 ± 11.4[A]	50.57 ± 9.52[A]	-	-	-
	3 months	46.5 ± 12.2[A]	50.4 ± 4.3[A]	44 ± 12[A]	43.8 ± 12.4[A]	55.14 ± 13.28[A]	-	-	-
	6 months	45.4 ± 14.1[A]	-	-	-	-	-	-	-
Low density lipoprotein cholesterol (LDL) - mg/dL	Before	102.6 ± 27.4[A]	170.8 ± 11.3[A]	121 ± 26[A]	116 ± 27[A]	128.64 ± 28.5[A]	-	-	-
	3 months	117.4 ± 34.4[A]	152.7 ± 14[A]	122 ± 31[A]	118 ± 29[A]	116.14 ± 38.7[A]	-	-	-
	6 months	111.4 ± 36.5[A]	-	-	-	-	-	-	-
Triglycerides - mg/dL	Before	166.4 (116.5 to 212)[C]	172.1 ± 14.2[A]	128 (98 to 167)[C]	126 (86 to 162)[C]	136.05 ± 46.2[A]	-	-	-
	3 months	157.9 (120 to 220.1)[C]	154.3 ± 15.9[A]	119 (98 to 152)[C]	132 (106 to 157)[C]	138.52 ± 51.64[A]	-	-	-
	6 months	167.5 (73 to 213.6)[C]	-	-	-	-	-	-	-
Systemic biomarkers of inflammation									
High-sensitivity C-reactive protein (hsCRP) - mg/L (blood serum))	Baseline	3.4 (3.4 to 5.4)[D]	3.75 ± 0.5[A]	8.33 ± 7.78[A]	4.33 (1.85 to 6.29)[C]	-	-	-	-
	3 months	3.3 (3.2 to 5.4)[D]	2.62. ± 0.2[A]	8.57 ± 7.92[A]	3.64 (1.62 to 6.32)[C]	-	-	-	-
	6 months	3.3 (3.2 to 8.2)[D]	-	-	-	-	-	-	-

Tumor necrosis factor-α (TNF-α) - pg/mL (blood serum)	Before	12.8 (10.5 to 15)[D]	-	17.23 ± 9.86[A]	19 ± 11.7[A]	-	-	-	-
	3 months	11.3 (7.2 to 16.1)[D]	-	13.9 ± 5.37[A]	14.4 ± 4.7[A]	-	-	-	-
	6 months	3.8 (2.6 to 6.4)[D]	-	-	-	-	-	-	-
	12 months	-	-	-	-	-	-	-	-
Tumor necrosis factor-α (TNF-α) - pg/mL (gingival crevicular fluid)	Before	-	-	-	-	9.0 ± 6.1[A]	-	-	-
	3 months	-	-	-	-	7.2 ± 5.9[A]	-	-	-
Interleukin (IL-6) - pg/mL (blood serum)	Before	2.23 (1.8 to 4.6)[D]	-	3.79 ± 2.04[A]	2.93 ± 1.31[A]	-	-	-	-
	3 months	2.13 (1.8 to 3)[D]	-	3.38 ± 2.48[A]	2.52 ± 1.44[A]	-	-	-	-
	6 months	2.04 (1.8 to 2.4)[D]	-	-	-	-	-	-	-
	12 months	-	-	-	-	-	-	-	-
Interleukin (IL-6) - pg/mL (gingival crevicular fluid)	Before	-	-	-	-	3.61 ± 4.43[A]	-	-	-
	3 months	-	-	-	-	1.76 ± 2.29[A]	-	-	-
Complement C3 (blood serum)	Before	-	-	-	128 ± 18[A]	-	-	-	-
	3 months	-	-	-	129 ± 28[A]	-	-	-	-
	Before	-	-	-	-	21.53 ± 39.55[A]	-	-	-

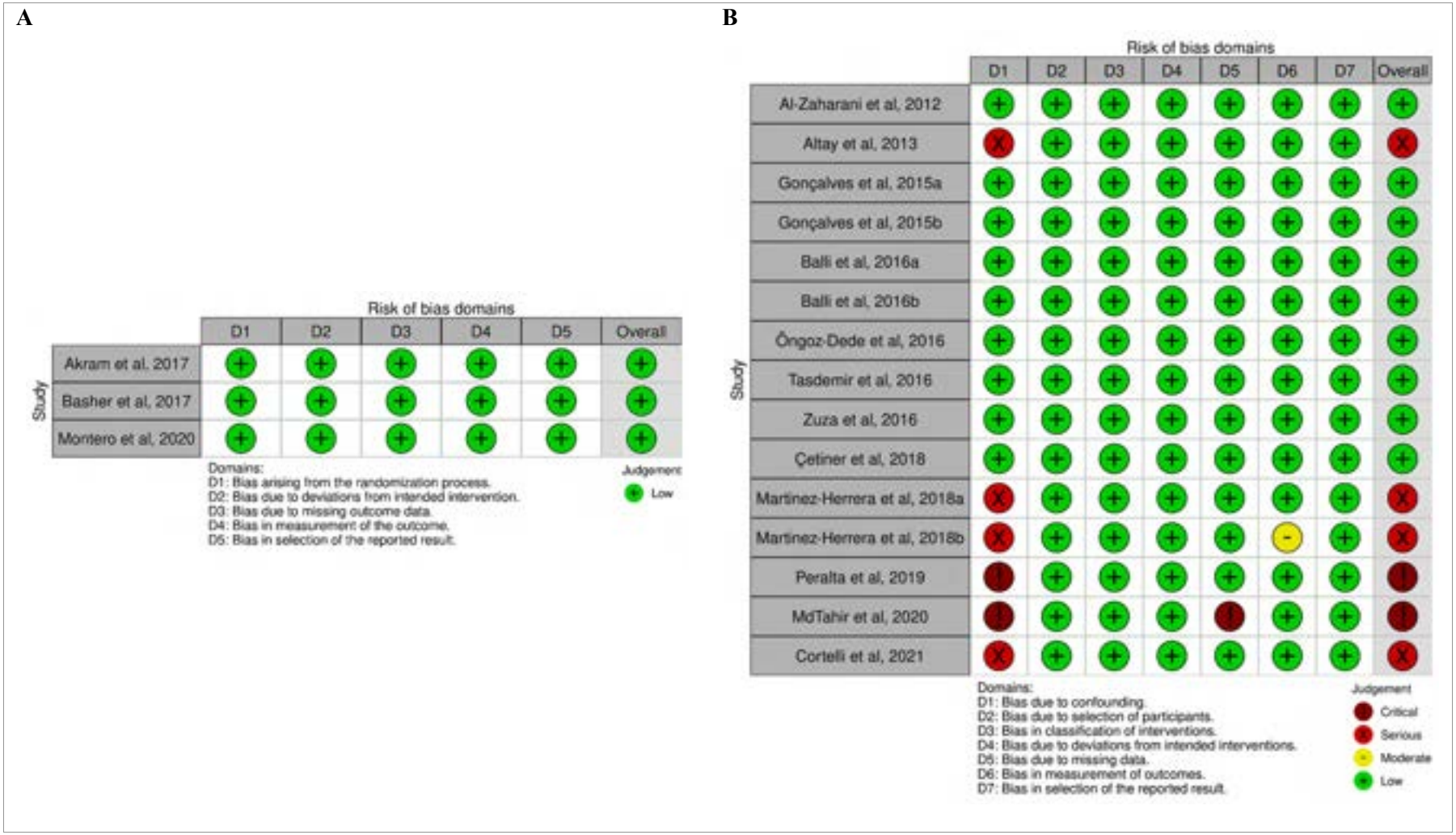
Visfatin - pg/mL (gingival crevicular fluid)	3 months	-	-	-	-	6.96 ± 3.49[A]	-	-	-
Resistin - ng/mL (blood serum)	Before	-	-	-	-	-	-	14.7 (10.8 to 18.5)[E]	-
	3 months	-	-	-	-	-	-	17.6 (12.4 to 22.7)[E]	-
Pentraxin-related protein 3 (PTX3) (blood serum)	Before	4.76 (3.1 to 7.9)[D]	-	-	-	-	-	-	-
	3 months	4.50 (3 to 6.9)[D]	-	-	-	-	-	-	-
	6 months	4.62 (3 to 6.8)[D]	-	-	-	-	-	-	-
Periodontal pathogens count									
Porphyromonas gingivalis (total bacterial count[†] or x 10^6 copy cells[§])	Before	-	-	-	-	-	17.06 ± 4.62[F†]	1.7 (1.5 to 2)[E§]	-
	3 months	-	-	-	-	-	3.65 ± 1.22[F†]	1.5 (1.3 to 1.7)[E§]	-
	6 months	-	-	-	-	-	9.81 ± 2.81[F†]	-	-
	9 months	-	-	-	-	-	13.88 ± 5.49[F†]	-	-
	Before	-	-	-	-	-	58.52 ± 18.77[F†]	0.6 (0.4 to 0.8)[E§]	-

Tannerella forsythia (total bacterial count[†] or x 10^6 copy cells[§])	3 months	-	-	-	-	-	22.05 ± 7.2[F†]	0.7 (0.5 to 0.9)[E§]	-
	6 months	-	-	-	-	-	55.87 ± 16.24[F†]	-	-
	9 months	-	-	-	-	-	33.24 ± 8.79[F†]	-	-
Prevotella intermedia (x 10^6 copy cells)	Before	-	-	-	-	-	-	1.0 (0.7 to 1.3)[E]	-
	3 months	-	-	-	-	-	-	0.6 (0.4 to 0.9)[E]	-
	6 months	-	-	-	-	-	-	-	-
	9 months	-	-	-	-	-	-	-	-
Treponema denticola (total bacterial count)	Before	-	-	-	-	-	18.14 ± 6.01[F]	-	-
	3 months	-	-	-	-	-	5.64 ± 1.51[F]	-	-
	6 months	-	-	-	-	-	14.77 ± 4.09[F]	-	-
	9 months	-	-	-	-	-	7.14 ± 2.32[F]	-	-
Aggregatibacter actinomycetemcomitans (total bacterial count)	Before	-	-	-	-	-	92.0 ± 20.7[F]	-	-
	3 months	-	-	-	-	-	65.6 ± 36.6[F]	-	-
	6 months	-	-	-	-	-	48.2± 15.4[F]	-	-
	9 months	-	-	-	-	-	21.1 ± 6.6[F]	-	-
Quality of Life									

OHqOL	Baseline	-	-	-	-	-	-	-	40.76 ± 5.69[A]
	6 months	-	-	-	-	-	-	-	44.88 ± 6.46[A]
OIDP	Baseline	-	-	-	-	-	-	-	43.24 ± 56.49[A]
	6 months	-	-	-	-	-	-	-	18.66 ± 42.41[A]

Legend: BAS, before-and-after (pre-post) studies, corresponding to data from intervention group of patients with obesity; *n*, sample size; TNF-α, tumor necrosis factor alpha; IL-6, interleukin-6; OHQoL, oral-related health quality of life; Δ, mean difference from 2 months follow-up to baseline; [A], mean ± standard deviation; [C], median (25 to 75 percentil); [D], median (minimum to maximum); [E], median (95 % confidence interval); [F], number ± standard error; -, variable not assessed by the authors; NA, data not available.

FIGURE 4. Bias risk analysis dashboard using Cochrane tools: A, “Revised Cochrane risk-of-bias tool for randomized trials” (RoB 2); and B, “Risk Of Bias In Non-randomized Studies - of Interventions” (ROBINS-I) tool for (uncontrolled) before-and-after studies



DISCUSSION

Recognizing the limited number of studies on the subject and analyzing the results of this study with caution, the literature suggests benefits of periodontal therapy improves cardiometabolic, inflammatory and microbiological parameters in patients with obesity and periodontitis.

The significant reduction in systolic and diastolic blood pressure three months after effective periodontal therapy (Montero et al., 2020) corroborated the meta-analysis by Muñoz Aguilera et al. (2020). Law et al. (2009) associated periodontal therapy with 10 mmHg reduction in systolic blood pressure or a 5 mmHg reduction in diastolic blood, and 25 % to 30 % reduction of cardiovascular events. This can be considered a significant benefit, especially due to suboptimal adherence to pharmacotherapy for hypertension (Joffres et al., 2013; Eskås et al., 2016; Burnier, 2017; Burnier and Egan, 2019). The serum levels of total cholesterol, LDL and triglycerides also improved after periodontal therapy in the before-and-after analysis (Zuza et al., 2016).

Periodontal therapy was effective in reducing HbA1c and blood pressure at 3-months follow-up, suggesting early benefits of the periodontitis-treatment for metabolic control and vascular function (Tonetti et al., 2007; Teeuw et al., 2014; Montero et al., 2020). According to the literature, effective periodontal maintenance care helps to maintain the positive effect of periodontal therapy on glycemic control (Koromantzos et al., 2011; D'Aiuto et al., 2018). Therefore, the lack of repeated periodontal interventions during the study (Montero et al., 2020) appears to explain the late reversal of HbA1c improvement.

Non-surgical periodontal therapy reduced hsCRP by 30.8% from baseline values and showed a difference of 1.2 mg/L at 6-months follow-up compared with the CG (Montero et al., 2020), reducing the cardiovascular risk (Ridker et al., 2018). The periodontal therapy has the potential to decrease hsCRP levels by 30% in patients with coronary heart disease and periodontitis (Bokhari et al., 2012). Otherwise, the results from the Periodontitis and Vascular Events (PAVE) study suggest that periodontal therapy is not able to maintain the reduction of serum hsCRP levels at 6-months follow-up in these patients. The serum levels of hsCRP also improved after periodontal therapy in the BAS analysis (Al-Zahrani et al., 2012; Zuza et al., 2016), although some authors reported non-significant reduction in hsCRP after NSPT (Altay et al., 2013; Taşdemir et al., 2016; Martinez-Herrera et al., 2018a, 2018b). Despite the divergent results, the BAS and RCT studies suggest an improvement in CRP after periodontitis-treatment

in the person with obesity. In this context, the findings reported by Montero et al. (2020) appear to be associated with severe periodontitis in MS patients (Offenbacher et al., 2009).

Most studies address the effects of obesity on different matrices of the oral cavity and on the effectiveness of periodontal therapy obesity (Zimmermann et al., 2013; Keller et al., 2015; Akram et al., 2016; Martinez-Herrera et al., 2017), but the literature remains scarce on the benefits of periodontitis-therapy in patients with obesity. One RCT study reported a significant decrease in serum levels of IL-1β and TNF-α at 3-months follow-up in the IG compared to the CG, and no difference between groups for IL-1β, IL-6, IL-8 and TNF-α six months after periodontal therapy (Montero et al., 2020). The BAS analyzes pointed out a decrease in TNF-α levels in both serum and GCF matrices (Altay et al., 2013; Balli et al., 2016b; Taşdemir et al., 2016; Martinez-Herrera et al., 2018a, 2018b). Contrasting results such as no significant change in GCF levels of IL-6, TNF-α and resistin, and in the serum levels of any adipokines at any time-point after therapy (Gonçalves et al., 2015b; Taşdemir et al., 2016; Çetiner et al., 2018), reinforce the need for more RCT studies on the subject.

Non-surgical periodontal therapy improved the levels of some circulating proinflammatory cytokines and C3 and decreased insulin resistance in patients with obesity and periodontitis, compared to baseline (Altay et al., 2014; Martinez-Herrera et al., 2018a). Resistin levels are elevated in person with obesity (Zimmermann et a., 2013) and individuals with chronic periodontitis (Furugen et al., 2008; Saito et al., 2008), and the presence of inflammatory chronic diseases and chronic periodontitis might further increase the levels of this adipokine (Giannobile et al., 2009; Gokhale et al., 2014). Akram et al. (2017) reported a significant reduction in resistin after periodontal therapy in the IG but not in the CG, but the authors did not correlate the change in salivary resistin level after NSPT with improvement in PD or CAL. Only shallow and moderate sites showed improvement, and this may have influenced the result. According to the authors, saliva might not be sensitive enough to detect changes in cytokine levels caused by localized inflammatory conditions. In that sense, using GCF would be a better choice. In addition, resistin levels were higher in the CG than in the IG at baseline ($p < 0.05$), introducing a risk of bias in the results. This also limited the comparison of changes in resistin level between the CG and the IG, and the difference in resistin levels between groups at baseline was related to pre-established eligibility criteria. Despite the inclusion of smokers is considered an important potential confounder (Bergström, 2004; Genco and Borgnakkle, 2013; Chapple et al., 2018), smoking did not significantly affect periodontal outcomes in the study by Akram et al. (2017). Zimmermann et al. (2013) and Patel and Raju (2014) reported and association between periodontal therapy and decreasing saliva resistin levels, suggesting the need for further studies.

Increased inflammatory factors, disturbances in glycolipid metabolism and adipokines overexpressed in obesity can be worsened in person with obesity and periodontitis (Li et al., 2018). Although serum and GCF concentrations of leptin, adiponectin and oxidative stress biomarkers remain uncertain and underexplored in the patient with obesity and periodontitis, adipokines in GCF such as chemerin, vaspin, omentin-1 and visfatin improved after periodontal therapy (Balli et al., 2016a, 2016b; Çetiner et al., 2018). In the study by Öngöz Dede et al. (2016), 8-OHdG, a powerful periodontal disease marker (Paredes-Sánchez et al., 2018), significantly decreased in plasma, saliva and GCF after periodontal therapy.

The improvement of the pro-inflammatory state represents a huge benefit of periodontal therapy for patients with obesity, as it interferes with insulin resistance and metabolic disorders, hepatic steatosis and cardiovascular diseases (Hotamisligil et al., 1993; Visser et al., 1999; Hotamisligil, 2006; Shoelson et al., 2006; Ouchi et al., 2011; Czech, 2013; Lau et al., 2017; Shibata et al., 2017; Oikonomou and Antoniades, 2019; Pérez et al., 2020). In addition, subcutaneous and visceral adipose, CRP and IL-6 also represent a risk of developing type 2 DM (Pradhan et al., 2001; Samaras et al., 2010).

In terms of microbial composition, patients with obesity and periodontitis have higher proportions of subgingival periodontal pathogens than eutrophic individuals, increasing the risk of progressive attachment loss and the development of periodontitis (Maciel et al., 2016). Previous studies show that mean *Pg*, *Tf*, and *Pi* counts can be reduced by 7 to 45 % at 12 weeks after periodontitis-therapy (Cugini et al., 2000; Predin et al., 2014) and ranged from 18 to 99 % after NSPT of patients with diabetes and periodontitis (Christgau et al., 1998; Buzinin et al., 2014). In this study, BAS data pointed to a positive effect of periodontal therapy on *Pg*, *Pi*, *Aa*, *Tf* and *Td* counts for three months (Peralta et al., 2019; Md Tahir et al., 2020), although Md Tahir et al. (2020) reported no significant changes in mean *Pg* and *Tf* counts at 12-weeks follow-up. Diagnostic criteria for periodontitis, the full-mouth disinfection protocol (Quirynen et al., 2006; Zhao et al., 2020) and the periodontal maintenance phase (Shiloah and Patters, 1996; Santos et al., 2004; Haffajee et al., 2009) adopted by Peralta et al. (2019) may explain this divergence. The SRP strategy with and without chlorhexidine should not respond to this difference (Swierkot et al., 2009; Fonseca et al., 2015), although the difference between the response to one-stage full-mouth therapy and quadrant-by-quadrant root planning could be expected (Greenstein, 2002).

Montero et al. (2020) adopted azithromycin as an adjuvant antibiotic for NSPT and used 0.12 % chlorhexidine and 0.05 % cetylpyridinium chloride twice daily for 14 days post-therapy. The authors reported a decrease in anaerobic bacteria and *Pg* counts after periodontal therapy and associated this result with significant reductions in hsCRP. This is the first clinical trial to demonstrate such an association. To date, one cross-sectional study has described an independent

significant association between significant subgingival bacterial burden and levels of periodontal pathogens with surrogate measurements of atherosclerotic risk as intima-media thickness or hsCRP (Desvarieux et al., 2005).

Commensal microbiota and complement were both necessary for *Pg*-induced bone loss, confirmed in germ-free or C3a- and C5a receptor-deficient mice inoculated with *Pg*. On the pathogenicity of key species in periodontitis, *Pg* was able to subvert complement receptor 3 and anaphylotoxin C5a receptor signaling. Even a single low-abundance species can disrupt homeostasis, leading to dysbiosis, inflammatory events, and disease. In this context, effective periodontal therapy should require activation of the inductive or effector pathways of the complement (Hajishengallis, 2010; Ricklin et al., 2010; Hajishengallis et al., 2011). Therefore, the improvement in *Pg* counts and serum levels of C3 reported in the studies may be linked.

The study by Montero et al. (2020), however, may have relevant limitations. One is that the IG consisted of a combination of subgingival debridement and the adjunctive administration of azithromycin. Azithromycin was associated with immunomodulatory properties on cytokine and chemokines levels (Bartold et al., 2013). Macrolides decrease the formation of pro-inflammatory cytokines, adhesion molecules, reaction to chemoattractants, oxidative burst and the adaptive immunity, and promote the release of anti-inflammatory cytokines, neutrophil apoptosis, neutrophil degranulation (Culić et al., 2001; Bartold et al., 2013). The pharmacological effects of azithromycin on the various cytokines are very complex and are dependent on dose, target cell and temporal differences in terms of host modulatory function (Ianaro et al., 2000; Hodge and Michalowicz, 2001; Kurdowska et al., 2001; Culić et al., 2002; Shinkai et al., 2006, 2008). Therefore, the cardiovascular effect shown in this study can be attributed to antibiotics rather than periodontal therapy. Another possible limitation could be the selection of hsCRP as a surrogate for cardiovascular risk. Although hsCRP is the most frequently reported biomarker for cardiovascular risk (Greenland et al., 2010; Piepoli et al., 2016), its predictive value may be limited (Yousuf et al., 2013).

Before-and-after analysis suggested improved quality of life in patients with obesity and periodontitis after periodontal therapy (Cortelli et al., 2021); however, according to Basher et al. (2017), the quality of life improved after periodontal therapy in both CG and IG. The slow and progressive nature of chronic periodontitis allows the patient to adapt to clinical symptoms and seek dental care later. Therefore, little or limited perception from patients to acknowledge chronic periodontitis as a condition may affect the OHRQoL— multidimensional construct that includes a subjective evaluation of the individual's oral health, functional well-being, emotional well-being, expectations and satisfaction with care, and sense of self (Sischo and Broder, 2011; Basher et al., 2017).

To strengthen the quality of this systematic review, no restrictions were applied to databases, records, and other sources in the screening process. The search and selection of articles, data collection and synthesis were performed independently by two researchers and a validated quality assessment tool was used. The certainty of evidence was also evaluated following the GRADE approach. Publication bias cannot be excluded, as studies with positive results tend to be more easily published (Thornton, 2000). Performing a meta-analysis was considered; however, the included studies used different criteria to define periodontitis and obesity, different periodontal therapy protocol, periodontal maintenance phase and objects of investigation, making a meta-analysis difficult. Despite the methodological heterogeneity and scarcity of publications on the subject, some clear pattern was established.

The strength of our review is the number of databases evaluated, the methods described in supplementary material and the inclusion of RCT and BAS studies, limiting the control group and baseline data, respectively, to the absence of periodontal therapy with subgingival approach. The main disadvantage of BAS analysis is the lack of a comparison or control group, making it unfeasible to establish cause-and-effect relationships. The pre-, during-, post-therapy variables suggest intervention effects on the outcomes of interest, although they are inconclusive. The results of the BAS studies, while not tightly controlled, suggest effects of an intervention and support further well-designed clinical research and hypothesis testing. Furthermore, short follow-up periods limits understanding the effects of periodontal therapy. Although more controlled and well-planned clinical trials are needed, to our knowledge this is the first systematic review to summarize the main benefits of periodontal therapy for these patients.

CONCLUSION

It is acknowledged that the present systematic review has several limitations, and thus, the present results must be interpreted with caution. The current findings suggest that periodontitis-therapy has the potential to improve blood pressure, serum levels of total cholesterol, LDL, triglycerides, HbA1c, insulin resistance, hsCRP, IL-1β, TNF-α and C3, GCF levels of TNF-α, chemerin, vaspin, omentin-1, visfatin and 8-OHdG, and *Pg*, *Pi*, *Aa*, *Tf* and *Td* counts. According to the authors, further studies are needed to ensure the systemic benefits of periodontitis-treatment in patients with obesity and to establish the best levels of evidence in this regard.

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Conflict of interest

None of the authors has any type of conflict of interest related to the study, as well as related to the peer review process of the manuscript. None of the universities and public agencies that support research in Brazil represents a conflict of interest in this study.

Contribution statement

All authors made substantial contributions to the study and were equally responsible for its design, execution, and content, and agreed to its submission for publication.

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CAPÍTULO 5

Serum C-reactive Protein and Periodontitis-Treatment: An Umbrella Review

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ABSTRACT

Background: Although the relationship between periodontitis and circulating C-reactive protein (CRP) levels have been investigated in recent years, evidence on the systemic effects of periodontitis-treatment in this biomarker remains unclear.

Objective: This umbrella review aimed to answer the focused question: "What is the evidence from secondary studies on the effect of periodontal treatment on circulating C-reactive protein levels in patients with periodontitis?"

Methods: A systematic literature search was performed in six databases, complemented by gray literature, manual-search and contact with experts until November 2021. Databases alerts were set to retrieve new publications, until the manuscript submission process. Systematic reviews and meta-analysis studies on the effect of periodontitis-treatment on C-reactive protein levels were included. Secondary studies with synthesis of data from pilot and observational studies, patients using immunomodulators, anti-inflammatory drugs or antibiotics, syndromic, poorly defined periodontal diagnostic criteria, or with follow-up < 3 months were excluded. Risk of bias within

studies was assessed using Risk of Bias in Systematic Reviews (ROBIS) tool. All steps were conducted by three blind reviewers and discussed with a fourth reviewer when necessary.

Results: After screening the 1,320 initial results, the selection process resulted in 12 suitable studies, three systematic reviews and nine meta-analysis. Most meta-analyses of better methodological quality showed a reduction in serum CRP levels after periodontitis-treatment in patients with type 2 diabetes mellitus, pre-hypertensive and hypertensive, undergoing hemodialysis and peritoneal dialysis. Two other reviews reported improvement in CRP post-periodontal treatment in patients with and without comorbidities, but there were inaccurate data in both studies.

Conclusion: Current evidence suggests that periodontitis-treatment has the potential to reduce serum CRP levels in patients with chronic non-communicable diseases.

Protocol record: PROSPERO [CRD42021270654].

Keywords: Periodontal diseases; periodontitis; dental scaling; root planning. C-reactive protein.

INTRODUCTION

Periodontitis is a multifactorial chronic inflammatory disease associated with dysbiotic biofilms and characterized by the progressive destruction of the dental support apparatus.[1] The relationship between bacterial load and host response is a plausible biological mechanism that links periodontitis to several chronic inflammatory diseases such as diabetes mellitus (DM), cardiovascular diseases,[2,3] kidney diseases,[4] preterm and/or low birth weight infants[5] not only as an oral disease, but a public health problem.

Inflammation of periodontal tissues leads to superficial ulcers in the gingival sulcus or periodontal pocket, exposing blood capillaries to pathogenic microorganisms.[6] In periodontitis, the number of blood vessels and the extent of blood vessels in the gingiva are increased, favoring bacteremia and endotoxemia.[7-11] Elevated concentrations of lipopolysaccharides (LPS) in the periodontal pockets and in the serum increase the levels of circulating inflammatory markers and reactive oxygen species, favoring the systemic impacts of periodontitis.[12-15]

Chronic exposure to periodontal bacteria, their products and cytokines impacts the pathogenesis of systemic diseases, stimulates the host's immune system leading to a hyperinflammatory state and compromising tissue and organ homeostasis,[6,16-24] including liver damage.[26-36] The liver plays an important physiological role in LPS detoxification,[37] arising

bacteremia, endotoxemia and circulating inflammatory mediators that may influence C-reactive protein (CRP) levels.[38]

High sensitivity C-reactive protein (hsCRP) "represent a summation of the patient's overall systemic inflammation, which may in part be influenced by periodontitis, but otherwise is an 'unexplained' inflammatory burden that be valuable to assess in collaboration with the patient's physicians", as described in the current classification and case definition of periodontal diseases.[39] It is envisaged that in the future it will be possible to link periodontitis grade to the potential systemic impact of the disease. However, according to these authors, the assessment of the risk of systemic impact of periodontitis based on the hsCRP levels and biomarkers still lacks specific evidence. Therefore, in line with the 2017 World Workshop on the Classification of Periodontal and Peri-Implant Diseases and Conditions[1] and some authors,[38-40] this umbrella review aimed to summarize the evidence on the effect of periodontitis treatment on serum levels of CRP, based on systematic reviews of clinical trials.

METHODS

***Protocol and Registration*.** This study was conducted according to The Joanna Briggs Institute Reviewers' Manual 2014: Methodology for JBI Umbrella Reviews.[41] The review protocol was registered in the PROSPERO database (http://www.crd.york.ac.uk/PROSPERO) under the number [CRD42021270654].

***Focused question and study selection criteria*.** This umbrella review aimed to answer the focused question: "What is the evidence from secondary studies on the effect of periodontal treatment on circulating C-reactive protein levels in patients with periodontitis?"

Systematic reviews and meta-analysis studies on the effect of periodontal treatment on C-reactive protein levels in patients with periodontitis, based on interventional studies such as randomized controlled trials, non-randomized controlled clinical trials were included.

The eligibility criteria were based on the *PICOs* principle in which systematic reviews were included considering — the *Population*: patients with periodontitis without restriction related to systemic condition; the *Intervention*: periodontal treatment with subgingival instrumentation*; the appropriate *Control (or comparator)*: no periodontal treatment with subgingival instrumentation, included non-periodontal treatment, only supragingival plaque and calculus removal, or delayed treatment arm; the *Outcomes* of interest: C-reactive protein level; and the study design of interest: systematic reviews and meta-analyses.

*No restriction was imposed in the search concerning the periodontal treatment. Periodontal interventions were based on scaling and root planing (SRP) sections (i.e. non-surgical periodontal treatment), one-stage/intensive full mouth SRP, full-mouth disinfection and surgical procedures (i.e. periodontal flap surgery), supra- and subgingival biofilm and calculus removal [Intervention (I)]. Mechanical treatment associated with local or systemic drug use (i.e. antimicrobial, anti-inflammatory or others), or with photodynamic therapy/laser therapy, were also considered for inclusion. Besides, no restriction by sex, age, smoking, date and language of publication were made.

The following exclusion criteria were used: i- pilot studies; ii- observational data; iii- chronic use of immunomodulators, glucocorticoids, NSAIDs or other anti-immunoinflammatory; iv- use of antimicrobials or anti-inflammatory drugs in the six months prior to diagnosis and periodontal treatment performed in the studies; v- no description of the periodontitis diagnostic criteria used; vi- studies that evaluated the circulating C-reactive protein levels within less than three months of follow-up; vii- participants with congenital syndrome affecting teeth and/or periodontal tissues, or associated with bone pathologies of the jaws; and viii- unavailability of the full text copy.

Search strategy. Considering the MeSH terms, entry terms and free keywords used for PubMed, search strategies were customized for each database, Web of Science, Cochrane Library, other sources (gray literature), protocol registration databases, and manual search. Similarly, DeCS/MeSH terms, Emtree terms and Index terms were used for electronic searches in LILACS, Embase and Scopus databases. All terms were combined by the Boolean operators "OR" and "AND" (Table 1), without applying filters. The electronic searches were performed in November 2021. Databases alerts set to identify studies published after the time of the searches, until the manuscript submission process.

TABLE 1

Search strategies customized for each database	
Database	**Search strategy**
PubMed and other sources	(periodontal debridement[MeSH] OR subgingival curettage[MeSH] OR dental scaling[MeSH] OR root planing[MeSH] OR dental prophylaxis[MeSH] OR debridement*[tiab] OR curettage*[tiab] OR scaling[tiab] OR periodontal therapy[tiab] OR periodontal treatment[tiab] OR planing*[tiab] OR full-mouth therapy[tiab] OR periodont*[tiab]) AND (c-reactive protein[MeSH] OR acute-phase proteins[MeSH] OR c-reactive protein[tiab] OR acute-phase protein*[tiab] OR c reactive protein[tiab] OR hscrp[tiab] OR hs-crp[tiab] OR acute phase protein*[tiab] OR acute phase reactant*[tiab] OR acute-phase reactant*[tiab] OR proteins, acute phase [tiab] OR glycoprotein*[tiab]) AND (systematic review[Publication type] OR systematic reviews as topic[MeSH] OR systematic reviews[tiab] OR systematic review[tiab] OR meta-analysis[Publication type] OR meta-analysis as topic[MeSH] OR meta-analysis[tiab] OR meta-analyses[tiab] OR meta analysis[tiab] OR meta analyses[tiab])

Web of Science	#1 TS=("periodontal debridement" OR "subgingival curettage" OR "dental scaling" OR "root planning" OR "dental prophylaxis" OR debridement* OR curettage* OR scaling OR "periodontal therapy" OR "periodontal treatment" OR planing* OR "full-mouth therapy" OR periodont*) #2 TS=("c-reactive protein" OR "acute-phase proteins" OR "c-reactive protein" OR acute-phase protein* OR "c reactive protein" OR hscrp OR hs-crp OR acute phase protein* OR acute phase reactant* OR acute-phase reactant* OR "proteins, acute phase" OR glycoprotein*) #3 TS=("systematic review[Publication type]" OR "systematic reviews as topic" OR "systematic reviews" OR "systematic review" OR "meta-analysis[Publication type]" OR "meta-analysis as topic" OR "meta-analysis" OR "meta-analyses" OR "meta analysis" OR "meta analyses") #4 #3AND#2AND#1
Cochrane Library	#1 MeSH descriptor: [Periodontal Debridement] explode all trees #2 MeSH descriptor: [Subgingival Curettage] explode all trees #3 MeSH descriptor: [Dental Scaling] explode all trees #4 MeSH descriptor: [Root Planing] explode all trees #5 MeSH descriptor: [Dental Prophylaxis] explode all trees #6 (debridement* OR curettage* OR scaling OR periodontal therapy OR periodontal treatment OR planing* OR full-mouth therapy OR periodont*):ti,ab,kw #7 #1 OR #2 OR #3 OR #4 OR #5 OR #6 #8 MeSH descriptor: [C-Reactive Protein] explode all trees #9 MeSH descriptor: [Acute-Phase Proteins] explode all trees #10 (c-reactive protein OR acute-phase protein* OR c reactive protein OR hscrp OR hs-crp OR acute phase protein* OR acute phase reactant* OR acute-phase reactant* OR proteins, acute phase OR glycoprotein*):ti,ab,kw #11 #8 OR #9 OR #10 #12 MeSH descriptor: [Systematic Review] explode all trees #13 MeSH descriptor: [Systematic Reviews as Topic] explode all trees #14 MeSH descriptor: [Systematic Reviews as Topic] explode all trees #15 MeSH descriptor: [Meta-Analysis] explode all trees #16 MeSH descriptor: [Meta-Analysis as Topic] explode all trees #17 MeSH descriptor: [Network Meta-Analysis] explode all trees #18 (systematic reviews OR systematic review OR meta-analysis OR meta-analyses OR meta analysis OR meta analyses):ti,ab,kw #19 #12 OR #13 OR #14 OR #15 OR #16 OR #17 OR #18 #20 #7 AND #11 AND #19
Embase	#10. #7 AND #8 AND #9 #9. #5 OR #6 #8. #3 OR #4 #7. #1 OR #2 #6. 'c reactive protein'/exp OR 'c reactive protein blood level'/exp OR 'acute phase protein'/exp #5. 'c-reactive protein':ti,ab,kw OR 'acute-phase protein*':ti,ab,kw OR hscrp OR 'hs crp' OR 'acute phase reactant*':ti,ab,kw OR 'acute-phase reactant*':ti,ab,kw OR 'proteins, acute phase':ti,ab,kw OR glycoprotein*:ti,ab,kw #4. 'systematic reviews':ti,ab,kw OR 'meta-analysis':ti,ab,kw OR 'meta-analyses':ti,ab,kw OR 'meta analyses':ti,ab,kw #3. 'systematic review'/exp OR 'systematic review (topic)'/exp OR 'systematic review topic'/exp OR 'meta analysis'/exp OR 'meta analysis (topic)'/exp OR 'meta analysis topic'/exp #2. debridement*:ti,ab,kw OR curettage*:ti,ab,kw OR scaling:ti,ab,kw OR 'periodontal treatment':ti,ab,kw OR planing*:ti,ab,kw OR 'full-mouth therapy':ti,ab,kw OR periodont*:ti,ab,kw

	#1. 'dental debridement'/exp OR 'dental curettage'/exp OR 'dental scaling'/exp OR 'root planing'/exp OR 'dental prophylaxis'/exp OR 'periodontal therapy'/exp
Scopus	(INDEXTERMS (periodontal AND debridement) OR INDEXTERMS (subgingival AND curettage) OR INDEXTERMS (dental AND scaling) OR INDEXTERMS (root AND planing) OR INDEXTERMS (dental AND prophylaxis) OR TITLE-ABS-KEY (debridement*) OR TITLE-ABS-KEY (curettage*) OR TITLE-ABS-KEY (scaling) OR TITLE-ABS-KEY (periodontal AND therapy) OR TITLE-ABS-KEY (periodontal AND treatment) OR TITLE-ABS-KEY (planing*) OR TITLE-ABS-KEY (full-mouth AND therapy) OR TITLE-ABS-KEY (periodont*)) AND (INDEXTERMS (c-reactive AND protein) OR INDEXTERMS (acute-phase AND proteins) OR TITLE-ABS-KEY (c-reactive AND protein) OR TITLE-ABS-KEY (acute-phase AND protein*) OR TITLE-ABS-KEY (c AND reactive AND protein) OR TITLE-ABS-KEY (hscrp) OR TITLE-ABS-KEY (hs-crp) OR TITLE-ABS-KEY (acute AND phase AND protein*) OR TITLE-ABS-KEY (acute AND phase AND reactant*) OR TITLE-ABS-KEY (acute-phase AND reactant*) OR TITLE-ABS-KEY (proteins, AND acute AND phase) OR TITLE-ABS-KEY (glycoprotein*)) AND INDEXTERMS (systematic AND review[publication AND type]) OR INDEXTERMS (systematic AND reviews AND as AND topic) OR TITLE-ABS-KEY (meta-analysis[publication AND type]) OR TITLE-ABS-KEY (meta-analysis AND as AND topic) OR TITLE-ABS-KEY (systematic AND reviews) OR TITLE-ABS-KEY (systematic AND review) OR TITLE-ABS-KEY (meta-analysis) OR TITLE-ABS-KEY (meta-analyses) OR TITLE-ABS-KEY (meta AND analysis) OR TITLE-ABS-KEY (meta AND analyses)
LILACS	(mh:(“periodontal debridement” OR “subgingival curettage” OR “dental scaling” OR “root planning” OR “dental prophylaxis”)) OR (tw:(debridement* OR curettage* OR scaling OR “periodontal therapy” OR “periodontal treatment” OR planing* OR “full-mouth therapy” OR periodont*)) AND (mh:(“c-reactive protein” OR “acute-phase proteins”)) OR (tw:(“c-reactive protein” OR “acute-phase protein*” OR “c reactive protein” OR hscrp OR hs-crp OR “acute phase protein*” OR “acute phase reactant*” OR “acute-phase reactant*” OR “proteins, acute phase” OR glycoprotein*)) AND (mh:(“systematic review” OR “systematic reviews as topic” OR “meta-analysis” OR “meta-analysis as topic”)) OR (tw:(“systematic reviews” OR “meta-analyses” OR “meta analysis” OR “meta analyses”))

Information sources. Searches were performed in the MEDLINE using the PubMed search engine (http://www.ncbi.nlm.nih.gov/sites/pubmed), Web of Science (https://www.webofknowledge.com) accessed through the Clarivate Analytics (https://clarivate.com), Cochrane Library (https://www.cochranelibrary.com), Embase (https://www.embase.com) through Elsevier (https://www.elsevier.com), Scopus (http://www.scopus.com) and LILACS via VHL (https://bvsalud.org). Other sources _ gray literature _ were consulted through Google Scholar (https://scholar.google.com.br) and System for Information on Grey Literature in Europe (SIGLE) through OpenGrey (www.opengrey.eu). Protocol registration databases included PROSPERO (https://www.crd.york.ac.uk/prospero/) and Open Science Framework – OSF (https://osf.io/). Handsearches were also performed in specialized periodicals (*Journal of Periodontology; Journal of Clinical Periodontology; Journal of Periodontal Research; Periodontology 2000; Journal of Dental research; The International*

Journal of Periodontics & Restorative Dentistry; The Journal of American Dental Association; Journal of Applied Oral Science; Journal of Periodontal & Implant Science; Journal of Oral Pathology & Medicine; and *Oral Surgery, Oral Medicine, Oral Pathology and Oral Radiology*) and in reference lists of included articles. To keep the search strategy updated, alerts were established for each database. Experts were identified using expertscape.com (https://expertscape.com) and contacted for other data sources.

Selection process. The retrieved articles were exported to rayyan™ reference manager (https://www.rayyan.ai) and duplicates were removed by the program and manually. Authors of studies that were not retrieved in full text were contacted by e-mail up to five attempts. If two studies had sample overlapping, and the same methodology criteria assessed, the least complete study was excluded. The selection process was conducted in two phases: Phase 1, three reviewers (DSB, CCP and MFF) independently examined the titles and abstracts of all identified references, applying the including process (blind process); and Phase 2, the same three reviewers independently applied the exclusion criteria to the other studies, based on the full text reading (blind process). Inter-reviewer reliability in the study selection process was determined by the Cohen κ test, assuming an acceptable threshold value of 0.80.[42] Disagreement at any stage were resolved by discussion on consensus meetings with a fourth reviewer (MCMB). The final decision/selection was always based on the full text of the publication. The reasons for studies exclusion were reported (Figure 1).

Data collection process. Data were extracted by three independent reviewers (DSB, CCP and MFF) from the included studies and reported after a consensus meeting with the fourth reviewer (MCMB). When there were unclear or missed information, lack of data or the full text was not available, weekly attempts were made for up to five times to contact the authors. In cases of no response regarding data reported in graphs, the digital program WebPlotDigitizer™ online (https://automeris.io/WebPlotDigitizer/) was used to retrieve the information of interest. The accuracy of extracted data was confirmed by another author (MCMB). Google translator program was used in case of studies in a foreign language not provided by the researchers (https://translate.google.com.br/?hl=pt-BR).

Data items and synthesis. Data were independently extracted by the three reviewers (DSB, CCP and MFF [blinded process]) using a standardized sheet.[43] The following data were extracted: study | registered database, written-oriented checklist, PICO, searches, number and design of included studies, quality assessment/risk of bias tool | overall quality/risk of bias, meta-analysis for CRP outcome based on randomized controlled trial (RCT) and controlled clinical trial (CCT) studies, certainty of the evidence, conclusion, conflict of interest, funding support (Table

2), systemic condition, controlled for other comorbidities (apart from periodontitis), controlled for smoking, periodontal diagnoses, types of periodontal interventions, control group, supportive periodontal care, evidence of periodontal treatment efficacy, follow-up, and main results (Table 3), and meta-analysis data (Table 4). Descriptive results were presented in the form of text, figure, and tables.

Risk of bias within studies. The evaluation of quality and risk of bias in clinical studies was performed by three authors independently (DSB, CCP and MFF [blinded process]), using a specific risk of bias and methodological quality assessment tool for systematic review and meta-analysis: Risk of Bias in Systematic Reviews (ROBIS) tool.[44,45] ROBIS domains: 1- study eligibility criteria; 2- identification and selection of studies; 3- data collection and study appraisal; and 4- synthesis and findings. Each domain was classified as "low concern", "unclear concern" and "high concern". The overall risk of bias of the reviews was established by the majority risk of bias in the four domains. The authors of reports were contacted to retrieve any possible bias of missing data; the contact was done by e-mail up to five attempts.

RESULTS

Study selection. There were 820 records identified on the electronic databases and registers. After removing 190 duplicates, 596 reports were excluded based on the title and abstract reading (Phase 1), and three studies were removed for lack of author response from contacted authors. Systematic reviews and meta-analysis studies that did not include controlled trials with appropriate comparison groups, or that considered observational studies or studies of different designs in data synthesis and meta-analyses were excluded: 19:31 studies were excluded when reading full texts (Phase 2) since they were: commentary of previous study (n = 2); study design or compromised results due to methodological heterogeneity (n = 10); gingivitis and periodontitis grouped in data synthesis (n = 1); ineligible comparison groups (n = 4); information bias-(n = 1); and not a systematic review (n = 1). No records were included from the other sources and hand-searches. In total, twelve studies were included: three qualitative reviews[46-48] and nine meta-analyses[40,49-56] (Figure 1). The inter-reviewer reliability in the study selection process was $\kappa \geq 0.9$ for all databases.

Study characteristics. Only four among the 12 reviews reported a protocol register.[40,47,55,56] Nine studies followed reporting checklists: PRISMA statement (n = 6),[40,47,51,52,54,55] PRISM-P (n = 1),[56] QUORUM statement (n = 1),[53] and Cochrane standards for systematic reviews (n = 3);[48,54,55] while three studies did not mention any reporting checklist.[46,49,50] Only two studies described the PICO structure.[47,56] Regarding the information sources, the

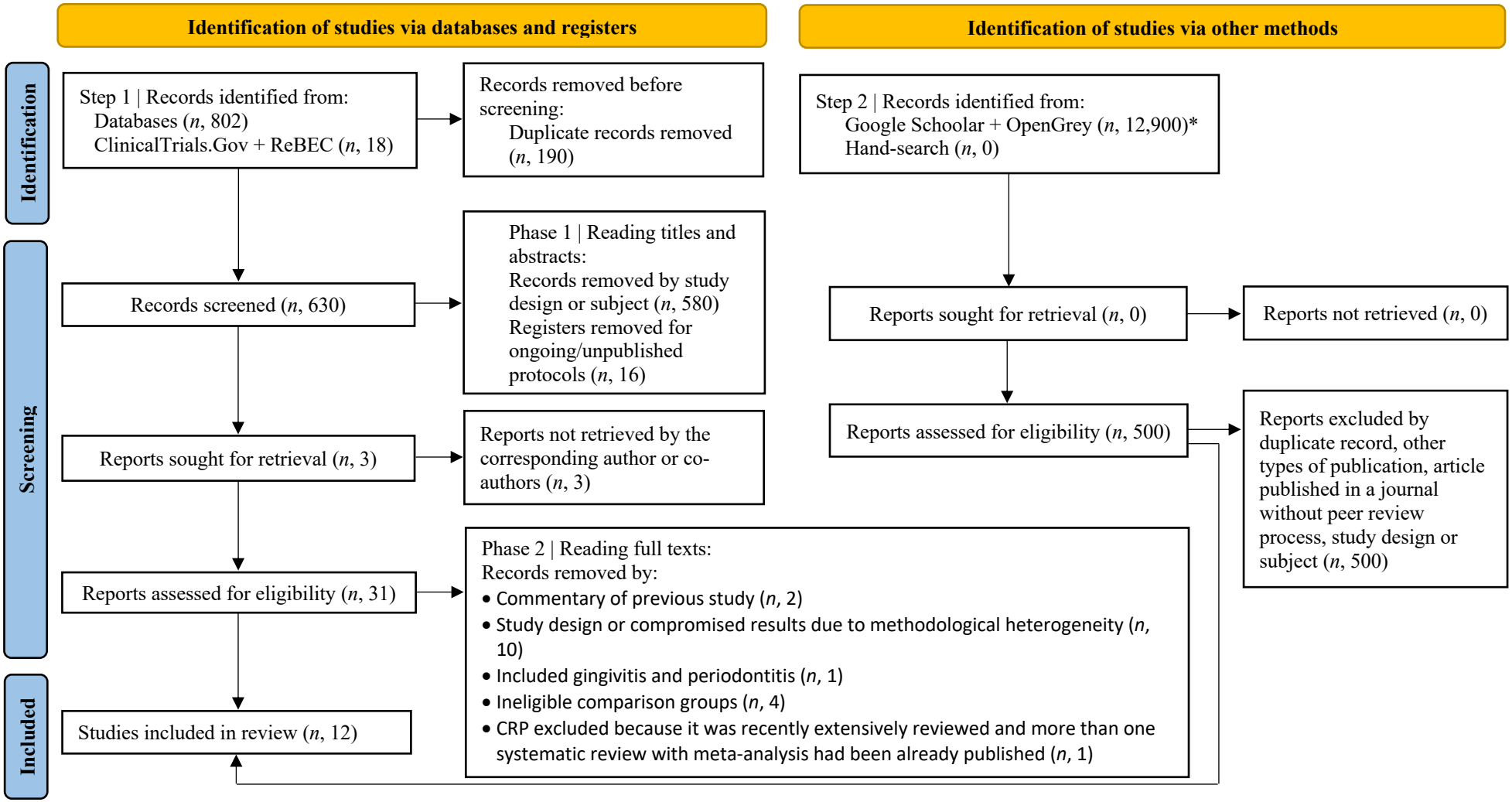
reviews assessed one,[50] two,[46,49,54] three,[52] four,[40,48,53] and five databases.[47,51,55,56] Five reviews assessed other sources,[40,47,48,51,53] and six reviews performed handsearches.[40,48,52,53,55,56] Five studies did not report restrictions such as date or language of publication, or systemic condition.[47,48,52,53,56] Despite the risk of bias within the studies being a premise of the systematic reviews, three reviews did not report the overall risk of bias[51] or used an inadequate tool for quality assessment of the primary studies included.[49,50] Data synthesis of all reviews included only RCT and CCT studies, but barely three reviews applied the GRADE tool to evaluate the certainty of evidence: moderate[52] and very low[48] certainty of evidence, and insufficient evidence to recommend for or against the effect of periodontal treatment on serum CRP levels (Table 2).[56]

Systemic conditions, diagnostic criteria for periodontitis, types of periodontal treatment, supportive periodontal care, and follow-up periods varied widely among the studies. For details, see Table 3.

The most reported systemic diseases in the studies were cardiovascular disease[48] and family history of cardiovascular disease,[49] prehypertension and hypertension,[56] DM,[40,46,54] patients undergoing hemodialysis and/or peritoneal dialysis,[55] rheumatoid arthritis,[51,53] pregnant women,[47] and other comorbidities (i.e. metabolic syndrome, obesity, dyslipidemia, hyperlipidemia, hypercholesterolemia).[52] Only one study did not report the systemic condition of the study population.[50] Most studies controlled for other comorbidities and smoking (Table 3).[47-49,51,52,54,55]

All systematic reviews and meta-analyses considered cases of periodontitis with periodontal probing depth (PPD) ≥ 4 mm and clinical evidence of attachment loss or radiographic finding of loss of dental support apparatus in > 1 tooth in the data analyses. Three reviews reported improvement in periodontal parameters after periodontitis-treatment,[49,51,56] and da Silva et al.[47] reported periodontal improvement in an included primary study. There was no pattern between the periodontal treatment protocols analyzed and the results reported in the systematic reviews and meta-analyses. All reviews included non-surgical SRP per quadrant or intensive care (one-stage or full mouth SRP), four included open flap debridement,[40,49,50,52] one encompassed the use of anti-inflammatory,[49] seven reported the use of local or systemic antibiotics/antimicrobials,[40,46,49,50,52,55,56] and three the use of mouthwashes as adjuvants to periodontal treatment.[46,47,52] Most meta-analysis studies that reported significant improvement in CRP levels after periodontitis treatment [3:5 (60 %)] involved supportive periodontal care,[40,55,56] while only 2:7 (28.6 %) reviews that showed no benefit of periodontitis-treatment for CRP levels reported supportive periodontal care (Table 3).[48,52]

FIGURE 1. PRISMA flow diagram for new systematic reviews which included searches of databases, registers, and other sources of the screening process



From: Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ 2021;372:n71. doi: 10.1136/bmj.n71. For more information, visit: http://www.prisma-statement.org/

Legend: *, the first 500 results (approximately 3.88 %) of Google Schoolar search results were accessed for the eligibility criteria.

TABLE 2

Evidence table summarizing general data of systematic reviews and meta-analysis evaluating the effect of periodontal treatment on circulating levels of CRP										
Study | Registered database	**Written-oriented checklist**	**PICO**	**Searches**	**Number and design of included studies**	**Quality assessment/risk of bias tool | Overall quality/risk of bias**	**Meta-analysis for CRP outcome based on RCT/CCT studies**	**Certainty of the evidence**	**Conclusion by the authors**	**Conflict of interest**	**Funding support**
Ioannidou et al., 2006 NR	NR	NR	Databases: MEDLINE (OVID), and Cochrane CENTRAL Other sources: NR Restrictions: English language Publication date: Between 1966 and July 2005	3 RCTs, and 7 single cohorts––only RCT studies were included in the meta-analysis	IT	DerSimonian and Laird (1986) random-effects model [data for each study were entered as sample size, mean difference, and standard deviation for both the comparison groups (intervention vs control) – summary measure = mean difference, and 95% CI] The combined overall effect (weighted average) was considered significant if $p < 0.05$	NR	"There is now a large body of evidence to indicate that systemic inflammation is present in patients with periodontal disease. Thus, information from RCTs and single-cohort studies does not support the hypothesis that periodontal treatment can reduce systemic CRP levels."	NR	NR
Teeuw et al., 2010 NR	NR	NR	Databases: MEDLINE/PubMed, and Cochrane Library Other sources: NR In addition, the hand search was performed	2 RCTs, and 2 CCTs	Standard assessment form developed by the Dutch Cochrane Centre and the Dutch Institute for Healthcare Improvement	No	NR	"The present meta-analysis suggests that periodontal treatment leads to an improvement of glycemic control in type 2	No	College of Health Insurances (CvZ), Amsterdam, the Netherlands, which supplied a grant for literature reviews related to the effects of periodontal treatment in patients

			Restrictions: English language Publication date: Between January 1960 and 31 March 2009		CBO (http://www.cochrane.nl/nl/newPage1.html) RCT studies: +, good quality CCT studies: +/-, doubtful quality			diabetic patients for at least 3 months."		with chronic medical conditions
de Freitas et al., 2012 NR	NR	NR	Databases: MEDLINE/PubMed Other sources: NR Restrictions: English language Publication date: Up to June 2007	4 RCTs, and 7 interventional studies––only RCT and CCT studies were included in the meta-analysis	IT	The 4 RCTs were combined into a single analysis using a fixed-effect model, since no heterogeneity was observed between the studies (p = 0.311) – summary measure = mean difference, and 95% CI	NR	"The findings indicated that non-surgical periodontal treatment had a positive effect with regard to reduction of the serum levels of C-reactive protein."	NR	NR
Kaur et al., 2014 NR	PRISMA statement[1]	NR	Databases: MEDLINE/PubMed, DOSS, Embase, Scopus, and Lilacs Other sources: Web of Knowledge, MedNar, and ProQuest Theses, and Dissertations Restrictions: English language Publication date: Up to September 2013	3 RCTs, and 2 CCTs	Joanna Briggs Institute Meta-analysis of Statistics Assessment and Review Instrument (JBI-MAStARI, Joanna Briggs Institute, University of Adelaide) NR	FEM for homogeneous studies REM was used when studies were characterized by high heterogeneity [data for each study were entered as sample size, standardised mean difference, standard error, and 95% CI for both the comparison groups (intervention vs control)] – $I^2 > 50$ % indicated high	NR	"Based on clinical and biochemical markers, non-surgical periodontal treatment in individuals with periodontitis and RA could lead to improvements in markers of disease activity in rheumatoid arthritis. All studies had low subject numbers with the periods	No	Research staff and laboratory expenses: National Health & Medical Research Council of Australia Study: National Health and Medical Research Council of Australia (Grant number 1023747)

						heterogeneity between studies The combined overall effect (weighted average) was considered significant if $p < 0.05$		of intervention no longer than 6 months. Larger studies are required to explore the effect of non-surgical periodontal treatment on clinical indicators of rheumatoid arthritis, using more rigorous biochemical and clinical outcome measures as well as giving consideration to potential confounding factors of co-morbidity."		
Li et al., 2014 NR	Cochrane review [Cochrane Handbook for Systematic Reviews of Interventions version 5.1.0 (Higgins, 2011)][6]	NR	Databases: Cochrane Oral Health's Trials Register, Cochrane (CENTRAL), MEDLINE (OVID), Embase (OVID), and the Cumulative Index to Nursing and Allied Health Literature (CINAHL EBSCO) Other sources: US National Institutes of Health Trials Registry (ClinicalTrials.gov), the World Health Organization	1 RCT	Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0 [updated March 2011][6] and the Cochrane systematic review by Shi (2013) High risk of bias	No	The Grading of Recommendations Assessment, Development and Evaluation (GRADE) tool[2] Quality of the evidence: Very low	"We found very low quality evidence that was insufficient to support or refute whether periodontal treatment can prevent the recurrence of cardiovascular disease in the long term in patients with chronic periodontitis. No evidence on primary	No	Internal sources: West China College of Stomatology, Sichuan University, China; Chinese Cochrane Center, China; National University Student Innovation Test Plan, China; Grant Number: 101061001; Aubrey Sheiham Public Health & Primary Care Scholarship 2011, UK; School of Dentistry at The University of Manchester,

			International Clinical Trials Registry Platform, OpenGrey, Chinese BioMedical Literature Database, China National Knowledge Infrastructure, VIP database, and Sciencepaper Online In addition, the hand search was performed Restrictions: No Publication date: Up to 27 August 2017					prevention was found."		Manchester Academic Health Sciences Centre (MAHSC) and the NIHR; and Manchester Biomedical Research Centre, UK External sources: Cochrane Oral Health Global Alliance, UK; UK Cochrane Centre, UK; and National Institute for Health Research (NIHR), UK
Teeuw et al., 2014 NR	PRISMA statement[1]	NR	Databases: MEDLINE/PubMed, Embase, and Cochrane CENTRAL Other sources: NR In addition, the hand search was performed Restrictions: NR Publication date: Up to June 2013	19 RCTs, and 2 CCTs	IT (as proposed previously by Van der Weijden et al., 2009) Selected studies without co-morbidities (n = 7): Low risk of bias (n = 3), and moderate risk of bias (n = 4) Selected studies with co-morbidities (n = 14): Low risk of bias (n = 4), moderate risk of bias (n = 7), and high risk of bias (n = 3)	Weighted mean difference and 95% CI values between IG and CG groups at both baseline and end were calculated using a FEM or REM REM was used to calculate a weighted average on the treatment effects across the studies under review If there were ≤ 4 trials, FEM analysis was used [poor estimate of inter-trial variance (Van Strydonck et al., 2012)] hs-CRP outcome: Additional meta-analysis on RCTs with low estimated	The Grading of Recommendations Assessment, Development and Evaluation (GRADE) tool[2] Quality body of evidence for systemic inflammation and thrombosis, lipid and glucose metabolism, and vascular function: Moderate	"This systematic review and meta-analyses demonstrate that periodontal treatment improves endothelial function and reduces biomarkers of atherosclerotic disease, especially in those already suffering from cardiovascular disease and/or diabetes."	No	The Department of Periodontology ACTA, the Netherlands is supported in part by a grant of the University of Amsterdam for its participation in the focal point of "Oral infections and inflammation." Dr. H. Susanto is supported by the Bernouille Foundation of the University Medical Center Groningen, Univer- sity of Groningen, the Netherlands. Dr. F. D'Aiuto holds a Clinical Senior Lectureship Award supported by the

						risk of bias [highest level of evidence (Harbour and Miller, 2001)] If the data from the CG were used in more than one comparison, the number of subjects (*n*) in this group was divided by the number of comparisons A chi-square test resulting in a $p <$ 0.1 was considered an indication of significant statistical heterogeneity I^2 statistic of 0–40 % was interpreted as not to be important, and above 40 % moderate to considerable heterogeneity may be present (Higgins and Green, 2011)				UK Clinical Research Collaboration and works at UCLH/UCL and received a proportion of funding from the Department of Health's NIHR Biomedical Research Centres funding scheme
Artese et al., 2015 PROSPERO: ID CRD42015027750	PRISMA statement[1]	NR	Databases: MEDLINE, Embase, Cochrane CENTRAL, and Lilacs Other sources: ClinicalTRials.Gov, and OpenGrey In addition, the hand search was performed Restrictions: English language, IG with at least 3	6 RCTs, and 3 CCTs	The Cochrane Collaboration's tool for assessing risk of bias in randomised trials[3] Randomization was performed in all RCTs included, but only 3 of them appropriately described the	REM was used [data for each study were entered as sample size, mean difference, and standard deviation for both the comparison groups (intervention vs control) – summary measure = mean difference, and 95% CI]	NR	"The results of this meta-analysis support the hypothesis that periodontal treatment reduces serum levels of TNF- α and CRP in type 2 diabetes mellitus individuals. The decrease of inflammatory	No	Francesco D'Aiuto holds a Clinical Senior Lectureship Award supported by the UK Clinical Research Collaboration. Francesco D'Aiuto and Jean Suvan work at UCL, which received a proportion of funding from the Department of

			months follow- up, and at least 30 individuals included in the type 2 diabetes group Publication date: Up to November 2013		sequence of generation and allocation concealment These 3 studies also described adequate methods of examiner masking (low risk of bias) Other 3 studies included were not described as RCT and were hence deemed as being at high risk of bias due to lack of description about randomization scheme, allocation of treatment group concealment, masking of examiners, withdrawals and missed follow-up as described by Cochrane group. Follow-up period and dropouts were clearly described by all studies included	The combined overall effect (weighted average) was considered significant if $p <$ 0.05		burden has important implications for metabolic control and can, in part, explain the mechanisms linking periodontitis and increased risk for complications in people with type 2 diabetes mellitus."		Health's National Institute of Health Research (NIHR) Biomedical Research Centers funding scheme
Calderaro et al., 2017 NR	QUOROM statement[4]	NR	Databases: MEDLINE/PubMed, Cochrane Library, SciELO, and Lilacs	1 RCT, and 3 CCTs	PEDro scale for clinical trials[5] Quality assessment varied from 5	FEM for homogeneous studies REM was used when studies were	NR	"The reduction of DAS 28 in patients with rheumatoid arthritis after	No	NR

			Other sources: Clinical Trials In addition, the hand search was performed Restrictions: No Publication date: Up to December 2014		(fair) to 7 (good) points	characterized by high heterogeneity [data for each study were entered as sample size, mean difference, standard error, and 95% CI for both the comparison groups (intervention vs control)] – Q statistic ($p < 0.10$) and $I^2 > 50$ % indicated high heterogeneity between studies The combined overall effect (weighted average) was considered significant if $p < 0.5$		periodontal treatment suggests that the improvement of periodontal condition is beneficial to these patients. Further randomized controlled clinical trials are necessary to confirm this finding."		
da Silva et al., 2017 PROSPERO: ID CRD42015027750	PRISMA statement[1]	P: Pregnant women diagnosed with chronic periodontitis by clinical examination I: NSPT C: No periodontal treatment (untreated group) O: Inflamm	Databases: MEDLINE/PubMed, Web of Science, Cochrane Library, Scopus, and Lilacs Other sources: ProQuest, Open Grey, and Google Scholar Restrictions: No Publication date: Up to June 5, 2017	4 RCTs	Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0 [updated March 2011][6] None of the studies fulfilled all methodological quality criteria. Low risk of bias (1 study), moderate risk of bias (2 studies), and high risk of bias (1 study)	No	NR	"These results demonstrated that the intrapregnancy nonsurgical periodontal treatment decreased periodontal inflammatory biomarker levels from gingival crevicular fluid and some from serum blood, with no influence on inflammatory biomarker level from cord blood, and it did	No	No

		atory biomarkers followed till delivery						not consistently reduce adverse gestational adverse outcome occurrence.”		
Baeza et al., 2020 NR	The protocol was designed in accordance with the Cochrane standards for systematic reviews PRISMA statement (version not reported)	NR	Databases: MEDLINE/PubMed, and Cochrane CENTRAL Other sources: NR Restrictions: English language Publication date: Up to July 10, 2018	9 RCTs	The Cochrane Collaboration's tool for assessing risk of bias in randomised trials[3] Random sequence generation, allocation concealment, blinding of outcome assessment, incomplete outcome data and selective reporting: all studies showed low risk of bias Blinding of participants and personnel: low risk of bias (n = 1), high risk of bias [(n = 6) it was not possible to blind the participants and personnel for untreated CG], and unclear risk of bias (n = 2) Other bias (lack of information regarding	FEM for homogeneous studies REM was used when studies were characterized by high heterogeneity [data for each study were entered as sample size, mean difference, and standard deviation for both the comparison groups (intervention vs control) – summary measure = mean difference, and 95% CI] The combined overall effect (weighted average) was considered significant if $p <$ 0.05	NR	“SRP has an impact on metabolic control and reduction of systemic inflammation of patients with type 2 diabetes.”	No	Grant provided by Federación Iberopanamericana de Periodoncia (FIPP) and FONDEF IDEA ID18I10034

					control measures and possible changes in the management of type 2 diabetes mellitus or interventions performed by a general dentist and nonspecialist, and less clear situations such as those related to the contamination of the results (contamination bias) due to the effect of procedures in the CG (i.e. debridement and/or IHO): low risk of bias (*n* = 4), high risk of bias (*n* = 3), and unclear risk of bias (*n* = 3)					
Yue et al., 2020 PROSPERO: ID CRD42018112231	Cochrane Handbook[3] and PRISMA statement[1]	NR	Databases: PubMed, EMBASE, Cochrane CENTRAL, China National Knowledge Infrastructure (CNKI), and Chinese Medicine Premier's Wanfang database (WFPD) Other sources: NR	5 RCTs	The Cochrane Collaboration's tool for assessing risk of bias in randomised trials[3] Random sequence generation: low risk of bias (*n* =	FEM for homogeneous studies REM was used when studies were characterized by high heterogeneity [data for each study were entered as sample size, standardised mean difference, standard	NR	"NSPT can moderately reduce serum hs-CRP levels in HD and/or PD patients, but did not significantly change IL-6 or Alb levels. For TNF-α and lipid metabolism	No	Program for Innovation Team Building at Institutions of Higher Education in Chongqing in 2016 (CXTDG201602006)

			In addition, the hand search was performed Restrictions: English and Chinese language Publication date: Up to July 2019		3), and unclear risk of bias (n = 2) Allocation concealment, and blinding of participants and personnel: low risk of bias (n = 2), and unclear risk of bias (n = 3) Blinding of outcome all studies showed unclear risk of bias Incomplete outcome data, selective outcome data, and other biases: all studies showed low risk of bias Overall risk of bias: all studies showed moderate risk of bias	error, and 95% CI for both the comparison groups (intervention vs control)] – Q statistic ($p < 0.10$) and $I^2 > 50$ % indicated high heterogeneity between studies The combined overall effect (weighted average) was considered significant if $p < 0.5$		markers, no sufficient evidence supports that these levels are changed after NSPT. Additional scientific research is necessary to assess the effects of NSPT on systemic inflammation and metabolic parameters in dialysis patients.”		
Sharma et al., 2021 PROSPERO: ID CRD42020173133	PRISMA-P[7]	P: Normotensive, prehypertensive and hypertensive individuals with moderate or severe	Databases: MEDLINE (OVID), EMBASE (OVID), Cochrane CENTRAL, Web of Science, and CINAHL Other sources: NR In addition, the hand search was performed Restrictions: No	8 RCTs	RoB 2 tool[8] Random sequence generation (selection bias): low risk of bias (6 studies) and unclear risk of bias (2 studies) Allocation concealment (selection bias): low risk of bias	FEM for homogeneous studies REM was used when studies were characterized by high heterogeneity [data for each study were entered as sample size, mean difference, and standard deviation for both the	Grade C (SORT C)[9]	“Intensive periodontal treatment leads to improvement of the cardiovascular health in hypertensive and prehypertensive individuals.”	No	1) Postgraduate research fund of Univeristy of Glasgow, UK; and 2) Statuatory grant of Jagiellonian Iniversity, Poland N41/DBS/000241

		periodontitis I: NSPT with both supra and subgingival instrumentation (intensive periodontal treatment) C: No intervention group or supragingival debridement only (control periodontal treatment) O: Changes in mean systolic blood pressure and diastolic blood pressure levels followin	Publication date: Up to 23 March 2020		(6 studies) and unclear risk of bias (2 studies) Blinding of participants and personnel (performance bias): low risk of bias (3 studies) and unclear risk of bias (5 studies) Blinding of outcome assessment (detection bias): low risk of bias (4 studies), unclear risk of bias (3 studies) and high risk of bias (1 study) Incomplete outcome data (attrition bias): low risk of bias (5 studies) and unclear risk of bias (3 studies) Selective reporting (reporting bias): low risk of bias Other bias: low risk of bias (7 studies) and unclear risk of bias (1 study)	comparison groups (intervention vs control) – summary measure = mean difference, and 95% CI] The statistical significance of the combined overall effect was not reported Correlations between baseline and follow-up measurements were assumed as sensitivity analyses				

		g periodontal treatment								

Legend: PROSPERO, international prospective register of systematic reviews; PRISMA, preferred reporting items for systematic reviews and meta-analyses; PICO, population-intervention-comparison-outcomes; NR, not reported; IT, inappropriate tool; NSPT, nonsurgical periodontal reatment; RCT, randomized controlled trial; RoB 2, revised Cochrane risk-of-bias tool for randomized trials.

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TABLE 3

Descriptive table summarizing the main outcomes of systematic reviews and meta-analysis evaluating the effect of periodontal treatment on circulating levels of CRP

Study	(P) Systemic condition	(P) Controlled for other co-morbidities (apart from periodontitis)	(P) Controlled for smoking	(P) Periodontal diagnoses	(I) Types of periodontal interventions	(C) Control group	(I/C) Supportive periodontal care	Evidence of periodontal treatment efficacy	Follow-up	Main results
Ioannidou et al., 2006	Healthy, family history of	Yes	Yes	The definition used for the diagnosis of periodontitis varied	The periodontitis treatment varied	NR	NR	Unreported (n = 1), significant	2 months, 3 months, 4 months, 6	Statistically significant decrease on CRP levels in the

	cardiovascular disease, and unreported CRP outcome: healthy (*n* = 2) and unreported (*n* = 1)			widely among the studies: Moderate to severe periodontitis (*n* = 1) PPD ≥ 4 mm (*n* = 1) 50 % of teeth with PPD > 4 mm (*n* = 1) ≥ 4 teeth with PPD ≥ 5 mm [*n* = 1 (RCT study)] ≥ 5 teeth with PPD ≥ 5 mm [*n* = 1 (RCT study)] 50 % of teeth with PPD ≥ 6 mm and bone loss ≥ 30 % [*n* = 4 (1:4 was RCT study)] ≥ 6 teeth with radiographic bone loss (*n* = 1)	widely among the studies: SRP (*n* = 1), SRP and OHI (*n* = 2), SRP in one session 4-6h (*n* = 1), 4 quads SRP and OHI (*n* = 1), OHI for two visits and SRP for four visits (*n* = 1), SRP and flurbiprofen (*n* = 1), SRP with or without local delivery of minocycline-HCl (*n* = 1), SRP with metronidazole (*n* = 1), SRP with minocycline microspheres (*n* = 1), SRP and surgery with systemic antibiotics (*n* = 1) RCT studies: 4 quads SRP and OHI (*n* = 1), SRP and flurbiprofen (*n* = 1), and SRP with or without local delivery of minocycline-HCl (*n* = 1)			PPD reduction (*n* = 9), and significant CPSS (clinical periodontal sum score) reduction (*n* = 1) RCT studies: Unreported (*n* = 1), and significant PPD reduction (*n* = 2)	months, and 24 months follow-up RCT studies: 24 months, 2 months, and 3 months follow-up	IG that received the highest dose of flurbiprofen (50 mg two times a day for 24 months) CRP levels in the two other NSAID groups (5 and 15 mg flurbiprofen) and the CG showed no differences (Ebersole et al., 1997)
										The study by Ide et al. (2004) did not show any significant difference in CRP levels with treatment
										D'Aiuto et al. (2005) - only the intensive periodontal treatment (subgingival mechanical instrumentation with adjunctive local delivery of minocycline-HCl) group triggered a significant reduction in CRP levels (*p* = 0.001)
										Although the overall effect was slightly in favor of periodontal treatment, the statistical analysis showed no significant

										difference between the two arms (p = 0.49)
Teeuw et al., 2010	Diabetes mellitus	NR	NR	Periodontitis The definition used for the diagnosis of periodontitis varied widely among the studies: Total ≥ 11 teeth, ≥ 2 sites with PPD ≥ 4 mm [n = 1 RCT (hs-CRP outcome)] Total ≥ 8 teeth, CPITN score ≥ 3 in ≥ 2 sextants (n = 1 RCT) Total ≥ 14 teeth with ≥ 8 sites with PPD ≥ 5 mm and CAL ≥ 5 mm (n = 1 CCT) Criteria not reported (n = 1 RCT and 1 CCT)	The periodontitis treatment varied widely among the studies: CCT studies: SRP and doxycycline (100 mg/day for 14 days), and SRP and extraction of teeth with periapical radiolucencies and sufficient periodontal destruction RCT studies: SRP, SRP and topical administration of 10 mg minocycline ointment in every periodontal pocket (hs-CRP outcome), and SRP and doxycycline (100 mg/day for 14 days) and chlorhexidine rinses (0.12 %, twice daily for 4 months)	No treatment (n = 1 RCT and 2 CCTs), OHI [n = 1 RCT (hs-CRP outcome)], and regular dental care (n = 1 RCT)	NR	NR	3 months, 4 months, 6 months, and 9 months follow-up hs-CRP outcome: 6 months follow-up	No significant change in hs-CRP was observed during the whole study Multiple regression analysis for significant variables associated with changes of A1C levels between baseline and 6 months follow-up: A1C decrease correlated with decreases in hs-CRP levels after periodontal treatment [0.33 (p = 0.03)] (Katagiri et al., 2009)
de Freitas et al., 2012	NR	NR	NR	Periodontal disease The definition used for the diagnosis of periodontitis varied widely among the studies:	The periodontitis treatment varied widely among the studies: Unclear design studies: SRP in	NR	NR	NR	Unclear design studies: Before and after data, 1, 3, 5, 7 and	The general mean difference in CRP levels from before to after treatment was -0.231 mg/L (p =0 .000)

				Chronic severe periodontitis (*n* = 1) PD < 4 mm, 4-6 mm or > 6 mm (*n* = 1) ≥ 5 teeth with a site with CAL ≥ 5 mm and bone loss in ≥ 2 quadrants [*n* = 1 (RCT study)] 50 % of teeth presenting bone loss > 4 mm [*n* = 1 (RCT study)] 50 % of the teeth presenting PD ≥ 6 mm and bone loss ≥ 30 % [*n* = 3 (1:3 was RCT study)] ≥ 50 % of teeth presenting PPD > 6 mm and CAL > 30 % [*n* = 1 (RCT study)] Bone loss > 25 % teeth (*n* = 1) CPSS (clinical periodontal sum score) and CRSS (clinical and radiographic sum score) (*n* = 1)	whole mouth (*n* = 1), SRP and OHI (*n* = 1), SRP and OHI and surgery (*n* = 1), SRP and metronidazole 500 mg (*n* = 1), OHI in 2 visits and manual SRP and SRP with ultrasound in 4 visits (*n* = 1), and scaling with ultrasound device and topical antibiotic (*n* = 1) RCT studies: Conventional SRP and intensive treatment (*n* = 1), OHI and conventional SRP and SRP with ultrasound (*n* = 1), SRP in a single session and local antibiotic, or only SRP in a single session (*n* = 1), and intensive treatment in a single session and local antibiotic (*n* = 1)				30 days, 6 weeks, 2 months, 3 months, and 6 months follow-up RCT studies: 15, 30, 60 and 120 minutes after treatment (Ide et al., 2004), 1, 7, 30, 60 and 180 days after treatment (Tonetti et al., 2007) 1 month, 2 months, and 6 months (D'Aiuto et al., 2005, 2006) follow-up	Periodontal treatment was seen to be a statistically significant protective factor for the serum levels of CRP
Kaur et al., 2014	Rheumatoid arthritis [American College of Rheumatology (Arnett	Yes	Yes (no smokers in the included studies)	Mild to severe periodontitis [1999 Consensus Classification of Periodontal	NSPT without the use of any adjunctive agents such as antibiotics or host-modulating medications	Age- and gender-matched individuals receiving no periodontal	NR	3:5 studies reported a significant reduction in PPD and CAL	6 weeks, 8 weeks, 3 months, and 6 months follow-up	There was no statistically significant decrease in CRP levels after NSPT compared to the CG

	et al., 1988)][1]			Diseases (Armitage, 1999)][2]		treatment for the duration of the study or baseline measure		1:5 study reported significant reduction in CAL 1:5 study reported no periodontal improvement	CRP outcome: 8 weeks and 6 months follow-up (Okada et al., 2013 and Pinho et al., 2009, respectively)	Effect of NSPT on CRP in patients with rheumatoid arthritis: no statistical association [p = 0.86 and 0.29 (Okada et al., 2013 and Pinho et al., 2009, respectively)]
										Meta-analysis confirmed this finding: overall SMD between the IG and the CG was -0.072 (95% CI: -0.497 to 0.352) CRP was not significantly reduced in patients with rheumatoid arthritis following NSPT
Li et al., 2014 NR	Cardiovascular disease (≥ 50 % blockage of one coronary artery or have had a coronary event within 3 years but ≥ 3 months previously)	Yes	Yes	Chronic periodontitis (≥ 6 natural teeth, including third molars, with ≥ 3 teeth with PPD ≥ 4 mm, ≥ 2 teeth with interproximal CAL ≥ 2 mm, and ≥ 10 % of sites having BOP)	OHI and a regimen of fullmouth SRP with local anaesthesia (30 % of the treatment being completed > 2 months after randomisation); 92.7 % of the participants received the treatment, and one participant received SRP outside the study	OHI and a copy of their oral radiographs, a letter stating the tentative oral findings, and were recommended to seek the opinion of a dentist (9 % of the participants in the control group got SRP outside	IG: 30 % of the treatment being completed > 2 months after randomisation CG: 9 % of the participants got SRP outside the study within 6 months and 11 % of them got SRP within the entire	NR	The participants were observed for 6 months to 25 months	Serum hs-CRP was tested at one year: SRP had no significant effect on serum hs-CRP compared to community care (mean difference = 0.62; 95% CI: 1.45 to 2.69)
										High CRP, defined as CRP > 3 mg/L, was reported at one year follow-up but the results were not statistically significant (RR = 0.77; 95% CI: 0.32 to 1.85)

						the study within six months and 11 % of them got SRP within the entire follow-up period)	follow-up period			
Teeuw et al., 2014	Patients with periodontitis and with or without co-morbidities [cardiovascular diseases (i.e. heart disease, coronary heart disease, coronary artery disease, carotid artery atherosclerosis, lower extremity atherosclerosis, hypertension, anti-hypertensive drugs, and ideopathic edema), cardiovascular risk markers (i.e.	Yes	Yes	The definition used for the diagnosis of periodontitis varied widely among the studies: Without co-morbidity (n = 6 RCTs): NR (n = 1), ≥ 6 sites with PPD ≥ 5 mm and CAL ≥ 2 mm (n = 1), ≥ 6 teeth with PPD ≥ 5 mm and ≥ 3 sites with CAL ≥ 3 mm (n = 1), ≥ 50 % of teeth with PPD ≥ 6 mm and ≥ 30 % alveolar bone loss (n = 2), and ≥ 20 teeth without periapical lesions and ≥ 5 teeth with PPD ≥ 6 mm and radiographic evidence of alveolar bone loss (n =1) With co-morbidity (n = 13 RCTs and 2 CCTs): Self-reported gingival swelling and bleeding, purulent	SRP - The periodontitis treatment varied widely among the studies: Without co-morbidity (n = 6 RCTs): SRP (n = 2 RCT), SRP and extraction of hopeless teeth (n = 1 RCT), SRP and chlorhexydine gel in all sites with PPD ≥ 4 mm and extraction of hopeless teeth (n = 1 RCT), SRP only or SRP and local delivery of minocycline (Arestin®) (n = 1 RCT), SRP and local application of antibiotics (Arestin®) and extraction of hopeless teeth (n = 1 RCT) With co-morbidity (n = 13 RCTs and 2 CCTs): SRP (n = 5 RCTs), SRP and	No periodontal treatment, except for 1 RCT without co-morbidity (supragingival scaling and polishing) and 2 RCTs with co-morbidity [supra-gingival scaling, and Supra-gingival scaling and 2 placebo tablets for antibiotics (3 times a day for 1 week)]	NR (n = 16 studies) Mouthwash every day for 6 months (n = 2 RCTs with co-morbidity) Mouthwash every day for 6 months (n = 1 CCT with co-morbidity) Subgingival debridement at 3 months follow-up, or supragingival prohylaxis at 3 months follow-up (n = 1 RCT with co-morbidity) SRP and local application	NR	Without co-morbidity: 2 months (n = 1 RCT), 3 months (n = 4 RCTs), and 6 months (n = 1 RCT) follow-up With co-morbidity: 2 months (n = 1 RCT), 3 months (n = 4 RCTs), 4 months (n = 1 CCT), 6 months (n = 7 RCTs and 1 CCT), and 12 months (n = 1 RCT) follow-up	Meta-analysis: A significant weighted mean difference including all available trials was found for hs-CRP [-0.50 mg/L; 95% CI: -0.78 to -0.22 (p = 0.0005)] Periodontitis patients with co-morbidity benefited the most from periodontal treatment. Subanalysis: significant weighted mean difference were observed for hs-CRP [-0.71 mg/L; 95% CI: -1.05 to -0.36 (p < 0.0001)] Patients with co-morbidity benefited the most from periodontal treatment was still present if only studies with a low risk of bias were included

	hemodialysis and peritoneal dialysis, impaired glucose tolerance, diabetes mellitus, metabolic syndrome, obesity, dyslipidemia, high blood pressure, elevated fasting glucose, hyperlipidemia, and hypercholesterolemia), and others (i.e. rheumatoid arthritis)			discharge, and tooth mobility, and ≥ 2 teeth with PPD ≥ 4 mm and CAL ≥ 3mm (*n* = 1 RCT), self-reported gingival swelling and bleeding, purulent discharge, and tooth mobility, and periodontitis definition NR (*n* = 1 RCT), > 3 sites with PPD > 4 mm (*n* = 1 RCT), ≥ 11 teeth and ≥ 2 sites with PPD ≥ 4 mm (*n* = 1 RCT), ≥12 teeth and ≥ 2 teeth with CAL ≥ 6 mm and ≥ 1 site with PPD ≥ 5 mm (*n* = 1 RCT), ≥12 teeth ≥ 4 sites with PPD ≥ 4 mm and 5 sites with CAL ≥ 6 mm (*n* = 1 RCT), ≥ 14 teeth ≥ 4 teeth with ≥ 1 pocket with PPD and with CAL ≥ 3 mm (*n* = 1 RCT), ≥ 14 teeth ≥ 4 teeth with ≥ 1 site with PPD ≥ 4 mm and CAL ≥ 3 mm and BOP > 20 % (*n* = 1 RCT), ≥16 teeth and mean CAL ≥ 1 mm (*n* = 1 RCT), ≥16 teeth and ≥ 8 sites with PPD ≥ 6	local application of antibiotics (minocyline 10 mg in every periodontal pocket) and extraction of hopeless teeth (*n* = 1 RCT), SRP and local application of antibiotics (Minocyline at every site with PPD ≥ 5 mm at baseline and the 3 months and 6 months follow-up) and extraction of hopeless teeth (*n* = 1 RCT), SRP and extraction of hopeless teeth and systemic antibiotics (metronidazol 250 mg and amoxicillin 500 mg 3 times a day for 1 week) (*n* = 1 RCT), SRP and antibiotics for 4 to 7 days and mouthwash every day for 6 months (*n* = 2 RCTs), SRP and 5 patients received open flap debridement (*n* = 1 RCT), SRP and periodontal surgery when indicated and extraction of hopeless teeth and		of antibiotics (minocyline at every site with PPD ≥ 5 mm at baseline and the 3 months and 6 months follow-up) and extraction of hopeless teeth (*n* = 1 RCT with co-morbidity)			Significant weighted mean difference was observed for hs-CRP [-0.96 mg/L; 95% CI: -1.86 to -0.06 (*p* = 0.04)] No significant weighted mean difference was observed in otherwise healthy periodontitis patients Subanalysis on hs-CRP levels by differentiating studies on smoking habits and average Body Mass Index: Non-smokers benefited the most from periodontal treatment [weighted mean difference hs-CRP: -0.56; 95% CI: -0.88 to -0.24 (*p* = 0.0007)], whereas study populations consisting of both smokers and non-smokers, did not show a significant difference between the IG and CG [weighted mean difference hs-CRP: -0.29; 95% CI: -0.88 to 0.30 (*p* = 0.34)]

				mm and ≥ 4 sites with CAL ≥ 5 mm distributed in ≥ 2 quadrants (*n* = 1 RCT), ≥ 20 teeth ≥ 5 mm PPD and > 30 % teeth with CAL > 4 mm or ≥ 60 % teeth with PPD > 4 mm and with CAL > 3 mm (*n* = 1 RCT), ≥ 20 teeth > 5 mm PPD and > 30 % teeth with CAL > 5 mm or > 60 % teeth with PPD > 4 mm and with CAL > 3 mm (*n* = 1 RCT), ~20 teeth and ≥ 2 teeth with CAL ≥ 6 mm and ≥ 1 tooth with PPD ≥ 5mm (*n* = 1 RCT), self-reported gingival swelling and bleeding, purulent discharge, and tooth mobility, and periodontitis definition NR (*n* = 1 CCT), and ≥10 teeth ≥1 pocket with PPD ≥ 4 mm and ≥ 4 teeth with CAL ≥ 3 mm (*n* = 1 CCT)	antibiotics (tinidazole 1.0 g , bid and ampicillin 0.25 g qid 3 days before and after periodontal intervention (*n* = 1 RCT), SRP and surgery and extraction of hopeless teeth and systemic antibiotics (tinidazole 1.0 g, bid and ampicillin 0.25 g, qid for 6 days) (*n* = 1 RCT), SRP and extraction of hopeless teeth and systemic antibiotics (doxycycline) and mouthwash twice a day (chlorhexydine) (*n* = 1 CCT), and SRP and antibiotics for 4 to 7 days and mouthwash every day for 6 months (*n* = 1 CCT)					Trials which included study subjects with on average normal weight (BMI < 25 Kg/m^2): significant weighted mean difference of -0.55 mg/L [95% CI: -0.77 to -0.34 (p < 0.00001)] for hs-CRP Trials with an "overweight" study population (BMI > 25 Kg/m^2): non-significant weighted mean difference of -0.44 mg/L [95% CI: -1.28 to 0.40 (p = 0.30)] for hs-CRP 7 trials with < 6 months duration, showed for hs-CRP a weighted mean difference of -0.89 mg/L [95% CI: -1.33 to -0.45 (p < 0.0001)], while another 8 trials with ≥ 6 months follow-up showed for hs-CRP a weighted mean difference of -0.22 mg/L [95% CI: -0.37 to -0.07 (p = 0.005)]

Artese et al., 2015	Type 2 diabetes mellitus [WHO diagnostic criteria, 2006 (fasting plasma glucose ≥ 126 mg/dL and/or 2h post-glucose challenge of 220 mg/dL)	NR	NR	The definition used for the diagnosis of periodontitis varied widely among the studies: ≥ 1 site with PPD ≥ 5 mm and 2 teeth with CAL ≥ 6 mm periodontitis [*n* = 1 (RCT study)] PD ≥ 5 mm in ≥ 4 sites and CAL ≥ 3mm in ≥ 4 sites periodontitis [*n* = 1 (CCT study)] CRP outcome: ≥ 2 sites with PPD ≥ 4 mm, indicating mild to severe periodontitis [*n* = 1 (RCT study)] Chronic periodontitis: ≥ 4 teeth in each jaw with a PPD ≥ 5 mm, CAL ≥ 4 mm, ≥ 2 single-rooted teeth with a PPD of 6 to 9 mm, and BOP [*n* = 1 (CCT study)] PPD > 5 mm, in > 30 % of sites; CAL > 4 mm, or > 60 % teeth with PPD > 4 mm and CAL > 3 mm [*n* = 1 (RCT study)] < 2 affected teeth with CAL ≥ 6 mm and < 1 affected tooth with PPD ≥ 5 mm were assigned to the group with	The periodontitis treatment varied widely among the studies: Full-mouth SRP with or without doxycycline [*n* = 1 (RCT study)] OHI and NSPT [*n* = 1 (CCT study)] CRP outcome: OHI and supra- and subgingival debridement and minocycline ointment during intervention sessions [*n* = 1 (RCT study)] NSPT (OHI and SRP) [*n* = 1 (CCT study)] OHI and fullmouth SRP and periodontal flap surgery when indicated. Antibiotics (tinidazole and ampicillin) for 3 days before and after interventions [*n* = 1 (RCT study)] OHI and SRP and professional plaque control program [n = 1 (CCT study)] Group 1: NSPT (SRP at baseline and additional subgingival debridement after 3 months). Group 2:	No periodontal treatment	NR (6:9 studies) RCT (*n* = 1): Oral hygiene reviewed twice a month. CRP outcome: CCT study (*n* = 1): Professional plaque-control program was performed at 3 months, 6 months, 9 months and 12 months post-treatment RCT study (*n* = 1): Additional subgingival debridement after 3 months or only supragingival prophylaxis after 3 months	NR	1 month, 3 months, 5 months, 6 months, and 12 months follow-up	Statistically significant reductions on CRP serum levels after NSPT (Kardesler et al., 2010; Sun et al., 2011; Chen et al., 2012) No statistically significant difference on serum hs-CRP/CRP after periodontal treatment follow-up (Katagiri et al., 2009; Kadesler et al., 2010; Auyeung et al., 2012; Chen et al., 2012; Lin et al., 2012; Koromantzos et al., 2012) No significant changes in hs-CRP from baseline to 1 month, 3 months, and 6 months between intervention and control groups after the follow-up period [*p* > 0.05 (Katagiri et al., 2009)] hs-CRP decreased significantly 3 months after periodontal treatment in IG compared to the CG [*p* < 0.01 (Sun et al., 2011)] No difference between CRP values at baseline

				mild periodontal disease. > 2 teeth with CAL ≥ 6 mm and > 1 tooth with a PPD ≥ 5 mm were assigned to the group with moderate to severe periodontal disease [*n* = 1 (CCT study)] Chronic periodontitis according to AAP2, with a mean clinical CAL ≥ 1 mm and ≥ 16 teeth [*n* = 1 (RCT study)] Moderate to severe periodontal disease (8 sites with PPD ≥ 6 mm, and 4 sites with CAL ≥ 5 mm, distributed ≥ 2 different quadrants [*n* = 1 (RCT study)] ≥ 20 teeth remaining in the mouth and ≥ 5 teeth with PPD ≥ 5 mm [*n* = 1 (RCT study)]	NSPT at the initial visit and only supragingival prophylaxis after 3 months [n = 1 (RCT study)] OHI and nonsurgical periodontal full-mouth SRP [n = 1 (RCT study)] SRP with or without subgingival minocycline administration [n = 1 (RCT study)]					and 12 months post-treatment for the group with moderate-to-severe periodontitis [*p* = 0.62 (Auyeung et al., 2012; CCT study)]
										NSPT with additional subgingival debridement after 3 months, and NSPT with supragingival prophylaxis at 3 months showed lower hs-CRP at 6 months ($p < 0.05$); hs-CRP showed no significant difference when compared with the CG after 6 months (Chen et al., 2012)
										Koromantzos et al. (2012): No statistical difference in hs-CRP values at 6 months follow-up between baseline and groups (IG and CG) [*p* = 0.06 (log-transformed hs-CRP values)]
										The latent growth curve modeling for log-transformed CRP showed no statistical significance for both SRP and SRP with minocycline groups after 6

										months (Lin et al., 2012) Meta-analysis: A significant mean difference at baseline and between IG and CG was found for hs-CRP [-1.28 mg/L; CI 95%: -2.07 to -0.48 ($p < 0.0001$)]
Calderaro et al., 2017	Rheumatoid arthritis	NR	NR	The definition used for the diagnosis of periodontitis varied widely among the studies: Generalized mild-to-moderate chronic periodontitis according to Armitage (1999)[2] ($n = 1$) Generalized severe chronic periodontitis according to Löe and Sillness (1963)[3] ($n = 1$) Periodontal disease according to Machtei et al. (1992)[4]: ≥ 2 teeth with CAL ≥ 6 mm and ≥ 1 tooth with PPD ≥ 5 mm ($n = 1$) Periodontitis as the presence of at least one site with CAL ≥ 4 mm (Okada et al., 2013)[5] ($n = 1$)	NSPT (SRP and plaque removal and OHI)	No periodontal treatment or OHI	NR	NR	6 weeks ($n = 1$), 8 weeks ($n = 2$), and 6 months ($n = 1$) follow-up	There was no evidence for an effect of periodontal treatment in the blood levels of CRP [OR: −0.16; 95% CI: −0.64 to 0.33 ($p = 0.53$)]
	Pregnant women	Yes	NR	Chronic periodontitis	NSPT and OHI ($n = 4$) with 0.2 %		Non-surgical	Of the four RCT	Unclear	Within CG, serum levels of CRP

da Silva et al., 2017					chlorhexidine rinse once a day (n = 1) or overhanging restoration adjustments (n = 1) CRP outcome: NSPT and OHI with (n = 1) or without (n = 1) 0.2 % chlorhexidine rinse once a day (Offenbacher et al., 2006 and Khaimar et al., 2015, respectively)	No periodontal treatment	supportive periodontal treatment can reduce raised serum CRP levels in pregnant females affected with periodontitis, as reported by Khaimar et al., 2015 (high risk of bias). Supportive periodontal care was not reported for the other RCT included	included, the authors reported improvement in PPD, CAL, and BOP only for Pirie et al. (2013) The effectiveness of periodontal treatment was not reported by the authors for the two RCTs that evaluated CRP (Offenbacher et al., 2006 and Khaimar et al., 2015)		increased during gestation NSPT can reduce (p < 0.05) raised serum CRP levels in pregnant females affected with periodontitis [1 study (Khairnar et al., 2015)] Serum levels of CRP did not differ between groups [1 study (Offenbacher et al., 2006)]
Baeza et al., 2020	Type 2 diabetes [World Health Organization (2016)[6] fasting plasma glucose >126 mg/dl and/or impaired oral glucose tolerance test at 2 h]	NR	Yes	The definition used for the diagnosis of periodontitis varied widely among the studies: Periodontitis (not specified) (n = 1) Periodontitis [AAP (Armitage, 1999)[2]] (n = 1) Periodontitis [AAP (Armitage, 1999)[2]]: CAL > 1 mm and >16 teeth [n = 1 (CRP outcome)] Mild to moderate periodontitis [AAP	OHI and NSPT, except for the study by Chen, et al. (2012), which included surgical debridement at 3 months follow-up CRP outcome: NSPT in 2 sessions (Koromantzos et al., 2012); and (a) scaling and root planing and surgical debridement at 3 months post initial treatment or (b) scaling and root	OHI (n = 2) Supragingival scaling (n = 1) No periodontal treatment (n = 6) CRP outcome: No periodontal treatment	NR	NR	3 months, 4 months, and 6 months follow-up CRP outcome: 6 months follow-up	The meta-analysis indicated a significant reduction from the start to the end of 6 months follow-up in favor of the IG

				(Armitage, 1999)[2]] (*n* = 1) Moderate periodontitis (*n* = 1) Moderate to severe periodontitis (≥ 30 % periodontal pocket) (*n* = 1) Moderate to severe periodontitis (Eke et al., 2012)[7] (*n* = 1) Severe periodontitis [AAP (Armitage, 1999)[2]] [*n* = 1 (CRP outcome)] Localized or generalized severe periodontitis [AAP (Armitage, 1999)[2]] (*n* = 1)	planing and supragingival debridement at 3 months post initial treatment (Chen et al., 2012)				
Yue et al., 2020	Patients undergoing haemodialysis and/or peritoneal dialysis	Yes	NR	The definition used for the diagnosis of periodontitis varied widely among the studies: CAL ≥ 1mm, including slight, moderate, and severe periodontitis and ≥ 16 teeth [*n* = 1 (hs-CRP outcome)] ≥ 2 sites with CAL ≥ 3 mm and PPD ≥ 4 mm [*n* = 1 (hs-CRP outcome)] ≥ 2 sites with CAL > 3 mm and PPD > 4 mm and ≥ 20 teeth [*n* = 1 (hs-CRP outcome)] ≥ 6 sites with CAL ≥ 4 mm and ≥ 14	NSP (OHI and SRP) [*n* = 4 (hs-CRP outcome)] NSP (OHI and SRP and minocycline when all sites with PD > 5 mm at the time of SRP) (*n* = 1)	OHI (*n* = 1) hs-CRP outcome: OHI (*n* = 1) or no periodontal treatment (*n* = 3)	NSP (OHI and SRP and minocycline when all sites with PD > 5 mm at the 3 months and 6 months follow-up (*n* = 1) hs-CRP: Supragingival prophylaxis at 3 months follow-up (*n* = 1) or NR (*n* = 3)	NR	3 months, and 6 months follow-up	Serum level of hs-CRP was significantly decreased at less than or equal to 2 months in dialysis after NSPT, compared with untreated periodontitis patients receiving dialysis

				teeth [*n* = 1 (hs-CRP outcome)] ≥ 2 teeth with CAL ≥ 6 mm and ≥ 1 site with PPD > 5 mm (*n* = 1)						
Sharma et al., 2021	Normotensive individuals [5 studies (*n* = 586)] Prehypertensive and hypertensive individuals [3 studies (*n* = 212)]	NR	NR	Generalized moderate and severe periodontitis	NSPT in the form of supra- and subgingival instrumentation: single root surface debridement combined or not with local or systemic antibiotics/antimicrobials, and many subsequent root surface debridement during 4, 8, 12 weeks	No periodontal treatment or supra-gingival scaling	Oral hygiene instruction only or with performing another root surface debridement or both; one study performed surgical treatment if necessary	All the reported studies demonstrated significant improvement in the clinical measures of periodontitis such as PPD, CAL and BOP assessment after treatment in the IG compared to the CG	The studies were categorized into time-point 1 (follow-up up to 3 months), time-point 2 (values at 6 months) and time-point 3 (values at 12 months follow-up)	Intensive periodontal treatment was associated with significant reductions in the serum levels of CRP at all time-points

Legend: IC, intervention group; CG, control group; OHI, oral hygiene instruction; SRP, scaling and root planing; NSPT, non-surgical periodontal treatment; PPD, periodontal probing depth;CAL, clinical attachment level/loss; BOP, bleeding on probing; CRP, C-reactive protein; hs-CRP, high-sensitivity CRP; IL-6, interleukin 6; IL-10, interleukin 10; IFN-γ, interferon gamma; HDL, high density lipoprotein; LDL, low density lipoprotein; TGs, triglycerides.

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Synthesis of results

Meta-analysis studies. Five meta-analyses reported a positive effect of periodontitis-treatment on serum CRP levels. According to Artese et al.,[40] only three RCT studies (50 %) described adequate methods of examiner masking; the other domains and studies showed high risk of bias. Baeza et al.[54] reported high risk of bias and unclear risk of bias for blinding of participants and personnel domain in 66.7 % and 22.2 % of RCT studies, respectively. The main studies were classified as high risk for another bias domain. Artese et al.[40] and Baeza et al.[54] included patients with type 2 DM. Yue et al.[55] evaluated the effect of periodontal treatment on CRP in patients with periodontitis and hemodialysis and/or peritoneal dialysis; the authors reported moderate overall risk of bias. Although most RCT studies have shown a low risk of bias,[46-49,51,52,54-56] the certainty of the evidence from the systematic review by Sharma et al.[56] was: insufficient to recommend for or against the inclusion of the condition in a periodic health examination, but recommendations may be made on other grounds—the periodontitis-treatment showed potential to reduce serum CRP levels in individuals with prehypertension and hypertension. De Freitas et al.[50] did not report the systemic condition of the study population nor the risk of bias within the primary studies (Table 4).

Four meta-analyses did not identify significant improvement in serum CRP levels after periodontal treatment.[49,51-53] Ioannidou et al.[49] included healthy patients with or without family history of cardiovascular disease, Kaur et al.[51] and Calderaro et al.[53] included patients with rheumatoid arthritis; the latter reported fair to good risk of bias within primary studies. In addition, the effect of periodontitis-treatment on serum CRP levels varied widely among meta-analyses and subgroup assessments in the study by Teeuw et al.[52] including patients with and without comorbidities. The risk of bias within primary studies and the double and triple data entry in the quantitative analyzes limited the study and made de evidence doubtful (Table 4).

TABLE 4

Descriptive table summarizing the meta-analyses evaluating the effect of periodontal treatment on circulating levels of CRP (primary outcome)

Studies	Outcomes	Effect model	*n*	Subgroups	Chi² | df (*p*-value)	I²	Effect size [mean[a] difference, standard mean difference[b], and odds ratio[c] (95% CI)]	Test for overall effect: Z (*p*-value)	Statistical significance
Ioannidou et al., 2006	Changes in the serum CRP levels in the three RCTs included in the meta-analysis	REM	2	Two RCTs including smokers, 4 quads SRP and OHI ($n = 1$), and SRP with and without local delivery of minocycline-HCl [$n = 1$ study with double data entry (data from two IGs from the same study)]	0.67, df = 2 ($p = 0.71$)	0%	-0.18 (-0.7 to 0.34)[a]	0.69 ($p = 0.49$)	No
de Freitas et al., 2012	Changes in serum levels of CRP from before to after the periodontal treatment	FEM	4	RCT studies	$p = 0.311$	NR	-0.231 ($p = 0.000$)[a]	NR	Yes
Kaur et al., 2014	Subgroup meta-analyses of the overall effect of periodontal intervention on serum levels of CRP in IG versus CG at different time-points (standardised mean difference pre-post treatment)	FEM	2	FEM meta-analysis	0.206, df = 1 ($p = 0.659$)	0%	-0.0724 (-0.497 to 0.352)[b]	NR	No
		REM	2	REM meta-analysis			-0.0724 (-0.497 to 0.352)[b]	NR	
Teeuw et al., 2014	Meta-analysis of hs-CRP levels of individual trials	REM	7	Otherwise healthy [$n = 1$ study with double data entry (data from two IGs from the same study)]	12.25, df = 6 ($p = 0.06$)	51%	-0.09 (-0.6 to 0.42)[a]	0.35 ($p = 0.73$)	No
		REM	15	With co-morbidity [$n = 1$ study with double data entry and 1 study with triple entry (data from two and three IGs from the same study, respectively)]	264.86, df = 14 ($p < 0.00001$)	95%	-0.71 (-1.05 to -0.36)[a]	4.01 ($p < 0.0001$)	Yes

		REM	1	Combined otherwise healthy and with co-morbidity	NA	NA	-0.2 (-0.73 to 0.33)[a]	0.74 ($p = 0.46$)	No
		REM	NA	Total (95% CI)	298.6, df = 22 ($p < 0.00001$)	93%	-0.5 (-0.78 to -0.22)[a]	3.46 ($p = 0.0005$)	Yes
		REM	4	Otherwise healthy | Studies with a low risk of bias [n = 1 study with double data entry (data from two IGs from the same study)]	5.28, df = 3 ($p = 0.15$)	43%	0.32 (-0.52 to 1.16)[a]	0.75 ($p = 0.45$)	No
		REM	4	With co-morbidity | Studies with a low risk of bias [n = 1 study with double data entry (data from two IGs from the same study)]	7.31, df = 3 ($p = 0.06$)	59%	-0.96 (-1.86 to -0.06)[a]	2.09 ($p = 0.04$)	Yes
		REM	NA	Total | Studies with a low risk of bias [95% CI (studies with a low risk of bias)]	33.18, df = 7 ($p < 0.0001$)	79%	-0.3 (-1.11 to 0.51)[a]	0.73 ($p = 0.47$)	No
		REM	13	Non-smokers [n = 1 study with double data entry and 1 study with triple entry (data from two and three IGs from the same study, respectively)]	275.93, df = 12 ($p < 0.00001$)	96%	-0.56 (-0.88 to -0.24)[a]	3.39 ($p = 0.0007$)	Yes
		REM	9	Combines non-smokers and smokers [n = 2 studies with double data entry (data from two IGs from the same study)]	14.38, df = 8 ($p = 0.07$)	44%	-0.29 (-0.88 to 0.3)[a]	0.96 ($p = 0.34$)	No
		REM	NA	Total (95% CI)	301.72, df = 21 ($p < 0.00001$)	92%	-0.49 (-0.77 to -0.21)[a]	3.38 ($p = 0.0007$)	Yes
		REM	12	BMI < 25 Kg/m^2 [n = 2 studies with double data entry and 1 study with triple entry (data from two and three IGs from the same study, respectively)]	30.47, df = 7 ($p = 0.001$)	64%	-0.55 (-0.77 to -0.34)[a]	5.01 ($p < 0.00001$)	Yes
		REM	8	BMI > 25 Kg/m^2 [n = 1 study with double data entry (data from two IGs from the same study)]	29.47, df = 7 ($p = 0.0001$)	76%	-0.44 (-1.28 to 0.4)[a]	1.03 ($p = 0.3$)	No

		REM	NA	Total (95% CI)	288.23, df = 19 (p < 0.00001)	93%	-0.56 (-0.88 to -0.25)[a]	3.55 (p = 0.0004)	Yes
	Meta-analysis of hs-CRP levels of individual trials using populations with co-morbidity and a follow-up time of <6 or ≥6 months	REM	7	< 6 months follow-up [n = 1 study with triple data entry (data from two IGs from the same study)]	181.71, df = 6 (p < 0.00001)	97%	-0.89 (-1.33 to -0.45)[a]	3.97 (p < 0.0001)	Yes
		REM	8	≥ 6 months follow-up [n = 2 studies with double data entry (data from two IGs from the same study)]	6.74, df = 7 (p < 0.46)	0%	-0.22 (-0.37 to -0.07)[a]	2.81 (p < 0.005)	Yes
		REM	NA	Total (95% CI)	264.86, df = 14 (p < 0.00001)	95%	-0.71 (-1.05 to -0.36)[a]	4.01 (p < 0.0001)	Yes
Artese et al., 2015	Difference between ΔCRP IG and CG in RCTs	REM	4	One study (Chen et al., 2012) with double data entry (data from two IGs from the same study)]	p = 0.000	97.8%	-1.28 (-2.07 to -0.48)[a]	NR	Yes
Calderaro et al., 2017	Effect of periodontal treatment in the blood levels of CRP	REM	2	2 CCT studies (8 weeks, and 6 months follow-up) – both studies reported no significant differences for CRP after periodontal treatment	NR	77%	-0.16 (-0.64 to 0.33)[c]	NR	No
Baeza et al., 2020	Periodontal treatment outcome: Change in CRP	REM	2	-	0.36, df = 2 (p = 0.83)	0%	1.89 [1.7 to 2.08)[a]	19.73 (p < 0.00001)	Yes
Yue et al., 2020	Difference between serum hs-CRP IG and CG at less than or equal to 2 months	REM	4	-	NR	NR	-1.53 (-2.95 to -0.11)[b]	NR	Yes
Sharma et al., 2021	Subgroup meta-analyses of the overall effect of periodontal intervention on serum levels of CRP in IG versus CG at different time-points (mean difference pre-post treatment)	REM	3	Time-point 1	3.7, df = 2 (p = 0.16)	46%	-0.7 (-1.37 to -0.03)[a]	2.05 (p = 0.04)	Yes
			5	Time-point 2	0.95, df = 4 (p = 0.92)	0%	-1.09 (-1.53 to -0.66)[a]	4.95 (p < 0.00001)	Yes
			1	Time-point 3	NA	NA	-0.95 (-1.72 to -0.18)[a]	2.43 (p = 0.02)	Yes

Legend: IC, intervention group; CG, control group; CRP, C-reactive protein; FEM, fixed effect model; REM, randomized effect model; n, number of studies considered in meta-analysis; Chi^2, chi-squared test; I^2, Higgs's inconsistency test; NA, not applicable.

Qualitative systematic reviews. Three qualitative reviews did not identify a significant improvement in serum CRP levels after periodontal treatment: Teeuw et al.[46] included two RCTs of good quality and two RCTs of doubtful quality in patients with DM; da Silva et al.[47] included a low-risk-of-bias RCT, two low-risk-of-bias RCTs, and a high-risk-of-bias RCT in pregnant women, and Li et al.[48] reported very low quality of evidence based on a high-risk-of-bias RCT focused on patients with cardiovascular disease (Table 2 and 3).

ROBIS assessment. Among the included studies, only three publication (25 %) were assessed as of high risk of bias,[40,50,53] while nine publications were of low risk of bias (Figure 2).[46,47-49,51,52,54-56] Two of the five meta-analysis studies were in favor of improvement of serum CRP levels after periodontal treatment[40,50] and one meta-analysis study that did not disclose this benefit of periodontitis-treatment were classified as at high risk of bias.[53] The methodological quality of the included meta-analysis studies reinforces the evidence of improvement in serum CRP levels after periodontitis-treatment in patients with type 2 DM,[54] hemodialysis and/or peritoneal dialysis,[55] pre-hypertension and hypertension.[56]

On the other hand, another four low-risk-of-bias meta-analyses found no significant improvement in CRP after periodontitis-treatment in healthy patients with or without a family history of cardiovascular disease,[49] with rheumatoid arthritis,[51,53] and patients with and without comorbidities.[52] Recognizing the limitations of the three qualitative systematic reviews, especially the number of primary studies included, the low risk of bias of these studies and the three meta-analyses[49,51,53] suggest that more studies are needed to substantiate with specific evidence the risk of systemic impact of periodontitis assessed by the levels of CRP and by other biomarkers. For details, see Table 5.

FIGURE 2. Overall risk of bias stratified by ROBIS domains for each systematic review and meta-analysis studies

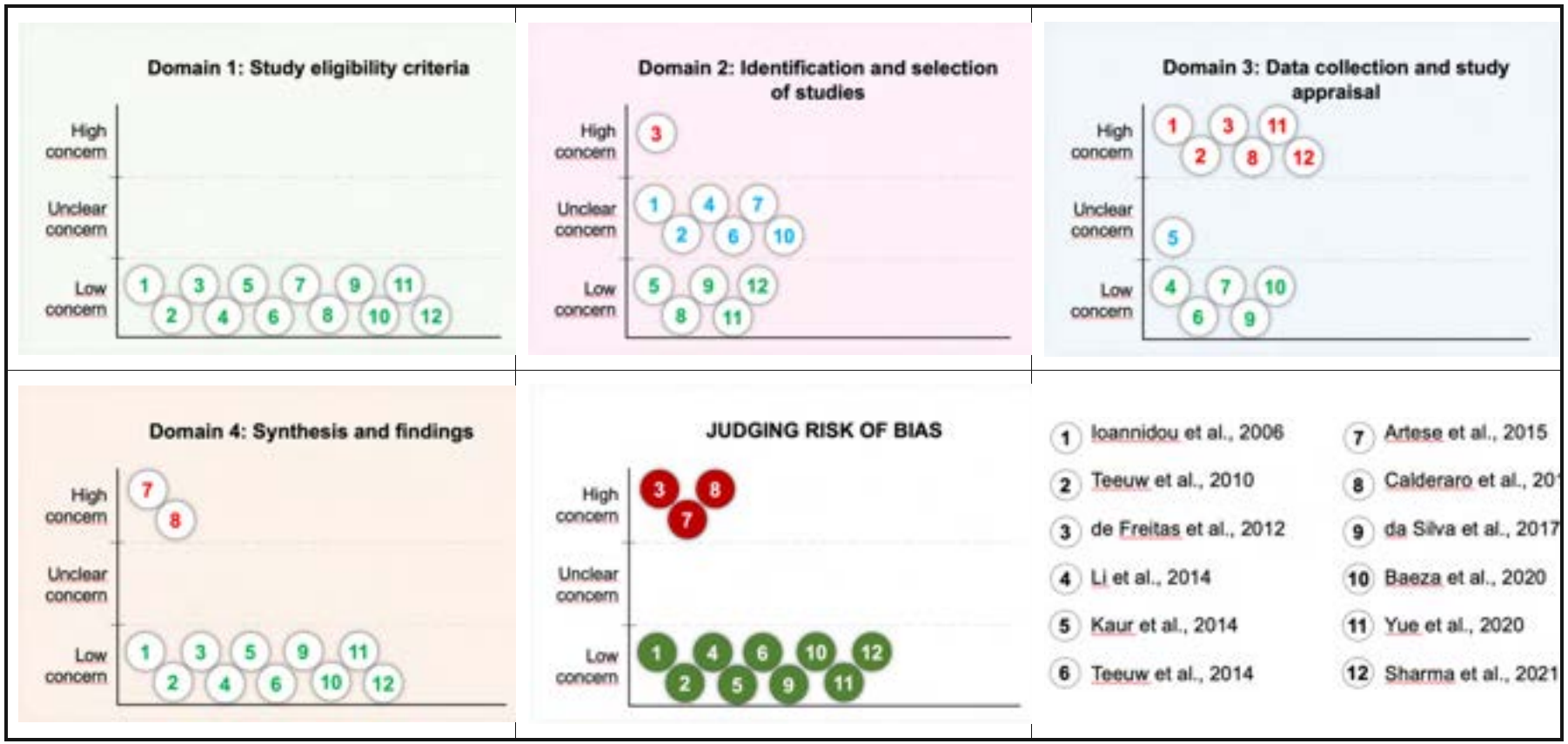

TABLE 5

Description of ROBIS domains and overall risk of bias within systematic reviews and meta-analysis studies

	Ioannidou et al., 2006	Teeuw et al., 2010	de Freitas et al., 2012	Kaur et al., 2014	Li et al., 2014	Teeuw et al., 2014	Artese et al., 2015	Calderaro et al., 2017	da Silva et al., 2017	Baeza et al., 2020	Yue et al., 2020	Sharma et al., 2021
Domain 1: Study eligibility criteria												
1.1 Did the review adhere to pre-defined objectives and eligibility criteria?	PY	PY	PY	PY	Y	PY	Y	PY	Y	PY	Y	Y
1.2 Were the eligibility criteria appropriate for the review question?	PY	Y	PY	PY	Y	Y	Y	PY	Y	Y	Y	PY
1.3 Were eligibility criteria unambiguous?	PY	PY	PY	PN	N	PY	PN	PY	Y	PY	PY	N
1.4 Were any restrictions in eligibility criteria based on study Y/PY/PN/N/NI characteristics appropriate (e.g. study design, date, sample size, study quality, outcomes measured)?	PY	PY	PN	Y	Y	PY	PY	PY	Y	PY	PY	Y
1.5 Were any restrictions in eligibility criteria based on sources of information appropriate (e.g. publication status or format, language, availability of data)?	PN	PN	PN	PN	Y	PN	PN	Y	Y	PN	PY	Y
Low concern - High concern - Unclear concern	Low concern	Low concern	High concern	Low concern	Low concern	Low concern	Low concern	Low concern	Low concern	Low concern	Low concern	Low concern
Domain 2: Identification and selection of studies												
2.1 Did the search include an appropriate range of databases/electronic Y/PY/PN/N/NI sources for published and unpublished reports?	PN	PY	PN	Y	Y	PY	Y	PY	Y	PY	PY	PY

2.2 Were methods additional to database searching used to identify Y/PY/PN/N/NI relevant reports?	N	Y	N	N	Y	Y	Y	Y	Y	N	Y	Y
2.3 Were the terms and structure of the search strategy likely to retrieve Y/PY/PN/N/NI as many eligible studies as possible?	PY	PN	PN	Y	PY	PN	NI	PN	Y	PN	PN	PN
2.4 Were restrictions based on date, publication format, or language Y/PY/PN/N/NI appropriate?	PN	PN	PN	PN	Y	PN	PN	Y	Y	PN	PY	Y
2.5 Were efforts made to minimise error in selection of studies?	Y	NI	NI	NI	Y	PY	Y	Y	Y	Y	PY	Y
Low concern - High concern - Unclear concern	Unclear concern	Unclear concern	High concern	Unclear concern	Low concern	Unclear concern	Unclear concern	Low concern	Low concern	Unclear concern	Low concern	Low concern
Domain 3: Data collection and study appraisal												
3.1 Were efforts made to minimise error in data collection?	PY	N	N	Y	Y	PY	Y	PY	Y	N	Y	Y
3.2 Were sufficient study characteristics available for both review authors Y/PY/PN/N/NI and readers to be able to interpret the results?	Y	Y	PN	Y	PN	Y	Y	PN	Y	Y	Y	PN
3.3 Were all relevant study results collected for use in the synthesis?	Y	Y	N	Y	N	Y	N	N	Y	Y	N	N

3.4 Was risk of bias (or methodological quality) formally assessed using Y/PY/PN/N/NI appropriate criteria?	N	N	N	Y	Y	PY	Y	Y	Y	Y	Y	Y
3.5 Were efforts made to minimise error in risk of bias assessment?	N	N	N	Y	Y	N	N	Y	Y	N	Y	Y
Low concern - High concern - Unclear concern	High concern	High concern	High concern	Low concern	Unclear concern	Low concern	Low concern	High concern	Low concern	Low concern	High concern	High concern
Domain 4: Synthesis and findings												
4.1 Did the synthesis include all studies that it should?	Y	Y	PY	PY	Y	Y	PY	PY	Y	Y	Y	PY
4.2 Were all pre-defined analyses reported or departures explained?	Y	Y	Y	Y	Y	Y	Y	PN	Y	PY	Y	Y
4.3 Was the synthesis appropriate given the nature and similarity in Y/PY/PN/N/NI the research questions, study designs and outcomes across included studies?	Y	Y	Y	Y	Y	Y	PN	PN	Y	Y	Y	Y
4.4 Was between-study variation (heterogeneity) minimal or Y/PY/PN/N/NI addressed in the synthesis?	Y	Y	PY	Y	NOT APPLICABLE	Y	Y	PN	Y	Y	Y	PN
4.5 Were the findings robust, e.g. as demonstrated through funnel Y/PY/PN/N/NI plot or sensitivity analyses?	NI	PN	NI	NI	N	PN	NI	NI	PN	Y	NI	Y
4.6 Were biases in primary studies minimal or addressed in the synthesis?	N	N	N	Y	Y	Y	N	N	PY	Y	PY	Y

Low concern - High concern - Unclear concern	Low concern	Low concern	Low concern	Low concern	Low concern	Low concern	High concern	High concern	Low concern	Low concern	Low concern	Low concern
Overall risk of bias	**LOW RISK OF BIAS**	**LOW RISK OF BIAS**	**HIGH RISK OF BIAS**	**LOW RISK OF BIAS**	**LOW RISK OF BIAS**	**LOW RISK OF BIAS**	**HIGH RISK OF BIAS**	**HIGH RISK OF BIAS**	**LOW RISK OF BIAS**	**LOW RISK OF BIAS**	**LOW RISK OF BIAS**	**LOW RISK OF BIAS**

DISCUSSION

This umbrella review aimed to address an evidence-based inconsistency about the systemic benefits of periodontal treatment reported by Tonetti et al.[39] in the framework and proposal of a new classification and case definition publication. Recognizing that current evidence that effective treatment of certain cases of periodontitis can reduce serum CRP levels is still limited, the results of the present umbrella review showed that periodontitis-treatment has the potential to reduce serum CRP levels in patients with chronic non-communicable diseases such as type 2 DM, pre-hypertension and hypertension and renal failure. In a prior publication, D'Aiuto et al.[57] reported moderate evidence that support a positive effect in reducing serum CRP levels after periodontal treatment, reinforced by this umbrella review for specific systemic conditions such as type 2 DM, pre-hypertension and hypertension, and patients undergoing hemodialysis and peritoneal dialysis.

Since the 1999 workshop, considerable evidence has emerged regarding the relationship of periodontitis to systemic conditions/diseases. Several biological mechanisms have been proposed in periodontal medicine, involving bacteremia, endotoxemia, inflammatory mediators and impaired homeostasis.[58-60] Gingival inflammation triggered by a dysbiotic biofilm is enriched with inflammatory mediators such as interleukin 1 beta (IL-1β), IL-6 and tumor necrosis factor alpha (TNF-α). Hematogenous spread of periodontal bacteria and virulence factors (i.e. bacterial lipopolysaccharide – LPS) occurs through the ulcerated epithelium of the periodontal pocket into the systemic circulation, as do inflammatory mediators from local periodontal damaged tissues.[19,61,62] Chronic low-grade inflammation can stimulate the synthesis of CRP in hepatocytes by IL-1β, IL-6, IL-8, TNF-α, and trained myelopoiesis in the bone marrow, stimulated by bacterial derivatives and by the gut inflammatory reaction to swallowed bacteria.[38,61,63-66] Case-control studies show that periodontitis contributes to the overall inflammatory burden,[52,67-69] strongly associated with cardiovascular disease and type 2 DM.[70-74] The opposite can also occur, and the overall systemic inflammatory burden can be a risk factor for periodontitis.[75]

Inflammation is a fundamental biological process in host defense and tissue repair throughout life; however, persistence of a systemic inflammatory state is related to future illness and associated complications. In this context, chronic inflammatory diseases must be treated as soon as possible, and baseline biomarkers must be established for risk prediction.[39,76-78] Although inflammatory markers must be interpreted in the clinical context and no single value can be used to determine or rule out a specific diagnosis, hCRP reflects the inflammatory burden and risk of systemic impact of periodontitis, related to the grade of disease progression.[39] C-reactive protein

level is directly related to the severity of periodontitis, averaging 4.5 mg/L for patients with PPD ≥ 4 mm in > 10 % teeth, compared to 3.3 mg/L in healthy subjects.[79] Other studies reported an association of elevated serum CRP level with increased severity of chronic periodontitis in patients with hypertension,[80] and aggressive periodontitis.[81] Periodontists should warn the patients about the effects of their gingival health and smoking on their cardiovascular condition.[82] Despite the potential of periodontitis to increase serum CRP levels and of periodontitis-treatment to improve the systemic inflammatory state, the considerable interpatient variability for most biomarkers can be attributed to high biological heterogeneity.[38,83]

C-reactive protein is an acute phase plasma protein that can be used as a biomarker for immune system activation,[84] associated with periodontitis and systemic conditions/diseases.[85-87] The study population varied widely among systematic reviews and meta-analyses. Reviews that included healthy individuals and pregnant women reported no significant improvement in CRP levels after periodontitis-treatment.[47,49] The same result was observed in two meta-analyses that included patients with periodontitis and rheumatoid arthritis.[51,53] In a qualitative review, Teeuw et al.[46] and Li et al.[48] also found no significant improvement in CRP levels after periodontal treatment in patients with DM and cardiovascular disease, respectively. Approximately half of the RCTs included in these reviews had fair to good methodological quality, except in the study by Li et al.[48] in which the authors reported very low quality of evidence and high risk of bias from the primary studies. In terms of ROBIS assessment, only the study by Calderaro et al.[53] was classified as high risk of bias. However, only two studies were included in each meta-analysis and the studies by Teeuw et al.[46] and Li et al.[48] considered only four and one study for qualitative analyses, respectively.

Meta-analyses that reported significant improvement in serum CRP levels after periodontitis-treatment considered more RCT studies than other reviews in the analyses. Artese et al.[40] and Baeza et al.[54] included patients with periodontitis and type 2 DM, Yue et al.[55] haemodialysis and/or peritoneal dialysis,[55] and Sharma et al. (2021) prehypertensive and hypertensive individuals. Half of the reviews reported moderate or low risk of bias within the primary studies. Only the study by Artese et al.[40] was ROBIS-high-risk-of-bias. Therefore, periodontitis-treatment plays an important role in the systemic improvement of patients with chronic non-communicable diseases such as type 2 DM, pre-hypertension and hypertension and renal failure. The negative result reported in the literature in patients with rheumatoid arthritis may be related to autoimmunity, in which the pro-inflammatory reversal and reduction in serum CRP levels after periodontitis-treatment are lower. Perhaps the impact of periodontitis on rheumatoid arthritis is synergistic rather than cumulative. Two other reviews reported

improvement in CRP post-periodontal treatment in patients with and without comorbidities,[50,52] but there were inaccurate data in both studies.

The study population of all reviews had periodontitis. The definition used for the diagnosis of periodontitis varied widely among the studies, but all cases showed high levels of CRP, in agreement with the literature.[79,80-82] Among the meta-analysis studies that reported significant improvement in CRP levels after periodontitis-treatment, only the data analysis by Baeza et al.[54] controlled for smoking variable. Information on smoking history and smoking cessation is critical in CRP studies, especially in patients with periodontitis. Smoking increases serum CRP levels and is also considered an important potential confounder in periodontics studies.[88-90] Smokers present increased susceptibility, greater severity and faster progression of periodontal disease compared with nonsmokers.[39,91-94] In addition, smoking negatively impacts clinical responses to non-surgical periodontitis-treatment.[95] Although it is well established that smoking significantly impacts the onset and course of periodontitis, the mechanisms involved, and the importance of CRP remain unclear.

The methodological heterogeneity of clinical trials evaluated in systematic reviews and meta-analyses does not allow us to state which type of periodontitis-treatment is more effective in reducing CRP or more indicated for each systemic condition. Local or systemic antibiotics/antimicrobials adjunct to subgingival instrumentation result in modest short-term reductions in CRP levels and therefore do not represent a major confounding factor.[96] Furthermore, it was not possible to assess the effectiveness of different supportive periodontal care for the observed outcomes. Overall, there is insufficient evidence to determine the superiority of different protocols or adjunctive strategies to control biofilm and reduce periodontal inflammation,[97,98] even in residual pockets[99] or smokers and non-smokers with aggressive periodontitis.[100] Despite this, the short-term benefits of topical administration of antimicrobials adjunctive to mechanical debridement should impact serum CRP levels soon after periodontitis-treatment.[99,101] Regarding smoking and periodontitis severity, it is important to consider that both are significant, but modest modifiers of patient compliance with supportive periodontal care and initial therapy, respectively.[102] In this context, patients with increased CPR associated with severe periodontitis[79-82] and smoking[88-90] represent a challenge for the periodontist.

The follow-up period also varied widely among studies, from 15 minutes to 25 months. Serum C-reactive protein levels rise from about 1 μg/mL to over 500 μg/mL within 24–72 hours of severe tissue damage. When the stimuli end, CRP values decrease exponentially over 18–20 hours, close to half-life.[87] Therefore, despite the importance of the late benefits of periodontitis-treatment, more follow-up time-points with shorter intervals are needed to establish the real effect of active periodontitis or periodontal treatment on this marker. Furthermore, considering that

bacteremia, endotoxemia and inflammatory mediators of the periodontal pocket impact the liver,[26-36] the reduction of CRP levels after active periodontitis-treatment and its maintenance during supportive periodontal care represents an additional hepatic benefit.

To strengthen the quality of this umbrella review, no restrictions were applied to databases, records, and other sources in the screening process. The search and selection of articles, data collection and synthesis were performed independently by three researchers and a validated quality assessment tool was used. The strength of our umbrella review is the information sources, the review protocol and the inclusion of systematic reviews and meta-analysis studies focused on clinical trials comparing the periodontitis-treatment and the absence of subgingival instrumentation. In addition, the authors do not have any type of conflict of interest or funding to disclosure, which could compromise the results of this study. Therefore, the synthesis of secondary data in the literature points to the potential of periodontitits-treatment to reduce serum CRP levels, especially in patients with acquired non-communicable chronic diseases.

CONCLUSION

Implications for practice. The current findings suggest that periodontitis-treatment has the potential to reduce serum CRP levels in patients with chronic non-communicable diseases such as type 2 DM, pre-hypertension and hypertension and renal failure. However, these findings must be carefully interpreted owing to methodological issues, including the limited number of studies, the quality and sample size of the primary studies, dissimilarities in diagnostic criteria, active periodontal treatment and supportive periodontal care, assessment of CRP and follow-up time points.

Future research. Despite the methodological heterogeneity and scarcity of publications on the subject, some clear pattern was established. Current evidence that effective treatment of certain cases of periodontitis can favorably influence serum CRP levels, although limited, is intriguing and requires well designed RCTs using uniform definitions and outcomes in terms of comparison groups, diagnostic criteria, periodontal treatment, and supportive periodontal care, with time-points suited to CRP physiology. Live systematic reviews on the subject should also be encouraged.

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Conflict of interest

None of the authors has any type of conflict of interest related to the study, as well as related to the peer review process of the manuscript. None of the universities and public agencies that support research in Brazil represents a conflict of interest in this study.

Contribution statement

All authors made substantial contributions to the study and were equally responsible for its design, execution, and content, and agreed to its submission for publication.

Supporting information (funding)

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CAPÍTULO 6

Intersections between endotoxemia and bacteremia by periodontal pathogens and liver—A scoping review

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ABSTRACT

Background. Considering the seriousness of systemic impacts of periodontitis and the uncertainties about the mechanism by which periodontal pathogens and lipopolysaccharide (LPS) translocate to the liver and the precise role of periodontal disease in the pathogenesis of nonalcoholic fatty liver disease (NAFLD), the authors attempted to summarize the literature on the intersection between endotoxemia and bacteremia by periodontal pathogens and liver abnormalities.

Methods. This scoping review was structured based on five steps methodology proposed by Arksey and O'Malley enhanced by the work of Levac and colleagues and followed the PRISMA-ScR recommendations. An extensive systematic and handsearch of the literature was performed, including databases, registers and other sources (gray literature), until May 2022. Alerts were created to identify studies published after the time of the search, until the manuscript submission process. Customized search strategies were used for each database composed of controlled vocabulary and free terms. A 2-phase selection process was conducted by 2 reviewers independently of each other, following pre-established eligibility criteria.. Data extraction and quality assessment (SYRCLE tool, and JBI checklist) process were also blinded. PRISMA-ScR was complemented by the SWiM reporting guideline for qualitative data synthesis The levels of evidence of the primary studies were established by 2011OCEBM.

Results. In total, 14 laboratory studies and six case reports met the eligibility criteria, out of the 639 results initially retrieved. Publication date ranged from 1986 to 2021. Experimental models varied between studies, but all reported liver abnormalities associated with endotoxemia and bacteremia by periodontal pathogens. Nonalcoholic fatty liver (NAFL) and nonalcoholic steatohepatitis (NASH) were strongly associated with *Porhyromonas gingivalis*, *Chlamydia pneumoniae* and *Aggregatibacter actinomycetemcomitans* bacteremia and LPS endotoxemia in inoculated animals. Periodontal pathogens and toxins, especially LPS, were detected in the blood and liver of animals and patients with NAFLD. Physiological, histological and molecular changes were described and summarized into biological models and clinical record that describe the mechanisms through which endotoxemia and bacteremia by periodontal pathogens increase NAFLD risk.

Conclusions and practical implications. Although further studies are needed to clarify the underlying mechanism by which endotoxemia and bacteremia by periodontal pathogens may be effective in initiation and progression of NAFLD, the authors propose for the first time a biological model and clinical records on the subject. Although limited, the existing evidence strongly suggests the translocation of periodontal pathogens and LPS to the liver via hematogenous dissemination and the oral-gut-liver axis, aggravating NAFLD.

Protocol record. osf.io/e5qfy (link: https://archive.org/details/osf-registrations-nyj5k-v1).

Keywords. Periodontal disease; bacteremia; endotoxemia; fatty liver.

INTRODUCTION

Periodontitis is a multifactorial chronic inflammatory disease associated with dysbiotic biofilms and characterized by the progressive destruction of the dental support apparatus.[1] The relationship between bacterial load and host response is a plausible biological mechanism that links periodontitis to several chronic inflammatory diseases[2,3] including, but not limited to, cardiovascular,[4,5] respiratory[6,7] and chronic kidney[8,9] diseases, rheumatoid arthritis,[10-12] cognitive impairment and dementia,[13,14] diabetes,[15-17] metabolic syndrome[18,19] and obesity.[18,20,21] Otherwise, periodontal therapy usually results in glycemic control in diabetic patients.[22,23] Recently, many animal and human studies have linked periodontitis with nonalcoholic fatty liver disease (NAFLD).

Liver diseases occur due to various causes, such as infectious diseases, leading to cell damage, necrosis, and subsequent development of hepatic dysfunction.[24,25] Like periodontitis,

NAFLD has been associated with obesity, diabetes, insulin resistance, oxidative stress and inflammation.[2,3,26,27-33] Despite this, the global prevalence of NAFLD of approximately 25% is not restricted to person with obesity or metabolic diseases.[33,34]

Inflammation of periodontal tissues leads to superficial ulcers in the gingival sulcus or periodontal pocket, exposing blood capillaries to pathogenic microorganisms.[35] In periodontitis, the number of blood vessels and the extension of blood vessels in gingiva are increased, favoring bacteremia and endotoxemia. Transient bacteremia can occur due to local stimuli, such as periodontal therapy, oral hygiene and chewing.[36-38] Endotoxemia also occurs as a result of the microulceration of the tissue, exposing the connective tissue and allowing the entry of bacterial lipopolysaccharide (LPS) into the bloodstream.[39,40] Endotoxemia, bacteremia and proinflammatory lead to an increase in circulating inflammatory cytokines such as tumor necrosis factor-α (TNF-α), interleukin-1β (IL-1β), interleukin-6 (IL-6), receptor activator of nuclear factor kappa-B ligand (RANKL) and prostaglandin E2, and reactive oxygen species, favoring the systemic impacts of periodontitis.[41-46]

In addition to breaking down nutrients absorbed by the intestine, the liver removes bacteria and other foreign substances from the blood that enter the portal vein, playing an important physiological role in LPS detoxification.[47,48] Liver damage associated with periodontitis has been described as hepatocellular steatosis, ballooning, hepatocyte apoptosis, oxidative damage to DNA and inflammatory infiltrate and fibrosis, similar to that observed in NAFLD.[27-32,49-56] Although cross-sectional studies are controversial, cohort studies suggest that periodontal pockets increase the risk of liver cancer and liver-related death and NAFLD, and a significant effect of advanced periodontitis on the incidence of chronic liver disease in individuals with NAFLD (hazard ratio = 6.94).[53,57] History of periodontitis was also associated with a higher NAFLD incidence rate (incidence rate ratio = 1.60).[53] Two systematic reviews reported that healthy periodontium may be essential for liver health,[54] and a significant association between periodontitis and NAFLD. However, meta-analyses adjusted for metabolic parameters suggested that these conditions, not periodontitis itself, were predisposing factors for NAFLD.[58]

According to Younossi et al., we are just beginning to understand the mechanisms of pathogenesis of liver diseases and the contribution of environmental and genetic factors to the risk of developing a progressive course of disease.[59] In this context, there has been lively debate about periodontitis as a risk factor for the onset and progression of NAFLD.[26] Understanding the intersection of periodontitis and liver abnormalities can help provide effective treatments for individuals with advanced nonalcoholic steatohepatitis (NASH) and prevention methods for individuals at high risk of NAFLD and progressive liver disease.[26,59]

In the field of research related to periodontal medicine, few papers to date have addressed the relationship between periodontal diseases and the organs of the digestive system.[26] In order to clarify the link between periodontitis and liver diseases, this scoping review aimed to summarize the literature on the intersection between endotoxemia and bacteremia by periodontal pathogens and liver abnormalities. Mechanistic insights and the main clinical findings on this relationship were also proposed.

METHODS

***Protocol and Registration*.** This scoping review was structured based on five steps methodology proposed by Arksey and O'Malley[60] enhanced by the work of Levac et al.,[61] and followed the PRISMA Extension for Scoping Reviews (PRISMA-ScR).[62] The review protocol was registered in the Open Science Framework (OSF) database (https://osf.io) under osf.io/e5qfy (link: https://archive.org/details/osf-registrations-nyj5k-v1).

***Step 1: Identifying the research question*.** The following question based upon the PCC [Population, Concept and Context (Figure 1)] elements of the inclusion criteria, as proposed by the Joanna Briggs Institute,[63] may be posed: "What associations between endotoxemia and bacteremia by periodontal pathogens and liver abnormalities have been reported?"

FIGURE 1

Focused question based upon the PCC framework		
PCC mnemonic elements		
P	Population	NA*
C	Concept	Liver abnormalities (e.g., infection, injury and others)
C	Context	Periodontitis and/or endotoxemia and/or bacteremia by oral pathogens via bloodstream

Legend: ***NA** here as the authors considered periodontitis and microbial challenge broadly, not a specific condition/population

Population ⇒ Important characteristics of participants should be detailed, including age and other qualifying criteria that make them appropriate for the objectives of the scoping review and match the review question.
Concept ⇒ The core concept examined by the scoping review should be clearly articulated to guide the scope and breadth of the inquiry should be explained.
Context ⇒ The context should be clearly defined and explained.

Reference: Peters M, Godfrey C, McInerney P, Soares C, Khalil H, Parker D. (2015). The Joanna Briggs Institute reviewers' manual 2015: methodology for JBI scoping reviews.[63]

Step 2: Identifying relevant studies

Eligibility criteria. Studies on the relationship between endotoxemia and/or bacteremia by periodontal pathogens via bloodstream and liver abnormalities were included, regardless of study design. Articles should report the occurrence of endotoxemia and/or bacteremia. The detection of these conditions in the blood or liver was considered sufficient, without restriction of the method. In addition, intravenous administration was considered bacteremia per se. Studies were excluded if: i) background information, editorials, expert opinion, and review studies; ii) did not confirm endotoxemia or bacteremia; iii) inaccurate or unavailable information related to liver abnormalities; iv) studies not related to the subject; and v) inability to access the full text. No data or language restrictions were applied.

Information sources. An extensive literature search was performed among MEDLINE using the PubMed search engine (http://www.ncbi.nlm.nih.gov/sites/pubmed), Cochrane CENTRAL (https://www.cochranelibrary.com), Web of Science – WOS (https://www.webofknowledge.com) accessed through the Clarivate Analytics (https://clarivate.com), Embase (https://www.embase.com) and Scopus (http://www.scopus.com) through Elsevier (https://www.elsevier.com), Scielo.org (https://scielo.org), and bvs|BIREME (https://bvsalud.org). Other sources (grey literature) were consulted through Google Scholar (https://scholar.google.com.br), and System for Information on Grey Literature in Europe (SIGLE) through OpenGrey (www.opengrey.eu) databases. The protocol registration databases ClinicalTrials.gov and ReBEC (*Registro Brasileiro de Ensaios Clínicos*) were also assessed. Handsearch was performed in specialized periodicals (Figure 2) and in reference lists of selected articles. Experts were identified using expertscape.com (https://expertscape.com) and contacted for other data sources.

Search. Search strategies were customized for each database from MeSH terms, entry terms and free keywords used to search in PubMed, Web of Science, Cochrane Library, Scielo.org, other sources (grey literature) and protocol registration databases. The search strategies for Embase, Scopus and bvs databases included Emtree, Index and DeCS/MeSH terms, respectively. All terms were combined by the Boolean operators "OR" and "AND", as presented in Figure 2. The electronic searches were performed in

May 2022 and databases alerts were created to identify studies published after the time of the search, until the manuscript submission process.

FIGURE 2

Customized database search strategies	
Search strategies	**Electronic databases**
(Periodontal Diseases[MeSH] OR Periodontitis[MeSH] OR Periodont*[TiAb]) AND (Bacteremia[MeSH] OR Sepsis[MeSH] OR Endotoxemia[MeSH] OR Endotoxins[MeSH] OR Bacterial Toxins[MeSH] OR Bacteremia*[TiAb] OR Sepsis[TiAb] OR Pyemia*[TiAb] OR Pyohemia*[TiAb] OR Pyaemia*[TiAb] OR Septicemia*[TiAb] OR Endotoxemia*[TiAb] OR Endotoxin*[TiAb]) AND (Liver Disease[MeSH] OR Liver Disease[TiAb] OR Liver Dysfunction[TiAb] OR Dysfunction, Liver[TiAb] OR Liver Dysfunctions[TiAb] OR NAFLD[TiAb] OR Nonalcoholic[TiAb] OR Fibrosis[MeSH] OR Fibrosis[TiAb] OR Cirrhosis[TiAb])	MEDLINE|PubMed
((ALL=((Periodontal Diseases OR Periodont*))) AND ALL=((Bacteremia* OR Sepsis OR Pyemia* OR Pyohemia* OR Pyaemia* OR Septicemia* OR Endotoxemia* OR Endotoxin* OR Bacterial Toxins))) AND ALL=((Liver Disease OR Liver Dysfunction OR Dysfunction, Liver OR Liver Dysfunctions OR NAFLD OR Nonalcoholic OR Fibrosis OR Cirrhosis))	Web of Science
ID Search Hits #1 MeSH descriptor: [Periodontal Diseases] explode all trees #2 MeSH descriptor: [Periodontitis] explode all trees #3 Periodontal* #4 #1 OR #2 OR #3 #5 MeSH descriptor: [Bacteremia] explode all trees #6 MeSH descriptor: [Sepsis] explode all trees #7 MeSH descriptor: [Endotoxemia] explode all trees #8 MeSH descriptor: [Endotoxins] explode all trees #9 MeSH descriptor: [Bacterial Toxins] explode all trees #10 Bacteremia* OR Sepsis OR Pyemia* OR Pyohemia* OR Pyaemia* OR Septicemia* OR Endotoxemia* OR Endotoxin* #11 #5 OR #6 OR #7 OR #8 OR #9 #10 #12 MeSH descriptor: [Liver Diseases] explode all trees #13 MeSH descriptor: [Fibrosis] explode all trees #14 Liver Disease OR Liver Dysfunction OR Dysfunction, Liver OR Liver Dysfunctions OR NAFLD OR Nonalcoholic OR Fibrosis OR Cirrhosis #15 #12 OR #13 #14 #16 #4 AND #11 AND #15	CENTRAL Cochrane
('Periodontal Diseases'/exp OR 'Periodontitis'/exp OR 'Periodont*':ti,ab,kw) AND ('Bacteremia'/exp OR 'Sepsis'/exp OR 'Endotoxemia'/exp OR 'Endotoxins'/exp OR 'Bacterial Toxins'/exp OR 'Bacteremia*':ti,ab,kw OR 'Sepsis':ti,ab,kw OR 'Pyemia*':ti,ab,kw OR 'Pyohemia*':ti,ab,kw OR 'Pyaemia*':ti,ab,kw OR 'Septicemia*':ti,ab,kw OR 'Endotoxemia*':ti,ab,kw OR 'Endotoxin*':ti,ab,kw) AND ('Liver Disease'/exp OR 'Fibrosis'/exp OR 'Liver Disease':ti,ab,kw OR 'Liver Dysfunction':ti,ab,kw OR 'Dysfunction, Liver':ti,ab,kw OR 'Liver Dysfunctions':ti,ab,kw OR 'NAFLD':ti,ab,kw OR 'Nonalcoholic':ti,ab,kw OR 'Fibrosis':ti,ab,kw OR 'Cirrhosis':ti,ab,kw) AND (‘article’/it)	Embase
(ALL (periodontal AND diseases OR periodont*)) AND (ALL (bacteremia* OR sepsis OR pyemia* OR pyohemia* OR pyaemia* OR septicemia* OR endotoxemia* OR endotoxin* OR bacterial AND toxins)) AND (ALL (liver AND disease OR liver AND dysfunction OR dysfunction, AND liver OR liver AND dysfunctions OR nafld OR nonalcoholic OR fibrosis OR cirrhosis)) AND (LIMIT-TO (DOCTYPE , "ar"))	Scopus

(Periodontal Diseases OR Periodont*) AND (Bacteremia* OR Sepsis OR Pyemia* OR Pyohemia* OR Pyaemia* OR Septicemia* OR Endotoxemia* OR Endotoxin* OR Bacterial Toxins) AND (Liver Disease OR Liver Dysfunction OR Dysfunction, Liver OR Liver Dysfunctions OR NAFLD OR Nonalcoholic OR Fibrosis OR Cirrhosis)	Scielo.org, bvs|BIREME, other sources (grey literature), and protocol registrations

Specialized periodicals

The Journal of American Dental Association; Journal of Clinical Periodontology; Journal of Periodontology; Periodontology 2000; Journal of Periodontal Research; Journal of Dental Research; Oral Diseases; Archives of Oral Biology; Journal of Applied Oral Science; Frontiers or Dental Medicine; The International Journal of Periodontics & Restorative Dentistry; Journal of Oral Pathology & Medicine; Oral Surgery, Oral Medicine, Oral Pathology and Oral Radiology; Frontiers in Microbiology; Frontiers in Cellular and Infection Microbiology; Journal of Oral Microbiology; Molecular Microbiology; BMC; Clinical Microbiology and Infection; International Journal of Medical Microbiology; Diagnostic Microbiology and Infectious Disease; European Journal of Clinical Microbiology & Infectious Diseases; FEMS Microbiology Letters; Journal of Applied Microbiology; Journal of Bacteriology; Molecular Oral Microbiology; Journal of Medical Microbiology; Letters In Applied Microbiology; The New England Journal of Medicine; JAMA; Nature; Science; Lancet; PLOS|ONE; Journal of Gastroenterology and Hepatology; and European Journal of Gastroenterology & Hepatology.

Step 3: Study Selection

Selection of sources of evidence. The retrieved articles were exported to rayyan™ reference manager (https://www.rayyan.ai) and duplicates were removed by the program (perfect match) and manually. Authors of studies not retrieved in full text were contacted by e-mail up to five attempts. If two studies presented sample overlapping and the same methodology criteria assessed, the least complete study was excluded. A 2-phase selection process was conducted by 2 reviewers independently of each other (conventional double-screening)—Phase 1, two reviewers (DSB and MFF) independently examined the titles and abstracts of all identified references, applying the inclusion criteria (blind process); and Phase 2, the same two reviewers independently applied the exclusion criteria to the other studies, based on reading the full text (blind process). Inter-reviewer reliability in the study selection process was determined by the Cohen κ test, assuming an acceptable threshold value of 0.80.[64] The disagreement at any stage was resolved by discussion and mutual decision (consensus meeting) with a third reviewer (MCMB). The final decision/selection was always based on the full text of the publication. The reasons for studies exclusion were reported (Figure 5, and Table 1).

Step 4: Charting the Data

Data charting process. Article screening process depicted in the PRISMA Flow Diagram (Figure 5). Literature data were grouped by study design as presented in Table 2-5 and Figure 6 and 9-11, with emphasis on Figure 9—mechanistic insights into the impacts of endotoxemia and bacteremia by periodontal pathogens on the liver. Complementary data from mechanistic insights (in vitro experiments) on the impacts of endotoxemia and/or bacteremia by periodontal pathogens on the liver are reported in Table 4 and Figure 10. The intersection between oral pathogens and liver disease in patients with periodontitis was summarized in Figure 11. Risk of bias analyzes of

laboratory studies and case reports are shown in Figure 7 and 8, respectively; bar chart and 3D line chart complemented these analyses. The results were presented in text, figures and tables.

Step 5: Collating, Summarizing and Reporting the Results

Data items. The full texts were evaluated and judged in the entire document. Authors were contacted through electronic mail, during five consecutive weeks, when necessary to obtain details on study design and data clarification. Data were extracted by two independent reviewers [DSB and MFF (blind process)] using a standardized sheet, as recommended by the Cochrane Collaboration's handbook for systematic review.[65] When there were unclear or missed information, lack of data or when the full text was not available, weekly attempts were made for up to five weeks to contact the authors. In case there were no return from the authors to identify data in graphs, we used the digital program WebPlotDigitizer™ online (https://automeris.io/WebPlotDigitizer/). The accuracy of extracted data was confirmed by another author (MCMB). Google translator program was used in case of studies in a foreign language not provided by the researchers (https://translate.google.com.br/?hl=pt-BR).

FIGURE 3

Outcomes of interest	
Primary	Liver abnormalities (e.g., pathogen detection, molecular signature, bloated and balooning hepatocytes, liver cell damage, necrosis, NAFLD (i.e. NAFL, NASH and cirrhosis) and gradual progression of inflammation and fibrosis transitioning into end-stage liver disease)
Secondary	Subgroup analysis: qualitative synthesis of data according to the type of study and level of evidence, and analysis of the methodological quality of the studies

Critical appraisal of individual sources of evidence. Once a detailed appraisal of the methods and results was performed, the studies were analyzed to determine the possibility of biased results, using specific risk of bias tools as secondary outcomes: i) SYstematic Review Center for Laboratory animal Experimentation (SYRCLE),[66] and JBI Critical Appraisal Checklist for Case Reports[67] (Figure 7 an 8, respectively).

Synthesis of results. PRISMA-ScR[62] was complemented by the SWiM reporting guideline for qualitative data synthesis.[68] Results were analyzed in subsets by study design, type of intervention or exposure and reported liver abnormalities, taking into account the methodological quality of the studies. The levels of evidence of the primary studies were established by Explanation of the 2011 OCEBM (Oxford Center for Evidence-Based Medicine) Levels of Evidence (Figure 4).[69] The results are presented in the text and Figure 12.

FIGURE 4

Oxford Centre for Evidence-Based Medicine 2011 Levels of Evidence Checklist					
Question	**Step 1 | Level 1***	**Step 2 | Level 2***	**Step 3 | Level 3***	**Step 4 | Level 4***	**Step 5 | Level 5**
How common is the problem?	Local and current random sample surveys (or censuses)	Systematic review of surveys that allow matching to local circumstances**	Local non-random sample**	Case-series**	n/a
Is this diagnostic or monitoring test accurate? (Diagnosis)	Systematic review of cross sectional studies with consistently applied reference standard and blinding	Individual cross sectional studies with consistently applied reference standard and blinding	Non-consecutive studies, or studies without consistently applied reference standards**	Case-control studies, or "poor or non-independent reference standard**	Mechanism-based reasoning
What will happen if we do not add a therapy? (Prognosis)	Systematic review of inception cohort studies	Inception cohort studies	Cohort study or control arm of randomized trial*	Case-series or case-control studies, or poor quality prognostic cohort study**	n/a
Does this intervention help? (Treatment Benefits)	Systematic review of randomized trials or *n*-of-1 trials	Randomized trial or observational study with dramatic effect	Non-randomized controlled cohort/follow-up study**	Case-series, case-control studies, or historically controlled studies**	Mechanism-based reasoning
What are the COMMON harms? (Treatment Harms)	Systematic review of randomized trials, systematic review of nested case-control studies, *n*-of-1 trial with the patient you are raising the question about, or observational study with dramatic effect	Individual randomized trial or (exceptionally) observational study with dramatic effect	Non-randomized controlled cohort/follow-up study (post-marketing surveillance) provided there are sufficient numbers to rule out a common harm. (For long-term harms the duration of follow-up must be sufficient.)**	Case-series, case-control, or historically controlled studies**	Mechanism-based reasoning
What are the RARE harms? (Treatment Harms)	Systematic review of randomized trials or *n*-of-1 trial	Randomized trial or (exceptionally) observational study with dramatic effect			
Is this (early detection) test worthwhile? (Screening)	Systematic review of randomized trials	Randomized trial	Non-randomized controlled cohort/follow-up study**	Case-series, case-control, or historically controlled studies**	Mechanism-based reasoning

Legend: * Level may be graded down on the basis of study quality, imprecision, indirectness (study PICO does not match questions PICO), because of inconsistency between studies, or because the absolute effect size is very small; Level may be graded up if there is a large or very large effect size. ** As always, a systematic review is generally better than an individual study. n/a, not applicable.

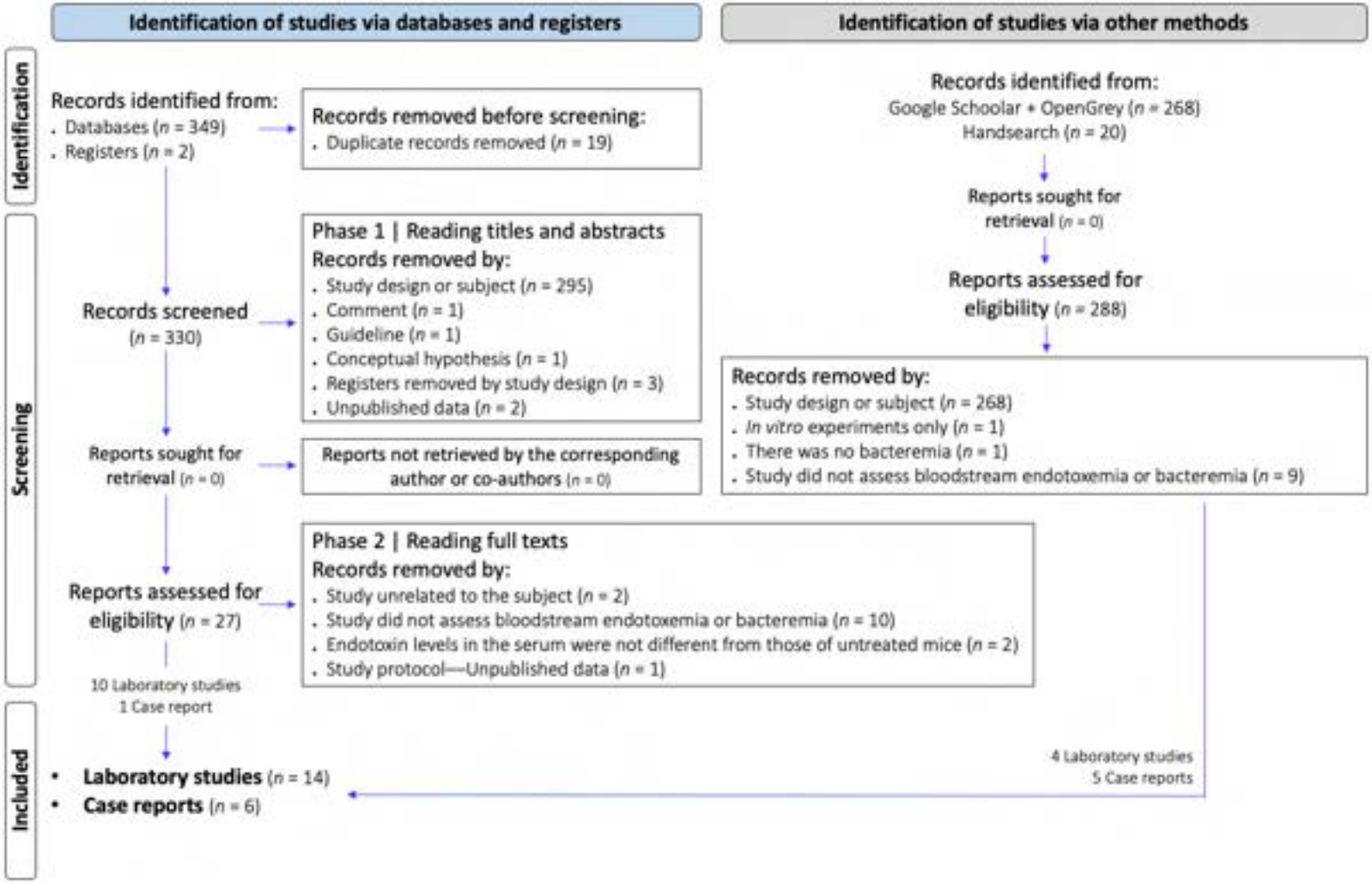
RESULTS

Selection of sources of evidence. In total, 639 results were retrieved from databases, records, and other sources. After removing 19 duplicates, 303 records were excluded in title/abstract screening (Phase 1). The reasons for excluding studies in the Phase 2 full-text screening were: unrelated to the subject (n = 2), did not assess bloodstream endotoxemia or

bacteremia (n = 10), endotoxin levels in the serum were not different from those of untreated mice (n = 2), and study protocol—unpublished data (n = 1). Of the 288 retrievals from other sources, only four laboratory studies and five case reports were added to the final selection. The references of the studies excluded when reading the full text were presented in Table 1. Fourteen studies[70-83] and six case reports[84-89] met the eligibility criteria and were included in this scoping review (article screening process depicted in Figure 5). There was a perfect inter-reviewer correlation for all the databases consulted ($\kappa \geq 90$ %).

Characteristics of sources of evidence. The publication date ranged from 2005 to 2021 among laboratory studies and from 1986 to 2021 among case reports. Six articles reported specific animal models for the study of steatosis and liver infection. Two studies conducted experiments with mice exposed to high-fat diet,[80,82] one with apoE-deficient mice,[73] one with lactoferrin knockout (LFKO$^{-/-}$) mice,[75] and one with germ-free mice.[79] The other studies inoculated New Zealand white rabbits,[70] Wistar rats,[72,78] BALB/C mice,[71] and C57BL/6J mice.[74,76,77,81,83] Three studies used endotoxemia models: topical application of *Escherichia coli* (*E. coli*) LPS and proteases from *Streptomyces griseus* (*S. griseus*) into the gingival sulcus;[72] endotoxin injected into the oral cavity [unlabeled LPS or radiolabeled LPS extracted by or biosynthesized in *Porphyromonas gingivalis* (*P. gingivalis*), respectively] in Wistar rats;[78] and intravenously injection of endotoxin (sonicated *P. gingivalis*) in C57BL/6J germ-free mice.[79] The other 11 studies induced bacteremia using live bacteria: cylindrical surgical grade steel chambers inoculated with *P. gingivalis* in New Zealand white rabbits;[70] mouse chamber model inoculated with *Campylobacter rectus* (*C. rectus*) in BALB/C mice;[71] *Chlamydia pneumoniae* (*C. pneumoniae*) intranasally, and *Aggregatibacter actinomycetemcomitans* (*A. actinomycetemcomitans*) inoculated intravenously in apoE-deficient mice;[73] pulp chamber infected with *P. gingivalis* in C57BL/6J mice;[74] *A. actinomycetemcomitans* inoculated intravenously in LFKO$^{-/-}$ mice;[75] gavage with *P. gingivalis* in C57BL/6J mice;[76,77] pulp chamber infected with *P. gingivalis* in Mice exposed to high-fat diet;[80,82] gavage with *P. gingivalis*, *Fusobacterium nucleatum* (*F. nucleatum*) and *Filifactor alocis* (*F. alocis*) in C57BL/6J mice;[81] and gavage with *P. gingivalis*, *Prevotella intermedia* (*P. intermedia*), *Actinomyces naeslundii* (*A. naeslundii*) and *Veillonella rogosae* (*V. rogosae*) in C57BL/6J mice[83] (Figure 6A). Endotoxemia and bacteremia were confirmed in the blood and/or liver or inoculated intravenously (Figure 6B, and Table 2). For details on the methods of the included studies, see Table 2.

FIGURE 5. Article screening process depicted in the PRISMA Flow Diagram



Legend: *n*, absolute frequency.
From: Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ 2021;372:n71. doi: 10.1136/bmj.n71. For more information, visit: http://www.prisma-statement.org/.

TABLE 1

List of excluded studies and reasons for exclusion in full text screening

	Reference	Type of publication	Reason for exclusion
1†	Barbero P, Garzino Demo MG, Milanesio M, Ottobrelli A. Valutazione odontoiatrica del paziente in attesa di trapianto epatico [The dental assessment of the patient waiting for a liver transplant]. Minerva Stomatol. 1996 Oct;45(10):431-9. Italian	Cross-sectional study	Study unrelated to the subject
2†	Pavlica Z, Petelin M, Juntes P, Erzen D, Crossley DA, Skaleric U. Periodontal disease burden and pathological changes in organs of dogs. J Vet Dent. 2008 Jun;25(2):97-105. doi: 10.1177/089875640802500210	Laboratory study	Study did not assess bloodstream endotoxemia or bacteremia
3§	Tomofuji T, Sanbe T, Ekuni D, Azuma T, Irie K, Maruyama T, Tamaki N, Yamamoto T. Oxidative damage of rat liver induced by ligature-induced periodontitis and chronic ethanol consumption. Arch Oral Biol. 2008 Dec;53(12):1113-8. doi: 10.1016/j.archoralbio.2008.05.015	Laboratory study	Study did not assess bloodstream endotoxemia or bacteremia
4†	Nemec A, Pavlica Z, Crossley DA, Zdovc I, Erzen D, Sentjurc M, Nemec M, Petelin M. Single oral inoculation with *Escherichia coli* (ATCC 25922) stimulates generalised production of nitric oxide in mice. Acta Vet Hung. 2009 Mar;57(1):127-38. doi: 10.1556/AVet.57.2009.1.13	Laboratory study	Study did not assess bloodstream endotoxemia or bacteremia
5†	Yamamoto T, Tomofuji T, Tamaki N, Ekuni D, Azuma T, Sanbe T. Effects of topical application of lipopolysaccharide and proteases on hepatic injury induced by high-cholesterol diet in rats. J Periodontal Res. 2010 Feb;45(1):129-35. doi: 10.1111/j.1600-0765.2009.01212.x	Laboratory study	Study did not assess bloodstream endotoxemia or bacteremia
6†	Naruishi K, Omori K, Maeda H, Sonoi N, Funakoshi K, Hirai K, Ishii M, Kubo K, Kobayashi H, Tomiyama T, Yamamoto D, Tanimoto I, Kunimatsu K, Takashiba S. Immune responses to porphyromonas gingivalis infection suppress systemic inflammatory response in experimental murine model. J Biol Regul Homeost Agents. 2011 Apr-Jun;25(2):195-202	Laboratory study	Study unrelated to the subject
7§	Helenius-Hietala J, Meurman JH, Höckerstedt K, Lindqvist C, Isoniemi H. Effect of the aetiology and severity of liver disease on oral health and dental treatment prior to transplantation. Transpl Int. 2012 Feb;25(2):158-65. doi: 10.1111/j.1432-2277.2011.01381.x	Comparative study	Study did not assess bloodstream endotoxemia or bacteremia

8†	Yoneda M, Naka S, Nakano K, Wada K, Endo H, Mawatari H, Imajo K, Nomura R, Hokamura K, Ono M, Murata S, Tohnai I, Sumida Y, Shima T, Kuboniwa M, Umemura K, Kamisaki Y, Amano A, Okanoue T, Ooshima T, Nakajima A. Involvement of a periodontal pathogen, *Porphyromonas gingivalis* on the pathogenesis of non-alcoholic fatty liver disease. BMC Gastroenterol. 2012 Feb 16;12:16. doi: 10.1186/1471-230X-12-16	Comparative study	Study did not assess bloodstream endotoxemia or bacteremia
9†	Segawa T, Saeki A, Hasebe A, Arimoto T, Kataoka H, Yokoyama A, Kawanami M, Shibata K. Differences in recognition of wild-type and lipoprotein-deficient strains of oral Streptococci *in vitro* and *in vivo*. Pathog Dis. 2013 Aug;68(3):65-77. doi: 10.1111/2049-632X.12049	Laboratory study	The authors did not investigate the relationship between bloodstream bacteremia/endotoxemia by periodontopathogen and liver disease
10†	Aberg F, Helenius-Hietala J, Meurman J, Isoniemi H. Association between dental infections and the clinical course of chronic liver disease. Hepatol Res. 2014 Mar;44(3):349-53. doi: 10.1111/hepr.12126	Short communication (Retrospective data)	Study did not assess bloodstream endotoxemia or bacteremia
11†	Morita T, Yamazaki Y, Fujiharu C, Ishii T, Seto M, Nishinoue N, Sasaki Y, Kawato T, Motohashi M, Maeno M. Serum γ-glutamyltransferase level is associated with periodontal disease independent of drinking habits in Japanese adults. Med Sci Monit. 2014 Oct 31;20:2109-16. doi: 10.12659/MSM.891204	Comparative study	Study did not assess bloodstream endotoxemia or bacteremia
12§	Ahmad A, Furuta M, Shinagawa T, Takeuchi K, Takeshita T, Shimazaki Y, Yamashita Y. Association of periodontal status with liver abnormalities and metabolic syndrome. J Oral Sci. 2015;57(4):335-43. doi: 10.2334/josnusd.57.335	Laboratory study	Study did not assess bloodstream endotoxemia or bacteremia
13§	Kuraji R, Ito H, Fujita M, Ishiguro H, Hashimoto S, Numabe Y. *Porphyromonas gingivalis* induced periodontitis exacerbates progression of non-alcoholic steatohepatitis in rats. Clin Exp Dent Res. 2016 Sep 28;2(3):216-225. doi: 10.1002/cre2.41	Laboratory study	There was no bacteremia
14†	Matsuda Y, Kato T, Takahashi N, Nakajima M, Arimatsu K, Minagawa T, Sato K, Ohno H, Yamazaki K. Ligature-induced periodontitis in mice induces elevated levels of circulating interleukin-6 but shows only weak effects on adipose and liver tissues. J Periodontal Res. 2016 Oct;51(5):639-46. doi: 10.1111/jre.12344	Laboratory study	Experimental model: ligature-induced periodontitis—endotoxin levels in the serum of ligated mice were not different from those of untreated mice
15§	Dos Santos Carvalho J, Cardoso Guimarães Vasconcelos AC, Herlany Pereira Alves E, Dos Santos Carvalho A, da Silva FRP, de Carvalho França LF, de Pádua Rocha Nóbrega Neto A, Di Lenardo D, de Souza LKM, Barbosa ALDR, Medeiros JR, de Oliveira JS, Vasconcelos DFP. Steatosis	Laboratory study	Study did not assess bloodstream endotoxemia or bacteremia

	caused by experimental periodontitis is reversible after removal of ligature in rats. J Periodontal Res. 2017 Oct;52(5):883-892. doi: 10.1111/jre.12459		
16[§]	Komazaki R, Katagiri S, Takahashi H, Maekawa S, Shiba T, Takeuchi Y, Kitajima Y, Ohtsu A, Udagawa S, Sasaki N, Watanabe K, Sato N, Miyasaka N, Eguchi Y, Anzai K, Izumi Y. Periodontal pathogenic bacteria, Aggregatibacter actinomycetemcomitans affect non-alcoholic fatty liver disease by altering gut microbiota and glucose metabolism. Sci Rep. 2017 Oct 24;7(1):13950. doi: 10.1038/s41598-017-14260-9. Erratum in: Sci Rep. 2018 Mar 12;8(1):4620	Observational study and Laboratory study	Study did not assess bloodstream endotoxemia or bacteremia
17[†]	Kuraji R, Fujita M, Ito H, Hashimoto S, Numabe Y. Effects of experimental periodontitis on the metabolic system in rats with diet-induced obesity (DIO): an analysis of serum biochemical parameters. Odontology. 2018 Apr;106(2):162-170. doi: 10.1007/s10266-017-0322-5	Laboratory study	Study did not assess bloodstream endotoxemia or bacteremia
18[§]	Nakahara T, Hyogo H, Ono A, Nagaoki Y, Kawaoka T, Miki D, Tsuge M, Hiraga N, Hayes CN, Hiramatsu A, Imamura M, Kawakami Y, Aikata H, Ochi H, Abe-Chayama H, Furusho H, Shintani T, Kurihara H, Miyauchi M, Takata T, Arihiro K, Chayama K. Involvement of Porphyromonas gingivalis in the progression of non-alcoholic fatty liver disease. J Gastroenterol. 2018 Feb;53(2):269-280. doi: 10.1007/s00535-017-1368-4	Observational study and Laboratory study	Study did not assess bloodstream endotoxemia or bacteremia
19[§]	Pessoa LS, Pereira-da Silva FR, Alves EH, França LF, di Lenardo D, Carvalho JS, Martins VB, Sousa FB, Drumond KO, Medeiros JV, de Oliveira JS, Vasconcelos DF. One or two ligatures inducing periodontitis are sufficient to cause fatty liver. Med Oral Patol Oral Cir Bucal. 2018 May 1;23(3):e269-e276. doi: 10.4317/medoral.22204	Laboratory study	Study did not assess bloodstream endotoxemia or bacteremia
20[†]	Sato K, Yokoji M, Yamada M, Nakajima T, Yamazaki K. An orally administered oral pathobiont and commensal have comparable and innocuous systemic effects in germ-free mice. J Periodontal Res. 2018 Dec;53(6):950-960. doi: 10.1111/jre.12593	Laboratory study	Endotoxin in the serum of *Lactobacillus salivarius*- and *Porphyromonas gingivalis*-administered mice were not different from those of sham-administered mice
21[§]	Ding LY, Liang LZ, Zhao YX, Yang YN, Liu F, Ding QR, Luo LJ. *Porphyromonas gingivalis*-derived lipopolysaccharide causes excessive hepatic lipid accumulation via activating NF-κB and JNK signaling pathways. Oral Dis. 2019 Oct;25(7):1789-1797. doi: 10.1111/odi.13153	Laboratory study	*In vitro* experiments only
22[§]	Mester A, Ciobanu L, Taulescu M, Apostu D, Lucaciu O, Filip GA, Feldrihan V, Licarete E, Ilea A, Piciu A, Oltean-Dan D, Scurtu I, Berce C, Campian RS. Periodontal disease may induce liver fibrosis in an experimental study on Wistar rats. J Periodontol. 2019 Aug;90(8):911-919. doi: 10.1002/JPER.18-0585	Laboratory study	Study did not assess bloodstream endotoxemia or bacteremia

23†	Kamata Y, Kessoku T, Shimizu T, Kobayashi T, Kurihashi T, Sato S, Kuraji S, Aoyama N, Iwasaki T, Takashiba S, Hamada N, Kodama T, Tamura T, Ino S, Higurashi T, Taguri M, Yamanaka T, Yoneda M, Usuda H, Wada K, Nakajima A, Minabe M. Efficacy and safety of PERIOdontal treatment versus usual care for Nonalcoholic liver disease: protocol of the PERION multicenter, two-arm, open-label, randomized trial. Trials. 2020 Mar 23;21(1):291. doi: 10.1186/s13063-020-4201-y	Study protocol (Multicenter, parallel-arm, randomized controlled trial)	Study protocol [Trial registration: University Hospital Medical Information Network (UMIN) Clinical Trials Registry, ID: UMIN000022079]
24§	Ahn JS, Yang JW, Oh SJ, Shin YY, Kang MJ, Park HR, Seo Y, Kim HS. *Porphyromonas gingivalis* exacerbates the progression of fatty liver disease via CD36-PPARγ pathway. BMB Rep. 2021 Jun;54(6):323-328. doi: 10.5483/BMBRep.2021.54.6.050	Laboratory study	Study did not assess bloodstream endotoxemia or bacteremia
25†	Guo JM, Xing HJ, Cai JZ, Zhang HF, Xu SW. H2S exposure-induced oxidative stress promotes LPS-mediated hepatocyte autophagy through the PI3K/AKT/TOR pathway. Ecotoxicol Environ Saf. 2021 Feb;209:111801. doi: 10.1016/j.ecoenv.2020.111801	Laboratory study	Study did not assess bloodstream endotoxemia or bacteremia
26†	Singh, Kuldeep, Alka Kanaujia, and Savita Singh. Effect of Periodontal Inflammation on Haematological and Liver Function Parameters--A Comparative Clinical Study from Uttar Pradesh, India. Journal of Evolution of Medical and Dental Sciences. 2021 May 3;10(18):1338-1343. doi: 10.14260/jemds/2021/282	Comparative study	Study did not assess bloodstream endotoxemia or bacteremia
Legend: †, Phase 2 of the study selection process (full-text screening); §, handsearch.			

FIGURE 6

Experimental models of bacteremia and endotoxemia and biological matrices tested

A

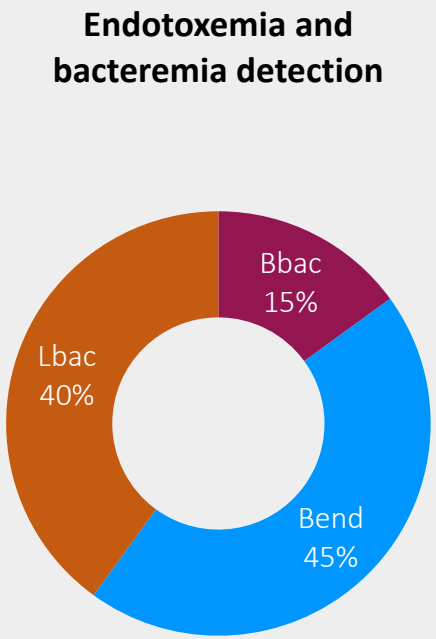
ENDOTOXEMIA

- Topical application of *E. coli* LPS and proteases from *S. griseus* into the gingival sulcus of both maxillary first molars in Wistar rats[72]
- Endotoxin injected into the oral cavity (unlabeled LPS or radiolabeled LPS extracted by or biosynthesized in *P. gingivalis*, respectively) in Wistar rats[78]
- Intravenously injection of endotoxin (sonicated *P. gingivalis*) in C57BL/6J germ-free mice[79]

BACTEREMIA

- Cylindrical surgical grade steel chambers inoculated with *P. gingivalis* in New Zealand white rabbits[70]
- Mouse chamber model inoculated with *C. rectus* in BALB/C mice[71]
- *C. pneumoniae* intranasally, and *A. actinomycetemcomitans* inoculated intravenously in apoE-deficient mice[73]
- Pulp chamber infected with *P. gingivalis* in C57BL/6J mice[74]
- *A. actinomycetemcomitans* inoculated intravenously in LFKO^{-}/$^{-}$ mice[75]
- Gavage with *P. gingivalis* in C57BL/6J mice[76,77]
- Pulp chamber infected with *P. gingivalis* in mice exposed to high-fat diet[80,82]
- Gavage with *P. gingivalis*, *F. nucleatum* and *F. alocis* in C57BL/6J mice[81]
- Gavage with *P. gingivalis*, *P. intermedia*, *A. naeslundii* and *V. rogosae* in C57BL/6J mice[83]

B



Legend: A, Experimental models of bacteremia and endotoxemia; and B, Biological matrices used to confirm endotoxemia and bacteremia—Bbac, bloodstream bacteremia; Bend, bloodstream endotoxemia; Lbac, liver bacteremia. *P. gingivalis*, *Porphyromonas gingivalis*; *A. actinomycetemcomitans*, *Aggregatibacter actinomycetemcomitans*; *F. nucleatum*, *Fusobacterium nucleatum*; *F. alocis*, *Filifactor alocis*; *A. naeslundii*, *Actinomyces naeslundii*; *V. rogosae*, *Veillonella rogosae*.

TABLE 2

Methods from primary studies

Study | Design	Animal model	Intervention	Comparator	Periodontal disease	Bacteremia	Endotoxemia	Liver
[§]Boggess et al., 2005[70] Laboratory study	Reproductive-aged female, *Pasteurella-free*, New Zealand White rabbits (*O cuniculus*)	Cylindrical surgical grade steel chambers surgically implanted subcutaneously on the dorsal side, between the scapulae 10-14 days after chamber placement, rabbits were then inoculated with *P. gingivalis* strain A7436 through the chamber Microbial exposure: 2 inoculums introduced into the implanted chamber – 10^9 CFU/mL heat-killed *P. gingivalis*,[A] which was followed 14-21 days later by inoculation with live *P. gingivalis* On day 7 of gestation, corresponding with day of implantation, does were sedated, and those previously inoculated with heat-killed *P. gingivalis*	Female rabbits inoculated with an equal volume of sterile media	NA	Central ear artery blood sampling was performed to confirm sensitization: *P. gingivalis*-specific IgG (checkerboard immunoblot)[B]	NA	Nested PCR for *P. gingivalis* from maternal and fetal liver biopsies

		were inoculated through the chamber with 5 x 10^8 CFU live *P. gingivalis*					
†Yeo et al., 2005[71] Laboratory study	Female BALB/C mice at 4 to 6 weeks of age	Mouse chamber model[C-F] implanted subcutaneously into the dorsolumbar region of each female mouse Intrachamber injection of 0.1 ml of either 10^7 CFU/mL or 10^9 CFU/mL live *C. rectus* strain ATCC 33238	Intrachamber injection of 0.1 mL of PBS	NA	Detection of *C. rectus* by PCR from whole maternal livers and placentas[G]	NA	Detection of *C. rectus* in maternal and fetal tissues using PCR
†Tomofuji et al., 2007[72] Laboratory study	Male Wistar rats at 8-week-old	Topical application of 25 mg/mL *E. coli* LPS and 2.25 U/mL proteases from *S. griseus* suspended in pyrogen-free water for 8 weeks[H] LPS (0.5 mL x three times) and proteases (0.5 mL x three times) was introduced into the gingival sulcus of both maxillary first molars daily for 8 weeks by micropipette	Topical application of pyrogen-free water Pyrogen-free water (0.5 µL x six times) was introduced into the gingival sulcus of both maxillary first molars daily for 8 weeks by micropipette	Experimental periodontitis Pathologic evaluation: histometric analyses of gingival sections were used to evaluate the degree of periodontitis[H]	NA	Level of serum LPS: kinetic *Limulus* amebocyte lysate test kit	<u>Cardiac puncture in week 8 and measurements of biochemical items:</u> • Activity of serum ALT – commercially available assay kit • Serum TNF-α concentrations – rat TNF-α ELISA kit • Serum levels of CRP – highly sensitive ELISA • Quantity of reactive oxygen species – H_2O_2 concentration was measured by a method that used phenylenediamine.[I] One unit was defined as equivalent to 1 µg H_2O_2/mL <u>Pathologic evaluation (immunohistochemical reactions,[J] and TUNEL method)[K]:</u> • Liver pathology was scored as follows: 1) steatosis (the percentage of liver cells containing fat): < 25 % = 1+; < 50 % = 2+; < 75 % = 3+; and > 75 % = 4+; and 2) inflammation and necrosis: one focus per low-power field = 1+; and two or more = 2+.[L] TNF-α-positive cells, TUNEL-positive cells, and total cells (including Kupffer cells and hepatocytes) were counted in the 10 standard (0.25 x 0.25 mm) areas. Ratios of TNF-α-positive cells or TUNEL-positive cells to the total cells were calculated for each rat

							• Measurement of 8-OHdG levels in mtDNA in Liver: mtDNA was isolated from rat liver with a DNA extraction kit, and analyzed by a competitive ELISA method with an 8-OHdG check kit[M]
[§]Hyvärinen et al., 2009[73] Laboratory study	Male apoE-deficient mice (B6.129P2-*Apoe*^{tm1Unc}/Crl) at 9 weeks of age	Short-term experiment (14 weeks): i) acutely infected with *C. pneumoniae* (acute CPN group) received viable *C. pneumoniae* (2 x 10^6 IFU/40 µL SPG) intranasally once at the age of 13 weeks; and ii) chronically infected CPN group (chronic CPN group) was inoculated with viable *C. pneumoniae* (2 x 10^6 IFU/40 µL SPG) intranasally three times at 2-week intervals Long-term experiment (24 weeks): i) *A. actinomycetemcomitans* strain AT445b (serotype b, fimbriated and aggregative phenotype) infection group was inoculated intravenously with live *A. actinomycetemcomitans* (10^7 CFU/50 µL 0.9 % NaCl) once a week for 10 consecutive weeks; ii) chronic CPN group received viable *C. pneumoniae* (2 x 10^6 IFU/40 µL SPG) intranasally three times at 2-week intervals; and iii) chronic *C. pneumoniae* plus *A. actinomycetemcomitans* infection (chronic CPN+AA	Short-term experiment (14 weeks): control group received vehicle (40 µL SPG) three times Long-term experiment (24 weeks): control group received a combination of vehicles (40 µL SPG and 50 µL 0.9 % NaCl)	NA	Serum analysis: *A. actinomycetemcomitans* IgG and IgA[L]	LPS activity was determined in sera using a *Limulus* amebocyte lysate test	Detection of bacteria in liver: *A. actinomycetemcomitans* and *C. pneumoniae* were detected by a RT-PCR;[M,N] negative samples were further examined by a semi conventional nested PCR with larger template volumes[O,P] <u>Histological analysis:</u> • Hepatic morphology (e.g., inflammatory changes, and microvesicular appearance) • Immunohistochemical stainings for CD68 and IL-1β • Frozen liver sections from the short experiment were stained with Oil Red O and Mayer's hematoxylin (e.g., neutral triacylglycerols and lipids) Liver lipid analyses: concentrations of choline-containing phospholipids and cholesterol, and liver triacylglycerols[Q] Tissue fatty acid analysis: total lipids from liver[R] RT-PCR of RNA from the liver tissue:[S] IL-1β, MCP-1, CD68, SREBP-1c, FAS, ACC2, LDLr, and GADPH

		group) was inoculated in the same manner as the groups with a single infection, starting with *C. pneumoniae* inoculations and followed by *A. actinomycetemcomitans* injections					
†Furusho et al., 2013[74] Laboratory study	Male C57BL/6J mice at 5-week-old	High-fat diet (HFD group) After 12 weeks of HFD feeding (fatty liver development): subgroups with and without dental infection of *P. gingivalis*, named HFD- *P. gingivalis*(+) and HFD- *P. gingivalis*(-), respectively Inoculation model: pulp chamber infected with 10^7 cells of *P. gingivalis* W83 strain	Chow-diet (CD group) Subgroups with and without dental infection of *P. gingivalis*, named CD- *P. gingivalis*(+) and CD- *P. gingivalis*(-), respectively	After *P. gingivalis* infection, extracted teeth with periodontal tissue were washed in sterilized PBS. The washing solution was plated on anaerobic blood agar and cultured in a 5 % CO_2 atmosphere at 37 °C. After a 4-day-cultivation, colonies were collected for DNA extraction and PCR analysis[T]	Immunolocalization of *P. gingivalis* in the periodontal tissue and liver using two antisera: rat antiserum against LPS obtained from *P. gingivalis* (*P. gingivalis*-LPS [1:1,000 dilution]) and rabbit antiserum against whole *P. gingivalis* (1:1,000 dilution) The IgG antibodies that reacted to the bacterial antigens were measured by the ELISA method published in a previous study[U]	Serum concentration of LPS was measured using Endospecy ES-50M Set	<u>Histomorphometric analysis</u>: • Grading inflammatory reaction in the liver (number of foci with more than 10 Mac2-positive macrophages) • Stages of fibrosis were evaluated with Azan-Mallory staining sections as no fibrosis (stage 0), only zone 3 perisinusoidal fibrosis (stage 1), as above with portal fibrosis (stage 2); as above with bridging fibrosis (stage 3), and cirrhosis (stage 4)[V] Cytokine levels of MCP-1, IL-1β, IL-6, IL-8, IL-17, IFN-γ, and TNF-α using a multiplex bead-based immunoassay kit Total RNA was extracted from the mouse liver tissue and used for cDNA synthesis. Amplification for TLR2, TLR4, inflammatory cytokines (IL-1β, IL-6, IL-8 and TNF-α) and inflammasomes (NLRP3 and Casp-1) was performed. RT-PCR was performed using specific primers and probe for TLR2 Formalin-fixed, paraffin-embedded human liver biopsy samples from 40 patients with NASH retrieved from the pathological file of Hiroshima University Hospital, included various degrees of fibrosis stages. Histological features related to fibrosis such as zone 3 perisinusoidal (pericentral vein) fibrosis, periportal fibrosis, bridging fibrosis and total fibrosis score were correlated with the presence of *P. gingivalis* infection in the liver

							Human liver samples: human liver biopsy samples from 40 patients with NASH including various degrees of fibrosis stages. Histological features related to fibrosis such as zone 3 perisinusoidal (pericentral vein) fibrosis (score 0-3), periportal fibrosis (score 0-3), bridging fibrosis (score 0-3) and total fibrosis score (sum of each score, score 0-9) were correlated with the presence of *P. gingivalis* infection in the liver
†Velusamy et al., 2014[75] Laboratory study	Male LFKO$^{-/-}$ mice at 8-week-old	Mice i.v. injected with *A. actinomycetemcomitans* (bacteria only) *A. actinomycetemcomitans* CU1000NRif were resuspended to 1 x 10^7 CFU per 0.1 mL of PBS and i.v. injected into the tail vein	Sham-infected control mice i.v. injected with PBS	NA	*A. actinomycetemcomitans* counts (CFU/mL of blood) from cardiac puncture and liver at different time intervals	NA	The serum proinflammatory cytokines were analyzed by Milliplex mouse cytokine/chemokine custom multicytokine detection, and the CRP levels were analyzed using mouse acute-phase kit Real-time RT-PCR gene expression analysis was carried out to evaluate hepatic cytokine expression levels (e.g., IFN-γ, TNF-α, IL-1β, IL6, IL10 and IL12)[W]
†Nakajima et al., 2015[76] Laboratory study	Male C57BL/6J mice at 6-week-old	10^9 CFUs of live *P. gingivalis* strain W83 suspended in 100 µL PBS with 2 % carboxymethyl cellulose was given to the oral cavity of each mouse through a feeding needle	Sham-administered 100 µL PBS with 2 % carboxymethyl cellulose without *P. gingivalis*	NA	Detection of *P. gingivalis* in blood using RT-PCR	Endotoxin levels were determined in sera collected 48 hours after the administration of *P. gingivalis* using a *Limulus* amebocyte lysate test	Liver microbiota analysis by 16S rRNA sequencing.[X] Taxonomic assignments and estimating relative abundance of sequencing data[Y-AA] PCoA using weighted or unweighted UniFrac distance based on OTU distribution across samples was performed to provide an overview of gut microbial dynamics in response to *P. gingivalis* administration[AB]
†Nakajima et al., 2016[77] Laboratory study	Male C57BL/6J mice at 8-week-old	Murine experimental periodontitis model adapted from Baker et al. (1994):[AC] mice did not receive antibiotic pretreatment before *P. gingivalis* administration 10^9 CFUs of live *P. gingivalis* strain W83 suspended in 100 µL PBS	Sham-administered 100 µL PBS with 2 % carboxymethyl cellulose without *P. gingivalis*	Quantification of alveolar bone loss (area surrounded by the margin of the submaxillary alveolar bone crest and the CEJ on the lingual side of	NA	Endotoxin levels were determined in sera using a *Limulus* amebocyte lysate test	Analysis of gene expression of the liver tissue using RT-PCR (e.g., *Plin2**, *Acox**, *G6pc**, *Irs1*, *Il6*, *Tnf*) *Genes associated with lipid droplet formation and gluconeogenesis Histological analysis of the liver tissue

		with 2 % carboxymethyl cellulose was given to each mouse via a feeding needle three times a week for 5 weeks		the first molar, using a stereomicroscope)			
†Fujita et al., 2018[78] Laboratory study	Male Wistar rats at 8-week-old	Obese rats: high-fat diet (HD group) for 12 weeks Endotoxin injected into the oral cavity: unlabeled LPS (LPS) or radiolabeled LPS (R-LPS) with ^{3}H and ^{14}C Groups: HD/LPS(-); HD/LPS(+); and HD/R-LPS	Non-obese rats: basal-diet (BD group) for 12 weeks Endotoxin injected into the oral cavity: unlabeled LPS (LPS) or radiolabeled LPS (R-LPS) with ^{3}H and ^{14}C Groups: BD/LPS(-); BD/LPS(+); and BD/R-LPS	Histopathological analysis of the maxilla was performed according to Kuraji et al. (2016, 2018)[AJ,AK] Autoradiogram analysis of R-LPS in the maxilla according to Hashimoto et al. (2014)[AL]	NA	*In vivo* distribution of R-LPS analyzed by liquid scintillation spectrometry at 5, 30, 60 minutes and 24 hours after endotoxin injection, from palatal mucosa, rat organs (e.g., liver), and blood samples	Histopathological analysis of the liver was performed according to Kuraji et al. (2016, 2018)[AJ,AK] NAFLD activity score (NAS) of the H-E stained liver sections was evaluated in accordance with Kleiner et al. (2005)[AM]
		Unlabeled LPS was extracted from *P. gingivalis* strain W83 according to the hot phenol-water method (Westphal and Jann, 1965)[AF] R-LPS was biosynthesized in *P. gingivalis* according to the method of Kim et al. (2014)[AG] SDS-PAGE of the purified LPS or R-LPS was performed according to Paramonov et al. (2005)[AH] Technique: injection into the palatine gingiva 2 mm away to center from the mesial gingival margin of the right maxillary first molar (Hashimoto et al., 2014):[AI] • 10 µL of saline or unlabeled LPS (20 µg, 2.81×10^{4} EU) was injected daily for 10 days to the rats R-LPS (^{3}H; 4.84 kBq and ^{14}C; 36.0 Bq/122 µg/1.72×10^{5} EU/10 µL) was injected once to the rats					

†Sazaki et al., 2018[79] Laboratory study	Male C57BL/6J germ-free mice at 8-week-old	High-fat diet 32 + i.v. injection of 10^8 CFUs sonicated *P. gingivalis* (endotoxins) suspended in 100 µL of physiological saline twice a week for 12 weeks (HFPg)	High-fat diet 32 + i.v. injection of physiological saline (HFco)	NA	NA	Endotoxin concentration in the sonicated *P. gingivalis* suspension of 5.7 ± 1.2 pg/mL HFPg mice were determined to be injected with 0.57 ± 0.12 pg LPS at each injection Plasma and bacterial endotoxin levels and sonicated *P. gingivalis* suspension were assessed by Wako ES-test kit	*In vivo* evaluation of visceral and subcutaneous fat using micro-computed tomography (microCT)— visceral fat and subcutaneous fat along the ribs qPCR as previously described by Komazaki et al. (2017)[AN] Liver histological analysis: tissue sections were stained with Oil Red O and counterstained with hematoxylin. Areas that did not include large vessels were chosen for histological analysis. Adipocyte cross-sectional area was measured Glycogen measurements from aliquots of liver lysates[AO,AP] Triglyceride measurements from aliquots of liver lysates[AQ,AR] Microarray analysis in the liver— KEGG pathways in the upregulated DEGs:[AS] • Metabolic pathways: *Impa2, Aldh3a2, Aox1, Bhmt, Cyp2b10, Cyp2b9, Cyp3a11, Cyp3a16, Gpil, Lipg, Acot2, Acot3, Acot4, Me1, Mtm1, Nat1, Rrm2, Uck1, Csad, Acot1, Ahcy, Hsd17b6, Acss3, Ugt1a10, Cyp2c68, Amt, Hao2, 9130409I23Rik, Cyp4a31, Etnppl, Ehhadh, Tusc3, Ces1d, Cyp3a41a, Cyp4a10, Cyp4a14,* and *Pklr* gene expression • Fatty acid degradation: *Aldh3a2, Cpt1b, Cyp4a10, Cyp4a14, Cyp4a31,* and *Ehhadh* gene expression • Fatty acid elongation: *Acot1, Acot2, Acot3,* and *Acot4* gene expression
§Nagasaki et al., 2020[80] Laboratory study	Mice exposed to high-fat diet for 12 weeks to develop fatty liver	High-fat diet (HFD group) After 12 weeks of HFD feeding (fatty liver development): subgroups with and without dental infection of *P. gingivalis*, named HFD- *P.*	Chow-diet (CD group) Subgroups with and without dental infection of *P. gingivalis*, named CD- *P.*	Histological analysis and immunohistochemistry (e.g., Ly-6B.2-positive neutrophils)[AT]	Immunolocalization of *P. gingivalis* in the liver	NA	NAFLD activity score (NAS): microscopic assessment focusing on steatosis, lobular inflammation, and hepatocellular ballooning[AU] Histological/morphometry analysis and immunohistochemistry,[AT] RT-PCR, and Western blotting: measurement of macrophage infiltration and fibrosis areas, *P. gingivalis*-infected focus

		gingivalis(+) and HFD- *P. gingivalis*(-), respectively Inoculation model: pulp chamber infected with 10^7 cells of *P. gingivalis* W83 strain[AT]	*gingivalis*(+) and CD- *P. gingivalis*(-), respectively				number in the liver, cytokine-mRNA expression of TGF-β1, Gal-3-positive cell area including hepatic stellate cells, hepatocytes, macrophages, and macrophage aggregations, red linear stained collagen fibers, pSmad2, number of hepatic crown-like structures which were Mac2-positive macrophage aggregates, PAR2, TLR2/4, α-SMA, type I collagen, Smad2/3, and ERK1/2
†Yamazaki et al., 2020[81] Laboratory study	Male C57BL/6NJcl[GF] mice at 5-week-old	Periodontitis-associated bacteria (P group) – pathobionts: 10^9 CFUs of live *P. gingivalis* (strain W83), *F. nucleatum* (ATCC25586) and *F. alocis* (ATCC35896) suspended in 100 µL PBS with 2 % carboxymethyl cellulose was given to the oral cavity of each mouse through a feeding needle twice a week for 5 weeks[AD]	Health-associated bacteria (H group) – commensals: 10^9 CFUs of live *S. mitis* (ATCC15910), *A. naeslundii* (ATCC19039) and *V. rogosae* (JCM15642) suspended in 100 µL PBS with 2 % carboxymethyl cellulose was given to the oral cavity of each mouse through a feeding needle twice a week for 5 weeks[AD]	Quantification of alveolar bone loss (distance from the alveolar bone crest to the CEJ using a stereomicroscope) on the mesial and distal roots, and the exposed root surface area of the mandibular first molar	Detection of bacterial DNA in blood and liver using RT-PCR Antibody responses to antigens of periodontopathic bacteria from cardiac puncture assessed by ELISA[AE]	Endotoxin levels were determined in sera using a *Limulus* amebocyte lysate test	Detection of bacterial DNA from culture of aliquots of liver lysates using RT-PCR Analysis of gene expression of the liver tissue using RT-PCR (e.g., *Acaca*, *Lipin1*, *Ddit4*, *Bmal1*, and *Tsc22d3*)
§Nagasaki et al., 2021[82] Laboratory study	Mice exposed to high-fat diet for 12 weeks to develop fatty liver	High-fat diet (HFD) mice with *P. gingivalis* odontogenic infection— *P. gingivalis* W83 strain dentally applied to mice (10^7 CFU per mouse)[AV] After 6 weeks of *P. gingivalis* infection, a 15-memberedring macrolide [azithromycin (AZM), dissolved in distilled water for injection at a concentration of 50 mg/mL]	HFD mice without *P. gingivalis* odontogenic infection (control group) Group without AZM application served as the *P. gingivalis* infection group (HP group)	Histological analysis and immunohistochemistry (e.g., Ly-6B.2-positive neutrophils)[AV]	Immunolocalization of *P. gingivalis* in the liver	NA	NAFLD activity score (NAS): microscopic assessment focusing on steatosis, lobular inflammation, and hepatocellular ballooning[AU] Histological/morphometry analysis and immunohistochemistry:[AV] measurement of macrophage infiltration and fibrosis areas, *P. gingivalis*-infected focus number in the liver, cytokine-mRNA expression of (TNF-α)/*Tnf-α* and (IL-1β)/*Il-1β*, Gal-3-positive cell area including hepatic stellate cells, hepatocytes, macrophages, and macrophage aggregations, pSmad2, number of hepatic crown-like structures which were Mac 2-

		was administered to three groups: HPS, with systemic AZM application; HPL, with local AZM application; and HPLS, with local and systemic AZM application • HPL and HPLS groups: pulp chambers were washed with AZM solution and a small cotton swab immersed in 50 µg (1 µL) AZM solution was applied into the pulp chambers and then sealed with Caviton • HPS and HPLS: mouse was made to fast for 6 h before the treatment; then, AZM (2 mg/body) was administered to the stomach directly with a flexible oral administration tube					positive macrophage aggregates, and red linear stained collagen fibers
†Yamazaki et al., 2021[83] Laboratory study	Male C57BL/6N mice at 6-week-old	Periodontitis-associated bacteria: 10^9 CFUs of live *P. gingivalis* strain W83, *P. intermedia* (ATCC25611), *A. naeslundii* (ATCC19039), or *V. rogosae* (JCM15642) suspended in PBS with 2 % carboxymethyl cellulose was given to the oral cavity of each mouse through a feeding needle 5 times a week for 3 weeks[AW-AY]	Sham-administered PBS with 2 % carboxymethyl cellulose without bacteria was given to the oral cavity of each mouse through a feeding needle 5 times a week for 3 weeks Negative control group that was only administered the vehicle only until	NA	NA	Endotoxin levels were determined in sera using a *Limulus* amebocyte lysate test	Liver histology and biochemical analyses to visualize collagen fibrils Liver triglycerides were determined using a triglyceride quantification colorimetric kit Serum levels of ALT and AST were analyzed using commercially available kits Quantitative analysis of gene expression in the liver using RT-PCR[AZ] Quantitation of liver metabolites using a nuclear magnetic resonance spectroscopy[BA,BB]

		At 1 week after the commencement of infection, the diet was changed to CDAHFD60 (HFD) To analyze the effect of bacteria alone, an experimental group without diet change was also set	the end of the experiment (regular chow [RC])				*In vitro* experiments: HepG2 cells were stimulated with LPS (1 mg/mL *P. gingivalis* or *P. intermedia* LPS, and 1 ng/mL *E. coli* LPS) for 4 hours. Total RNA was extracted from the cells and used for RT-PCR

Legend: [†], Phase 2 of the study selection process (full-text screening); [§], handsearch; NA, data not available; *P. gingivalis*, *Porphyromonas gingivalis*; CFU, colony forming unit; IgG, immunoglobulin G; PCR, polymerase chain reaction; *C. rectus*, *Campylobacter rectus*; PBS, phosphate buffered saline; *E. coli*, *Escherichia coli*; *S. griseus*, *Streptomyces griseus*; O_2, oxygen; ALT, alanine aminotransferase; AST, aspartate aminotransferase; TNF-α, tumor necrosis factor-alpha; ELISA, enzyme-linked immunosorbent assay; CRP, C-reactive protein; H_2O_2, hydrogen peroxide; TUNEL, terminal deoxynucleotidyl transferase (TdT)-mediated deoxyuridine triphosphate (dUTP)-biotin nick-end labeling; 8-OHdG, 8-hydroxydeoxyguanosine; mtDNA, membrane-associated DNA; *C. pneumoniae*, *Chlamydia pneumoniae*; IFU, inclusion-forming units; SPG, sucrose-phosphate-glutamic acid buffer; *A. actinomycetemcomitans*, *Aggregatibacter actinomycetemcomitans*; NaCl, sodium chloride; IgA, immunoglobulin A; RT-PCR, real-time polymerase-chain reaction; CD68, cluster of differentiation 68; IL-1β, interleukin 1-beta; HFD, high-fat diet; CD, chow-diet; CO_2, carbon dioxide; Galectin-3/Mac2, β-galactoside-binding lectin that is highly expressed in and secreted by monocytes/macrophages; MCP-1, monocyte chemoattractant protein-1; IL-6, interleukin 6; IL-8, interleukin 8; IL-17, interleukin 17; IFN-γ, interferon gamma; RNA, ribonucleic acid; cDNA, complementary deoxyribonucleic acid; TLR2/4, Toll-like receptor 2/4; NLRP3, nod-like receptor 3; Casp-1, caspase-1; NASH, nonalcoholic steatohepatitis; i.v., intravenously; IL-10, interleukin 10; IL-12, interleukin 12; PCoA, principal coordinate analysis; UniFrac, UniFrac metric measures the distance between communities, reflects differences between the lineages that are adapted to live specifically in one environment or the others, and has been used to cluster many different environments according to shared similarities in community composition; OUT, operational taxonomic unit; CEJ, cemento-enamel junction; *Plin2*, perilipin 2; *Acox*, Acyl-CoA Oxidase 1; *G6pc*, glucose-6- phosphatase; *Irs1*, insulin receptor substrate 1; *Il6*, interleukin 6; *tnf*, tumor necrosis factor; *Tnfα*, tumor necrosis factor-alpha; *Il1β*, interleukin 1-beta; *Acaca*, acetyl-coenzyme A carboxylase alpha; *Fitm2*, fat storage-inducing transmembrane protein 2; *Plin2*, perilipin 2; *G6pc*, glucose-6- phosphatase; ^{3}H, tritium; ^{14}C, carbon-14; SDS-PAGE, sodium-dodecyl-sulfate polyacrylamide-gel-electrophoresis; R-LPS, radiolabeled lipopolysaccharide; NAFLD, nonalcoholic fatty liver diseases; NAS, NAFLD activity score; microCT, micro-computed tomography; qPCR, quantitative polymerase-chain reaction; *Impa2*, inositol monophosphatase 2; *Aldh3a2*, aldehyde dehydrogenase 3 family member a2; *Aox1*, aldehyde oxidase 1; *Bhmt*, Betaine--homocysteine s-methyltransferase; *Cyp2b10*, cytochrome P450, family 2, subfamily b, polypeptide 10; *Cyp2b9*, cytochrome P450, family 2, subfamily b, polypeptide 9; *Cyp3a11*, cytochrome P450, family 3, subfamily a, polypeptide 11; *Cyp3a16*, cytochrome P450, family 3, subfamily a, polypeptide 16; *Gpil*, genetic programming for inductive learning; *Lipg*, endothelial lipase gene; *Acot2*, Acyl-CoA thioesterase 2; *Acot3*, Acyl-CoA thioesterase 3; *Acot4*, Acyl-CoA thioesterase 4; *Me1*, malic enzyme 1; *Mtm1*, myotubularin 1; *Nat1*, N-acetyltransferase 1; *Rrm2*, ribonucleotide reductase regulatory subunit m2; *Uck1*, uridine-cytidine kinase 1; *Csad*, cysteine sulfinic acid decarboxylase; *Acot1*, Acyl-CoA thioesterase 1; *Ahcy*, adenosylhomocysteinase; *Hsd17b6*, hydroxysteroid 17-beta dehydrogenase 6; *Acss3*, Acyl-CoA synthetase short chain family member 3; *Ugt1a10*, UDP-glucuronosyltransferase 1a10; *Cyp2c68*, Cytochrome P450, family 2, subfamily c, polypeptide 68; *Amt*, aminomethyltransferase; *Hao2*, hydroxyacid oxidase 2; *9130409I23Rik*, RIKEN cDNA 9130409I23 gene; *Cyp4a31*, cytochrome P450, family 4, subfamily a, polypeptide 31; *Etnppl*, ethanolamine-phosphate phospho-lyase; *Ehhadh*, enoyl-CoA hydratase and 3-hydroxyacyl CoA dehydrogenase; *Tusc3*, tumor suppressor candidate 3; *Ces1d*, Carboxylesterase 1d; *Cyp3a41a*, cytochrome P450, family 3, subfamily a, polypeptide 41a; *Cyp4a10*, cytochrome P450, family 4, subfamily a, polypeptide 10; *Cyp4a14*, cytochrome P450, family 4, subfamily a, polypeptide 14; *Pklr*, pyruvate kinase l/r; *Cpt1b*, carnitine palmitoyltransferase 1b; TGF-β1, TGF-β1, transforming growth factor beta 1; Gal-3, galectin-3; PAR2, protease-activated receptor 2; α-SMA (α-smooth muscle actin), monoclonal antibody used for immunohistochemical detection of hepatic myofibroblasts; ERK1/2, extracellular signal-regulated kinase 1/2; *F. nucleatum*, *Fusobacterium nucleatum*; *F. alocis*, *Filifactor alocis*; *S. mitis*, *Streptococcus mitis*; *A. naeslundii*, *Actinomyces naeslundii*; *V. rogosae*, *Veillonella rogosae*; DNA, deoxyribonucleic acid; *Lipin1*, phosphatidate phosphatase-1; *Ddit4*, DNA-damage-inducible transcript 4; *Bmal1*, brain and muscle ARNT-Like 1; *Tsc22d3*, TSC22 domain family member 3; AZM, azithromycin; pSmad2, phosphorylated Smad2; *P. intermedia*, *Prevotella intermedia*; CDAHFD60 diet, CDAHFD60, choline-deficient, l- amino acid-defined, high-fat diet with 60 kcal % fat and 0.1 % methionine; HepG2 cell, cell line exhibiting epithelial-like morphology that was isolated from a hepatocellular carcinoma.

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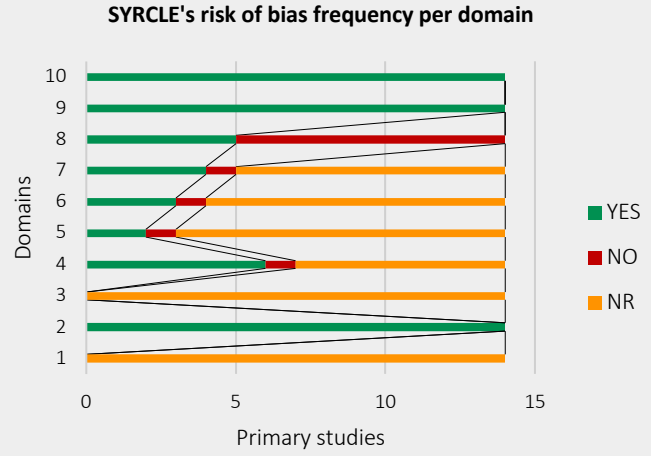
Critical appraisal within sources of evidence. The methodological quality of laboratory studies was positive for baseline characteristics and selective reporting of results, according to the SYRCLE's tool. All studies clarified the methodology and detailed the results of the experiments. However, most studies did not report or did not perform randomization, allocation concealment, and blinding strategies. The incomplete outcome data refers to data not shown in five studies this bias did not compromise the eligibility criteria (Figure 7). Quality assessment pointed to a risk of bias from laboratory studies attributed to lack of methodological detail (data not reported) and failure in the domains of selection bias, performance bias, detection bias, and attrition bias. In contrast, the JBI critical appraisal checklist criteria recommended the inclusion of case reports previously selected based on the quality of the studies (Figure 8).

FIGURE 7

SYRCLE's risk of bias analysis

Domain		Primary studies													
		1	2	3	4	5	6	7	8	9	10	11	12	13	14
A	1. Sequence generation	Nr	Nr	Nr	Nr	Nr	Nr	Nr	Nr	Nr	Nr	Nr	Nr	Nr	Nr
	2. Baseline characteristics	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
	3. Allocation concealment	Nr	Nr	Nr	Nr	Nr	Nr	Nr	Nr	Nr	Nr	Nr	Nr	Nr	Nr
B	4. Random housing	Nr	Yes	Yes	Yes	Yes	Nr	Nr	Nr	Nr	Yes	Yes	Nr	Nr	No
	5. Blinding	Nr	Nr	Nr	Yes	Nr	Nr	Nr	Nr	Nr	Nr	Nr	Yes	Nr	No
C	6. Random outcome assessment	Nr	Yes	Nr	Nr	Yes	Nr	Nr	Nr	Nr	Yes	Nr	Nr	Yes	No
	7. Blinding	Nr	Nr	Yes	Nr	Nr	Nr	Nr	Yes	Nr	Nr	Nr	Yes	Yes	No
D	8. Incomplete outcome data*	Yes	Yes	No	Yes	No	No	Yes	No	No	No	No	No	Yes	No
E	9. Selective outcome reporting	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes



Bar chart | Source: authors
Inter-observer variability: Kappa statistics for items 1–10 (κ = 100 %) based on two raters including 14 papers

Legend:

Domain: A, selection bias; B, performance bias; C, detection bias; D, attrition bias; E, reporting bias; *, the presence of incomplete outcome data means a risk of bias.

1, Boggess et al., 2005; 2, Yeo et al., 2005; 3, Tomofuji et al., 2007; 4, Hyvärinen et al., 2009; 5, Furusho et al., 2013; 6, Velusamy et al., 2014; 7, Nakajima et al., 2015; 8, Nakajima et al., 2016; 9, Fujita et al., 2018; 10, Sazaki et al., 2018; 11, Nagasaki et al., 2020; 12, Yamazaki et al., 2020; 13, Nagasaki et al., 2021; 14, Yamazaki et al., 2021. LRB, low risk of bias (green); URB, unclear risk of bias (yellow); and HRB, high risk of bias (red).

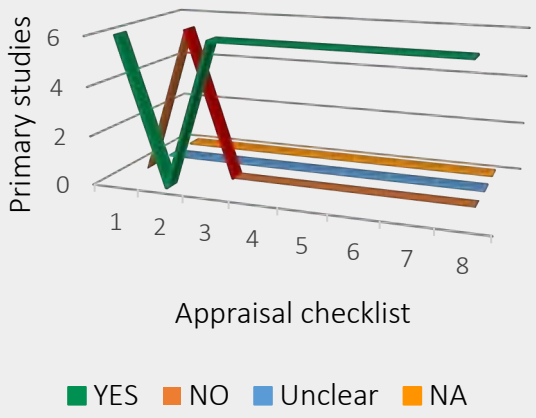
A "Yes" judgement indicates a low risk of bias; a "No" judgment indicates high risk of bias; the judgment will be "Unclear" if insufficient details have been reported to assess the risk of bias properly; and Nr indicates data not reported.

From: Hooijmans CR, Rovers MM, de Vries RB, Leenaars M, Ritskes-Hoitinga M, Langendam MW. SYRCLE's risk of bias tool for animal studies. BMC Med Res Methodol. 2014 Mar 26;14:43. doi: 10.1186/1471-2288-14-43.

FIGURE 8

JBI critical appraisal checklist for case reports

	A[84]	B[85]	C[86]	D[87]	E[88]	F[89]
1. Were patient's demographic characteristics clearly described?	Yes	Yes	Yes	Yes	Yes	Yes
2. Was the patient's history clearly described and presented as a timeline?	No	No	No	No	No	No
3. Was the current clinical condition of the patient on presentation clearly described?	Yes	Yes	Yes	Yes	Yes	Yes
4. Were diagnostic tests or assessment methods and the results clearly described?	Yes	Yes	Yes	Yes	Yes	Yes
5. Was the intervention(s) or treatment procedure(s) clearly described?	Yes	Yes	Yes	Yes	Yes	Yes
6. Was the post-intervention clinical condition clearly described?	Yes	Yes	Yes	Yes	Yes	Yes
7. Were adverse events (harms) or unanticipated events identified and described?	Yes	Yes	Yes	Yes	Yes	Yes
8. Does the case report provide takeaway lessons?	Yes	Yes	Yes	Yes	Yes	Yes
Overall appraisal: "Include", "Exclude", or "Seek further info"	Include	Include	Include	Include	Include	Include
Comments (Including reason for exclusion)	–	–	–	–	–	–



3D Line chart | Source: authors
Inter-observer variability: Kappa statistics for items 1–9 (κ = 100 %) based on two raters including 6 papers

Legend:

A, Farsakian and Bronny (1986); B, Yoneda et al. (2011); C, Omura et al. (2016); D, Schimmel et al. (2019); E, Soeiro et al. (2019); F, Collins and Diamond (2021).

"Yes"; "No"; "Unclear"; and "Na", not applicable.

From: Moola S, Munn Z, Tufanaru C, Aromataris E, Sears K, Sfetcu R, Currie M, Qureshi R, Mattis P, Lisy K, Mu P-F. Chapter 7: Systematic reviews of etiology and risk. In: Aromataris E, Munn Z (Editors). *Joanna Briggs Institute Reviewer's Manual*.The Joanna Briggs Institute, 2017. Available from https://reviewersmanual.joannabriggs.

Results of individual sources of evidence

Laboratory studies. Eight studies confirmed bloodstream bacteremia (Bbac)[75,76] and/or liver bacteremia (Lbac),[70,71,73,74,80,82] and seven studies confirmed bloodstream endotoxemia (Bend).[72-74,76-78,83] Two studies did not detect blood endoxemia,[79,81] but used intravenous inoculation models. Regarding the interventions tested, one study reported the viability of *C. rectus* in a mouse chamber model throughout the experiments,[71] four studies confirmed periodontal compromise in experimental models of periodontitis induction,[72,77,78,81] and three studies of pulp chamber infected with *P. gingivalis* described pulp necrosis and pathogen-associated periapical granuloma.[74,80,82] *P. gingivalis*-Lbac was demonstrated in two study using PCR analysis[70,74] and in three studies using immunocolocalization.[74,80,82] *A. actinomycetemcomitans* was detected in the liver by culture[75] and RT-PCR with *C. pneumoniae*.[73] *C. rectus*[71] and *F. nucleatum*[81] were also identified in liver specimens by PCR and RT-PCR, respectively (Table 3).

Serum levels of C-reactive protein (CRP)[72,75] and serum amyloid A protein (*Saa*)[73] were significantly increased by the endotoxemia of LPS[72] and *A. actinomycetemcomitans*-[75] and *A. actinomycetemcomitans* plus *C. pneumoniae*-bacteremia.[73] Interestingly, serum levels of liver enzymes aspartate aminotransferase (AST) and alanine aminotransferase (ALT were not influenced by endotoxemia or bacteremia.[72,82,83] Oxidative stress was associated with endotoxemia by LPS[72] and bacteremia by *P. intermedia* and even more by *P. gingivalis*.[83] Serum levels of hydrogen peroxide (H_2O_2),[72] TUNEL-positive cells [terminal deoxynucleotidyl

transferase (TdT)-mediated deoxyuridine triphosphate (dUTP)-biotin nick-end labeling] in liver,[72] and increased mitochondrial concentration of 8-hydroxydeoxyguanosine (8-OHdG) and upregulation of genes involved in the cell responses to oxidative and endoplasmic reticulum stress in the liver[83] have been reported. Proinflammatory genes were expressed in livers exposed to endotoxemia and bacteremia.[83] Increase in biomarkers TNF-α,[72,74,75,77,82] transforming growth factor beta 1 (TGF-β1),[80] IL-1β,[73-75,82] interleukin 6 (IL-6),[75,77] interleukin 10 (IL-10),[75] interleukin 12 (IL-12),[75] interleukin 17 (IL-17),[74] interferon gamma (IFN-γ),[75] monocyte chemoattractant protein 1 (MCP-1),[73] CD68 (cluster of Differentiation 68 expressed in cells in the monocyte lineage),[73] and TLR2+ (Toll-like receptor 2)[74] in the liver were reported in the studies. (Table 3).

Endotoxemia induced foci of inflammation and necrosis in the liver.[72,78] Both endotoxemia and bacteremia were associated with NAFLD.[72,74,77-80,82,83] Of these, *P. gingivalis* bacteremia induced NASH,[74] and *P. gingivalis*-LPS endotoxemia accelerated the progression from simple steatosis, also reported as NAFL (nonalcoholic fatty liver), to NASH.[78] NAS (NAFLD activity score) showed significant increase with odontogenic infection of *P. gingivalis*.[78,82] In addition, *P. gingivalis* infection exacerbated pathological progression of NASH. *P. gingivalis*-odontogenic infection exacerbated pathological progression of NASH through Gal-3 and TGF-β1/Smad pathway.[80] Local and systemic administration of azithromycin (AZM) led to a limited and transient improvement in hepatic parameters impacted by *P. gingivalis*.[82] LPS endotoxemia[72] and *P. gingivalis* bacteremia were associated with liver fibrosis.[74,80,82,83] Degree of fibrosis was progressively exacerbated with increasing bacterial burden of *P. intermedia* and *P. gingivalis*, with emphasis on the latter.[83] *P. gingivalis*-odontogenic infection aggravates inflammatory cell infiltration and liver fibrosis, in which TGF-β1/Smad and Gal-3 (galectin-3) pathway are involved.[80] Hepatic inflammation also occurred in animals infected with *C. pneumoniae* and *A. actinomycetemcomitans* (Table 3).[73]

Changes in hepatic lipid content and fatty acid profiles of liver exposed to *C. pneumoniae* and *A. actinomycetemcomitans* included: increased cholesterol, triacylglycerol, phospholipids, triacylglycerol/phospholipid ratio, saturated fatty acid (SFA), dihomo-γ-linolenic acid (DGLA) and arachidonic acid (ARA), and decreased monounsaturated fatty acids (MUFA), polyunsaturated fatty acids (PUFA) and γ-linolenic acid [GLA (DGLA precursor)].[73] *P. gingivalis*-infection increased macrovesicular lipid accumulation and hepatic crown-like structures (aggregation of macrophages and positively correlated with the extent of liver fibrosis).[80] The main histological changes in liver tissue were: lipid deposition/accumulation,[78-80] lipid droplets,[72,74,78,79] ballooning hepatocyte,[74] ballooning degenerations,[78] focal necrosis,[78] large necrotic areas,[72] spindle cells in the fibrotic area were immunopositive for α-SMA (α-smooth

muscle actin) indicating their myofibroblastic nature (hepatic stellate cells),[74] and accumulation of type I collagen around the hepatocytes[82] and hepatic stellate cells (Table 3).[74]

Gene expression patterns in the livers differed substantially between animals on a high-fat diet feeding with and without *P. gingivalis*. 41 % of upregulated DEGs [differentially expressed genes (microarray analysis)] with GO (gene ontology) terms were classified as "metabolic process" in the biological process category; 24 % of the downregulated DEGs were classified as "metabolic process"; metabolic pathway was significantly enriched in upregulated DEGs; fatty acid degradation and fatty acid elongation were enriched in upregulated DEGs, based on quantification of mRNA expression levels with qPCR; gene sets related to hypoxia, TNF-α signaling via NFκB (nuclear factor kappa-light-chain-enhancer of activated B cells), and adipogenesis, were upregulated, and gene set related to fatty acid metabolism was strongly upregulated in *P. gingivalis*-infected mice.[79] Regarding gene expression in the liver exposed to *F. nucleatum*: expression of the anti-inflammatory gene *Tsc22d3* (TSC22 domain family member 3) tended to be lower, expression of *Acaca* (acetyl-coenzyme A carboxylase alpha) and *Lipin1* (phosphatidate phosphatase-1)—genes involved in lipid metabolism was significantly higher, endoplasmic reticulum stress-related gene *Ddit4* (DNA-damage-inducible transcript 4) was upregulated, and expression of the circadian rhythmal control gene *Bmal1* (brain and muscle ARNT-Like 1) was significantly lower in the periodontitis-associated bacteria group.[81] Hierarchical clustering heatmap showed a robust effect of high-fat diet feeding on the liver, and the administration of *P. intermedia* and *P. gingivalis* induced additional and substantial changes in the expression profile of genes. The functional enrichment analysis revealed that: genes involved in the biosynthesis and metabolic processes of lipids, organic acids, oxoacids, steroids, and fatty acids were downregulated in *P. gingivalis* mice; and genes involved in the cell cycle, cell death, nuclear division, DNA replication, responses to oxidative and endoplasmic reticulum stress, regulation of intrinsic apoptosis, inflammatory response such as in the regulation of leukocyte migration, response to LPS, cellular response to inflammatory cytokines, NFkB pathways, and biological processes for circadian regulation of gene expression were upregulated in *P. gingivalis* mice. Progression from NAFL (simple steatosis) to NASH (steatohepatitis), fibrosis, and hepatocellular carcinoma was mediated by multiple parallel factors, including inflammation, endoplasmic reticulum stress, lipotoxicity, and altered circadian rhythms; GO terms and KEGG pathways implicated in these events were found to be significantly enriched in the clusters 1, 2, and 4 (pathways for steroid hormones, retinol, primary bile acids, arachidonic acid, amino sugars, and nucleotide sugars). As in the previous study,[81] the authors described an elevated expression of the *Tsc22d3* gene in *P. gingivalis* mice; weaker elevation of inflammatory genes was reported for this group. *Fgf21* (fibroblast growth factor 21) and *Trib3* (tribbles pseudokinase 3) genes, induced by endoplasmic reticulum stress and elevated in NAFLD, were

significantly upregulated in *P. gingivalis* mice. Fibrosis- and endoplasmic reticulum stress - related genes were enriched, and connective tissue growth factor was upregulated specifically by *P. gingivalis* administration. GO terms associated with the cell cycle process (potentially implicated in carcinogenesis and end-stage NAFLD) were enriched. In contrast, the expression of *Hnf6* (hepatocyte nuclear factor 6) gene (negatively associated with hepatocellular carcinoma malignancy) and *Hhex* (hematopoietically expressed homeobox) gene (related to decrease the expression of several proto-oncogenes and increases the expression of some tumor suppressor genes) were upregulated in *P. intermedia* mice. The GO terms associated with circadian rhythm control were enriched. The significant increase in *Per1* [period circadian regulator 1 (clock gene], in *P. gingivalis* mice corroborated the literature on fluctuations in circadian rhythm affecting metabolism and altering the expression of liver clock genes in NAFLD. For more details on DNA microarray analysis for representative genes involved in the pathological mechanisms of NAFLD, see Table 3.

TABLE 3

Results from primary studies				
Study | Design	**Intervention**	**Bacteremia**	**Endotoxemia**	**Liver abnormalities**
§Boggess et al., 2005[70] Laboratory study	NA	*P. gingivalis* detected by PCR in maternal and fetal livers	NA	Proportion of specimens with *P. gingivalis* detected by PCR: • Maternal liver: control = 0:4; and exposed animals = 1:3 (33 %)—p = NS • Fetal liver: control = 0:31; and exposed animals = 13:35 (34 %)—p = 0.002
†Yeo et al., 2005[71] Laboratory study	The fluid present in the subcutaneous chambers was collected on embryonic day 16.5 at the time of sacrifice and cultured in order to determine the presence and viability of *C. rectus* The authors were able to regrow *C. rectus* only from the chamber fluids of the challenged females, indicating that it survived within the chamber environment throughout the experimental study	*C. rectus* was detected by PCR in maternal liver	NA	*C. rectus* was detected by PCR in maternal liver samples (7:8 [87.5 %]); *C. rectus* was not detected in maternal livers of the control group
†Tomofuji et al., 2007[72] Laboratory study	Periodontitis group showed apical migration of the junctional epithelium and extension of blood vessels No histologic changes were observed in the control group Distance between the CEJ and the most apical portion of the junctional epithelium and the distance between the CEJ and the alveolar	NA	Serum levels of LPS in the periodontitis group were significantly higher than those in the control	Periodontitis group: • Obvious macrovesicular steatosis at the pericentral vein area and scattered foci of inflammation showing necrotic hepatocytes, mononuclear cells (Kupffer cells), lymphocytes, and a few neutrophils • Various-sized lipid droplets were detected by oil red O staining occasionally, large necrotic areas were found in the liver specimens of the periodontitis group (in ≅ 40 % of rats) • Hyperplasia of bile duct and slight fibrosis in the portal and sinusoidal • Prevalence of steatosis was 71 % (5:7), higher than that of the control group (p < 0.05) • Significant differences between the two groups in the ratios of: TNF-α-positive cells (p = 0.004), number of TUNEL-positive cells (p = 0.038), and concentration of mitochondrial 8-OHdG in the liver (p = 0.001)

	bone crest were significantly greater than in the control group (p = 0.026 and 0.017, respectively) Densities of blood vessels and PMNs within the junctional epithelium and the connective tissue subjacent to the junctional epithelium in the periodontitis group also were higher than in the control group (p = 0.001)		group (p = 0.001) The LPS levels of the two rats without hepatocellular steatosis were lower than those of the other rats in the periodontitis group	• Two rats without steatosis showed fewer TUNEL-positive cells and a lower mitochondrial 8-OHdG level in liver than the rats with steatosis in the periodontitis group The steatosis score was higher in the Periodontitis group ($p < 0.05$). Scores of inflammation and necrosis in liver were more evident in periodontitis ($p > 0.05$) <u>Relationship between serum and liver markers:</u> • Serum levels of CRP, and H_2O_2 in the periodontitis group were significantly higher than those in the control group (p = 0.001 and p = 0.013, respectively) • Serum levels of TNF-α in the periodontitis group was higher than that in the control group (p = 0.080) • There was no significant difference in serum level of ALT between the two groups (p = 0.589) • Significant positive relationships were observed between the serum LPS level and percentages of TNF-α– (p < 0.001) and TUNEL-positive cells (p = 0.011) and concentration of 8-OHdG in liver (p = 0.001) • Significant positive relationships were observed between the serum H_2O_2 level and concentration of 8-OHdG in liver (p = 0.009) • No significant relationship was observed between the serum H_2O_2 level and percentages of TNF-α– (p = 0.132) and TUNEL-positive cells (p = 0.302) in liver • Serum TNF-α level was not correlated with percentages of TNF-α– (p = 0.085) and TUNEL-positive liver cells (p = 0.180) or concentration of 8-OHdG in liver (p = 0.180)
[§]Hyvärinen et al., 2009[73] Laboratory study	NA	Short-term experiment––nonquantitative semiconventional PCR: 1/7 (14 %) and 2/7 (29 %) livers of the mice with chronic and acute infections were positive for *C. pneumoniae* bacteria Long-term experiment––	Serum LPS activities tended to be higher in all infected mice both in the short-term experiment (21.3 ± 6.0 versus 10.2 ± 3.4 EU/mL; p = 0.458) and in the long-term experiment (57.1 ± 4.7 versus 41.5 ± 4.9	Specimens with *C. pneumoniae* and *A. actinomycetemcomitans* detected by PCR <u>Histological changes in the hepatic tissue:</u> • Short-term experiment: i) chronic *C. pneumoniae* infection group displayed an increased microvesicular appearance (p = 0.007); ii) acute *C. pneumoniae* infection had only minor effects on liver morphology or inflammation status; and iii) degree of Oil Red O staining for neutral triacylglycerols and lipids remained the same in the chronic group but was lower in the acute group (p = 0.005) • Long-term experiment: i) chronic *C. pneumoniae* infection induced mild inflammation (p = 0.017) and an increased microvesicular appearance was observed (p = 0.001); ii) *A. actinomycetemcomitans* administered alone (p = 0.002), and in concert with *C. pneumoniae* (p = 0.023), induced moderate hepatic inflammation (e.g., infiltration of perivascular mononuclear inflammatory cells and neutrophils into the liver tissue) <u>Changes in the hepatic lipid content and fatty acid profiles:</u> • Phospholipid levels were lower in all infected mice compared to control mice • Changes in cholesterol and triacylglycerol levels were not significant, except that the concentration of triacylglycerols was lower in the acute *C. pneumoniae* infection group (p = 0.001) than in the control • Ratio of triacylglycerols to phospholipids was lowered in the acute *C. pneumoniae* infection group in the short-term experiment and increased in both chronic *C. pneumoniae* infection groups in both experiments as well as in the *A. actinomycetemcomitans*-infected mice

		nonquantitative semiconventional PCR: i) *C. pneumoniae* was not detected in the liver samples; and ii) *A. actinomycetemcomitans* was quantitatively detected in the livers of 6/20 (30 %) mice, with a median pathogen level of 10 (range, 3 to 1,654) GE/mg tissue	EU/mL; p = 0.075)	• Proportions of SFA were higher in the mice with acute *C. pneumoniae* infection (p = 0.010) and lower in the mice with chronic *C. pneumoniae* infection in the long-term experiment (p = 0.006) compared to control mice • Proportions of MUFA were lower in the mice with acute *C. pneumoniae* infection (p = 0.032) and higher in the mice with chronic *C. pneumoniae* infection in the short-term (p = 0.022) and long-term (p = 0.086) experiments • Proportions of PUFA were significantly lower in mice with chronic *C. pneumoniae* infection in the short-term experiment (p = 0.010) • Changes in the SFA, MUFA, and PUFA proportions in *A. actinomycetemcomitans*-infected mice were minor • Proportion of anti-inflammatory DGLA was higher in the short-term experiment in the mice with chronic *C. pneumoniae* infection (p = 0.008) and in the long-term experiment in the mice with *A. actinomycetemcomitans* infection (p = 0.025) • Proportion of the GLA was decreased in the short-term experiment in mice with acute (p = 0.003) and chronic (p = 0.003) *C. pneumoniae* infections • Proportions of anti-inflammatory *n*-3 PUFA (p = 0.022) and proinflammatory ARA (p = 0.007) were elevated in mice with acute *C. pneumoniae* infection Acute *C. pneumoniae* infection (p = 0.002 and p = 0.002) as well as *A. actinomycetemcomitans* administered alone (p < 0.001 and p = 0.002) and together with *C. pneumoniae* (p < 0.001 and p = 0.120) induced elevated relative RNA expression levels of genes encoding inflammation markers, IL-1β, and the macrophage marker CD68, respectively Compared to levels in the controls, the IL-1β production was 1.1- to 1.3-fold higher, whereas the CD68 production was 2.2- to 2.6-fold higher in infected mice; and ii) acute *C. pneumoniae* (p = 0.005) and *A. actinomycetemcomitans* (p = 0.003) infection also gave rise to increased relative RNA expression of MCP-1 Serum ALT (32.4 ± 3.4 versus 56.6 ± 7.5 U/liter; p = 0.010) was lower in mice acutely infected with *C. pneumoniae* *Saa* concentrations were higher in mice acutely infected with *C. pneumoniae* (296.4 ± 58.1 versus 20.4 ± 10.7 ug/mL; p = 0.003) and *A. actinomycetemcomitans* (217.1 ± 127.0 versus 61.1 ± 28.8 ug/mL; p = 0.368) Phospholipid transfer protein activity was significantly higher only in mice acutely infected with *C. pneumoniae* (16.1 ± 1.6 versus 11.1 ± 1.3 μmol/mL/h; p = 0.015) Hepatic microvesicular appearance displayed a negative correlation with serum *Saa* concentration (r = -0.443; p < 0.001) and the ratio of hepatic *n*-6 PUFA and n-3 PUFA (r = -0.394; p = 0.002) Hepatic inflammation correlated positively with serum *A. actinomycetemcomitans* IgG class antibody levels (r = 0.437; p = 0.005), serum LPS activity (r = 0.269; p = 0.040), the ratio of hepatic *n*-6 PUFA to *n*-3 PUFA (r = 0.472; p < 0.001) or to hepatic MUFA (r = 0.320; p = 0.013) Liver inflammation correlated negatively with serum phospholipids (r = -0.473; p = 0.035) and proportions of hepatic *n*-3 PUFA (r = -0.448; p < 0.001) and total PUFA (r = -0.290; p = 0.026)

†Furusho et al., 2013[74] Laboratory study	CD-*P. gingivalis*(+) and HFD- *P. gingivalis*(+) showed total pulp necrosis and periapical granuloma with infiltration of neutrophils and macrophages, and immunodetection of *P. gingivalis* Expression of the *mgl* gene was detected in DNA extracts of colonies grown from the extracted molars with *P. gingivalis* infection	*P. gingivalis* was detected in 21:40 biopsy specimens (52.5 %) *P. gingivalis* was identified as single and aggregated brown particles in hepatocytes *P. gingivalis*-positive cases showed significantly higher fibrosis scores than the *P. gingivalis*-negative cases: i) perisinusoidal fibrosis score ($p = 0.018$); ii) periportal fibrosis score ($p = 0.049$); and total fibrosis score ($p = 0.007$)	Serum LPS levels in CD- *P. gingivalis*(+) and HFD- *P. gingivalis*(+) were significantly higher than those in CD- *P. gingivalis*(-) and HFD- *P. gingivalis*(-) ($p < 0.05$) There was no significant difference in LPS levels between the CD- *P. gingivalis*(+) and the HFD- *P. gingivalis*(+)	Specimens with immunolocalization of *P. gingivalis* Dental infection of *P. gingivalis* induced significant upregulation of cytokine levels in the liver of HFD- *P. gingivalis*(+): MCP-1 ($p < 0.01$), TNF-α, IL-17 and IL-1β ($p < 0.05$) were significantly increased, compared to CD-*P. gingivalis*(-) at week 0 In both HFD groups at week 6, the cytokine production levels were significantly higher than those in the CD groups Significant increases of MCP-1, TNF-α and IL-17 production were observed in HFD-*P. gingivalis*(+) compared with HFD-*P. gingivalis*(-) ($p < 0.05$) Dental infection of *P. gingivalis* promoted pathological progression of HFD-induced NASH <u>Histological changes in the hepatic tissue:</u> CD-*P. gingivalis*(-): small foci of inflammatory cell infiltration HFD-*P. gingivalis*(-): i) marked steatosis, particularly in the central vein area, and fatty degeneration of hepatocytes; and ii) small foci of Mac2-positive macrophages and periportal inflammation HFD-*P. gingivalis*(+): i) the amount of fat deposited in hepatocytes showed a tendency to increase in comparison with HFD-*P. gingivalis*(-) group; ii) Mallory bodies were seen in a ballooning hepatocyte; iii) infiltration of Mac2-positive macrophages were more prominent; iv) focal fibrosis of the liver was observed only in HFD-*P. gingivalis*(+) group; v) spindle cells in the fibrotic area were immunopositive for α-SMA, indicating their myofibroblastic nature (hepatic stellate cells); vi) accumulation of collagen around the hepatic stellate cells; and vii) *P. gingivalis*-positive particles were detected in hepatocytes and Kupffer cells Number of foci of Mac2-positive cells in HFD-*P. gingivalis*(-) and HFD-*P. gingivalis*(+) were significantly higher than those in CD groups ($p < 0.01$) Number of foci of Mac2-positive cells in the HFD-*P. gingivalis*(+) was higher than that in HFD-*P. gingivalis*(-) ($p < 0.05$) <u>Staging of fibrosis:</u> i) Most cases in CD groups were in stage 0; ii) there were two of stage 2 and four of stage 3 in the HFD-*P. gingivalis*(-) group; and iii) HFD-*P. gingivalis*(+) included four of stage 3 and two of stage 4, indicating greater progression of fibrosis in HFD-*P. gingivalis*(+) than in the other experimental groups TLR2-positive hepatocytes were scattered in liver, whereas in HFD-*P. gingivalis*(+), numerous hepatocytes having lipid droplets strongly positively expressed TLR2 TLR2-mRNA expression levels in HFD groups were significantly higher than those of CD groups: 2.5-fold between HFD-*P. gingivalis*(-) and CD-*P. gingivalis*(-), and 3.3-fold between HFD-*P. gingivalis*(+) and CD-*P. gingivalis*(+) There was no difference in TLR2-mRNA expression level between CD-*P. gingivalis*(-) and CD-*P. gingivalis*(+) and between HFD-*P. gingivalis*(-) and HFD-*P. gingivalis*(+).

				The immunolocalization of *P. gingivalis* was detected in 21:40 biopsy specimens (52.5 %): i) *P. gingivalis* was identified as single and aggregated brown particles in hepatocytes; and ii) *P. gingivalis*-positive cases showed significantly higher fibrosis scores including perisinusoidal fibrosis score ($p = 0.018$), periportal fibrosis score ($p = 0.049$) and total fibrosis score, (a sum of each score, $p = 0.007$) than the *P. gingivalis*-negative cases
†Velusamy et al., 2014[75] Laboratory study	NA	Bacteremia was confirmed over time from *A. actinomycetemcomitans* clearance (baseline data of bacterial amounts from blood and different organs, including liver), expressed as CFU/mL blood or CFU/g wet tissue weight	NA	Specimens with *A. actinomycetemcomitans* detected *A. actinomycetemcomitans* significantly induced/increased the mRNA expression of IFN-γ, TNF-α, IL-1β, IL-6, IL-10, and IL-12 genes CRP levels were significantly greater in the bacterium-only group compared to the sham-infected group
†Nakajima et al., 2015[76] Laboratory study	NA	In parallel with decreased mRNA expression of tight junction proteins (*Tjp1* and *Ocln*), an influx of bacteria into the liver	Blood endotoxin levels were significantly increased 48 hours after *P. gingivalis* administration	No *P. gingivalis*-specific DNA was detected either in the liver of *P. gingivalis*-administered mice *P. gingivalis* administration clearly demonstrated significant impact on the liver microbiota composition and diversity

		was evident—the copy number of the 16S rRNA gene in the liver was significantly higher in *P. gingivalis*-administered mice compared with sham-administered mice		
†Nakajima et al., 2016[77] Laboratory study	Oral administration of *P. gingivalis* induced significant alveolar bone resorption	NA	Oral administration of *P. gingivalis* increased serum endotoxin levels ($p > 0.05$)	Oral administration of *P. gingivalis* significantly increased gene expression of *Plin2* and *Acox*, both of which are associated with lipid metabolism in the liver Oral administration of *P. gingivalis* slightly increased gene expression of *G6pc* expression, which positively regulates gluconeogenesis ($p < 0.05$) There was no significant change in the expression of the insulin signaling gene *Irs1* among the sham and *P. gingivalis* groups Gene expression of the proinflammatory cytokines IL-6 and TNF-α tended to be elevated from the administered *P. gingivalis* compared to sham group ($p > 0.05$) *Plin2* and *Acox* expression were associated with the hepatic steatosis induced by *P. gingivalis* administration
†Fujita et al., 2018[78] Laboratory study	<u>LPS(+), BD, and HD rats:</u> • Epithelial hyperplasia and rete ridge elongation • Disorder in the direction of the connective tissue fiber below the junctional epithelium • Greater infiltration of inflammatory cells in the gingival connective tissue compared to LPS(-) groups	NA	Radioactivity in serum of BD rats was the highest at 30 minutes, and was significantly higher (2.2 times) and more quickly than that in the	<u>Histological changes in the hepatic tissue:</u> • BD/LPS (+) group: slight perivenous lipid deposition and a few infiltrating inflammatory cells • HD/LPS (+) group: more severe lipid deposition, a number of large fat droplets, some focal necrosis with inflammatory cells, and numerous ballooning degenerations around the central vein • HD/LPS (-) group: moderate lipid deposition with small fat droplets <u>Total NAS:</u> • BD/LPS(+) group was higher than that in the BD/LPS(-) group (1.71 ± 0.20 and 0.33 ± 0.18, respectively [$p < 0.01$]) • Significantly higher in the HD/LPS(+) group than the HD/LPS(-) group (4.95 ± 0.21 and 2.57 ± 0.34, respectively [$p < 0.01$])

	<u>Total radioactivity in the LPS-injected side of palatal mucosa in BD rats:</u> • 5 minutes after injection: 27,964 ± 4,462 cpm—66.6 times that (420 ± 38 cpm) of the non-injected side; a similar tendency was confirmed in HD rats • 30, 60 minutes and 24 hours after injection: quickly decreased to 22.9, 17.0, and 15.0 % of that at 5 minutes, respectively; amounts in the palatal mucosa of HD rats slowly decreased until 24 hours (after 24 hours remained at more than 24.7 % of the level at 5 minutes) <u>Total radioactivity in the LPS-injected side of palatal mucosa in HD rats:</u> • 30, 60 minutes and 24 hours after injection: significantly higher by 2.8, 2.9, and 1.7 times than those in the BD animals, respectively ($p < 0.05$) <u>R-LPS diffusion into the palatine mucosa and hard palate:</u> • 5 minutes after injection: R-LPS diffused into the palatine mucosa and hard palate in the LPS-injected side of maxilla • 60 minutes after injection: R-LPS remained in the palatine mucosa, and migrated and reached the interdental space		HD rat serum after injection of R-LPS ($p < 0.05$) Maximum value of radioactivity in the HD rat serum was detected 60 minutes after injection	HD feeding and *P. gingivalis*-LPS injection accelerated the progression from simple steatosis to NASH <u>Radioactivity in organs of both BD and HD rats was mostly distributed in the liver throughout the experimental period:</u> • Reached maximum at 30 minutes and gradually declined until 24 hours in the liver of BD rats • Radioactivity level at 24 hours was 65.9 % of the 30 minutes value in the liver of BD rats • Maximum radioactivity was observed after 60 minutes in the HD liver • Minimal differences were observed between values at 30, 60 minutes and after 24 hours • More than 90 % of the 30 minutes value remained in the liver • Radioactivity levels in the liver of HD rats at 60 minutes and 24 hours were higher by 25.9 and 34.8 % as compared to those of BD rats, respectively ($p < 0.05$)

	between the first and second molars • The amount of radioactivity was maintained at the interdental region and the periodontal ligament space of the first molar even after 60 minutes			
†Sazaki et al., 2018[79] Laboratory study	Body weight of the HFPg mice was significantly increased 4 weeks after injection of endotoxin compared to that of the HFco mice; differences in body weight were increased throughout the experimental periods	NA	Endotoxin was not detected in the plasma collected from both groups after 3 days of sonicated *P. gingivalis* or saline injection	3D micro-CT analysis: total body fat, subcutaneous fat, and visceral fat volumes were significantly higher in HFPg mice than in HFco mice at 12 weeks <u>Histological changes in the hepatic tissue:</u> • Marked lipid accumulation in HFPg compared to that in HFco mice after 12 weeks • Total area of lipid droplets was significantly increased in HFPg mice compared to that in HFco mice ($p < 0.01$) • Hepatic triglyceride and glycogen levels were significantly increased after 6 hours of fasting at 12 weeks in HFPg mice compared to those in HFco mice • *P. gingivalis*-endotoxin increased mRNA expression levels of *Glut2*, *G6p*, *Glck*, and *Acc1* in the liver of HFPg mice • mRNA expression levels of *Tnfα*, *Il6*, and *Tgfβ* in the liver did not differ significantly between HFco and HFPg mice at 12 weeks <u>Liver microarray analysis after *P. gingivalis*-endotoxin or saline injection:</u> • Gene expression patterns in the livers of HFco and HFPg mice differed substantially • 41 % of upregulated DEGs with GO terms were classified as “metabolic process” in the biological process category • 24 % of the downregulated DEGs were classified as “metabolic process” • Metabolic pathway was significantly enriched in upregulated DEGs • Fatty acid degradation and fatty acid elongation were enriched in upregulated DEGs, based on quantification of mRNA expression levels with qPCR: *Acot1, Acot2, Acot3, Acot4, Aldh3a2, Cpt1b, Cyp4a10, Cyp4a14, Cyp4a31*, and *Ehhadh* were significantly increased after *P. gingivalis*-endotoxin administration • Gene set with a FDR$q < 0.25$: i) sets related to hypoxia, TNF-α signaling via NFκB, and adipogenesis, were upregulated in HFPg mice; and ii) gene set related to fatty acid metabolism was strongly upregulated (normalized enrichment score = 1.92, $q = 0.002$) in HFPg mice
§Nagasaki et al., 2020[80]	*P. gingivalis* was detected immunohistochemically in necrotic neutrophil accumulation in periapical granuloma and pulp of *P. gingivalis*-infected mice	Immunocolocalization: *P. gingivalis* was detected in	NA	Specimens with immunolocalization of *P. gingivalis* *P. gingivalis*-infection increased macrovesicular lipid accumulation and hepatic crown-like structures (aggregation of macrophages and positively correlated with the extent of liver fibrosis)

Laboratory study		hepatocytes with *P. gingivalis*-odontogenic infection		*P. gingivalis*-odontogenic infection exacerbated pathological progression of NASH through Gal-3 and TGF-β1/Smad pathway (key signaling molecule of TGF-β1, critical for hepatic stellate cells activation): • Among hepatocytes in HFD, Gal-3 positive spindle cells were scattered; Gal-3 positive hepatic crown-like structures and hepatocytes were observed • Strong pSmad2 nuclear expression, indicating TGF-β1 signaling activation, was detected in hepatic stellate cells and hepatocytes of *P. gingivalis*-infected mice • HFD group showed negative or weak reaction for pSmad2 • *P. gingivalis* was clearly detected in liver of *P. gingivalis*-infected mice • Number of hepatic crown-like structures in *P. gingivalis*-infected group was significantly increased ($p < 0.01$) • To analyze the degree of liver fibrosis, sirius red staining was performed. • Sirius red-positively stained collagen fibers are distributed among hepatocytes with lipid deposition • *P. gingivalis*-infected group indicated significantly increased sirius red positive fibrosis areas ($p < 0.05$) • *P. gingivalis*-odontogenic infection aggravated inflammatory cell infiltration and liver fibrosis, in which TGF-β1/Smad and Gal-3 pathway are involved
†Yamazaki et al., 2020[81] Laboratory study	One mouse in the periodontitis-associated bacteria group died No difference in body weight change during the experimental period between the two groups Alveolar bone resorption did not differ between the periodontitis-associated and health-associated bacteria groups	More bacteria were present in the liver of mice in the P group Only *F. nucleatum* was confirmed to be present in the liver; no colonies were formed from liver lysates	Endotoxin levels in the sera of mice did not differ between the two groups	More bacteria were present in the liver of mice in the periodontitis-associated bacteria group Only *F. nucleatum* was confirmed to be present in the liver; no colonies were formed from liver lysates <u>Gene expression in the liver:</u> • Expression of the anti-inflammatory gene *Tsc22d3* tended to be lower in the periodontitis-associated bacteria group ($p = 0.099$) • Expression of *Acaca* and *Lipin1* (genes involved in lipid metabolism) was significantly higher in the periodontitis-associated bacteria group ($p < 0.05$) • Endoplasmic reticulum stress-related gene *Ddit4* was upregulated in the periodontitis-associated bacteria group relative to the health-associated bacteria group ($p < 0.05$) • Expression of the circadian rhythmal control gene *Bmal1* was significantly lower in the periodontitis-associated bacteria group ($p < 0.05$) • The gene expression of inflammatory cytokines and other glucose-, lipid synthesis-, and bile acid synthesis-related genes did not differ between the two groups
§Nagasaki et al., 2021[82] Laboratory study	AZM improved the inflammation of periapical periodontitis induced by *P. gingivalis* odontogenic infection: • At 9 weeks of *P. gingivalis* infection: severe inflammation including neutrophil and	*P. gingivalis* was detected in the liver of HP by immunocolocalization	NA	Specimens with immunolocalization of *P. gingivalis* AZM significantly prevented liver fibrosis and inflammation induced by *P. gingivalis* odontogenic infection: • Orally inoculated *P. gingivalis* were sparsely observed in the livers of HP, HPS, HPL, and HPLS groups • *P. gingivalis*-accumulated areas were detected only in the liver of the *P. gingivalis*-infected group (HP); *P. gingivalis* is seen as granules in hepatocytes

	lymphocyte infiltration in the root canal and root apex area • Pulpal application of AZM in the HPL and HPLS groups induced a reduction of inflammatory cell infiltrations at both the root canal and the root apex area; systemic AZM application showed slight inflammatory cell infiltration in the root canal and apex area • *P. gingivalis* infection induced prominent accumulation of Ly-6B.2-positive neutrophils at the root apex area and pulp cavity • Elimination of *P. gingivalis* odontogenic infection by local AZM treatment remarkably inhibited neutrophil infiltration at the periapical area and pulp cavity; systemic AZM treatment alone could not remove neutrophil infiltration at the periapical area and pulp cavity to the same degree as HPL and HPLS groups • In the HP group, *P. gingivalis*-positive granules were detected in the neutrophil-accumulated area in pulp and periapical granuloma *P. gingivalis* was detected immunohistochemically in necrotic neutrophil accumulation in periapical granuloma and pulp of HP mice			• Although with odontogenic infection of *P. gingivalis*, local and systemic treatments did not change liver factors in the serum such as AST and ALT • *P. gingivalis* infection induced marked increase of lobular inflammation and hepatocellular ballooning with Mallory bodies • Both local and/or systemic applications significantly inhibited *P. gingivalis*-induced hepatocyte ballooning and lobular inflammation versus the HP group ($p < 0.001$) • AZM local application partially inhibited hepatocyte ballooning • Steatosis did not show marked changes with any AZM application • NAS score showed significant increase with odontogenic infection of *P. gingivalis* versus control (HFD) ($p < 0.0001$); all AZM applications prevented the increase ($p < 0.0001$) in NAS score related to odontogenic infection of *P. gingivalis* Elimination of *P. gingivalis* odontogenic infection using AZM significantly inhibited Gal-3 expression and hepatic crown-like structures formation in the liver: • Prominent increase of Gal-3-expressing cells including hepatic stellate cells, hepatocytes and macrophages, and macrophage aggregations (hepatic crown-like structures) was evident in the liver of the HP group; *P. gingivalis* odontogenic infection induced significant increase of the Gal-3-positive area by 2.8-fold ($p < 0.01$) • Local and/or systemic AZM significantly inhibited Gal-3-positive area ($p < 0.01$), which was comparable to control (HFD) • Number of hepatic crown-like structures in the HP group increased by 2.5-fold; number of hepatic crown-like structures in the local application group with or without systemic application of AZM significantly reduced in comparison with that in the HP group ($p < 0.05$) • Systemic AZM application alone showed a decreasing trend in the number of hepatic crown-like structures • *P. gingivalis* elimination by AZM systemic application on liver inflammation/fibrosis caused by *P. gingivalis* odontogenic infection was limited and transient • Local AZM application removed the infection focus in the root canal more efficiently than systemic AZM application • Cytokine-mRNA expression related to inflammation in the liver – odontogenic infection of *P. gingivalis* significantly increased the expression of *Tnfα* and *Il1β* by 6.7-fold and 2.5-fold, respectively ($p < 0.05$) • Local with or without systemic applications of AZM significantly inhibited *Tnfα* expression in the • liver with a trend of decreased expression in systemic application • HPLS group inhibited *Il1β* expression ($p < 0.05$) with the trend of decreased expression in both local and systemic applications (HPL and HPS groups) • Elimination of *P. gingivalis* infection using AZM inhibited inflammation of NASH by reducing cytokine expression Elimination of *P. gingivalis* odontogenic infection using AZM significantly inhibited liver fibrosis by reducing pSmad2 expression: • In the HP group, sirius red positive collagen fibers were distributed in the intercellular spaces of hepatocytes

				• *P. gingivalis* odontogenic infection significantly increased the sirius red positive fibrosis area by 10.7-fold ($p < 0.05$) • Not only systemic AZM-applied groups (HPS and HPLS) but also locally applied group (HPL) showed significantly decreased fibrosis areas compared to that in HP, resulting in the same fibrosis degree as in control (HFD) ($p < 0.05$) • pSmad2 expression was significantly increased in the *P. gingivalis*-infected group (HP) compared to the control (HFD)—TGF-β/Smad pathway was activated with odontogenic infection of *P. gingivalis* pSmad2 expression was detected in hepatic stellate cells and hepatocytes (fibrogenic mediator in the liver) • Not only systemic AZM-applied groups (HPS, HPLS) but also the local AZM application group (HPL) showed significantly decreased pSmad2 expression versus the HP group • Liver fibrosis progression caused by *P. gingivalis* odontogenic infection can be attenuated by removing the local infection focus
†Yamazaki et al., 2021[83] Laboratory study	Oral administration of bacteria did not affect body weight until commencement of the diet change, and no difference was observed among the sham, *A. naeslundii*, *V. rogosae*, *P. gingivalis*, and *P. intermedia* mice After changing the diet from regular chow to CDAHFD60 (high-fat diet), a gain in body weight was suppressed in all experimental groups in comparison with RC-fed mice	NA	Serum endotoxin level was increased with the increasing bacterial burden; the level was significantly higher in *P. intermedia* mice compared with that in RC-fed and sham mice, and it was further elevated in *P. gingivalis* mice	Liver-to-body weight ratio was significantly increased in sham, *A. naeslundii*, and *P. gingivalis* mice compared with that in RC-fed mice HFD feeding promoted hepatic steatosis in all experimental groups Degree of steatosis was greater with *P. intermedia* administration, and it was further aggravated by *P. gingivalis* administration Degree of fibrosis was progressively exacerbated with increasing bacterial burden (sham < *P. intermedia* < *P. gingivalis*) Bacterial administration induced minimal histological changes in the liver of RC-fed mice except for *P. gingivalis* mice, in which slight steatosis was observed Content of hepatic hydroxyproline increased with the increasing bacterial burden Triglyceride content, AST and ALT activities were significantly higher in HFD-fed groups, but bacterial administration had no effect on them <u>Hierarchical clustering heatmap:</u> • Robust effect of high-fat diet feeding on the liver, and the administration of both bacteria induced additional and substantial changes in the expression profile of genes • Expression profile of genes in the liver was clearly distinct between *P. intermedia* and *P. gingivalis* mice Functional enrichment analysis - seven clusters extracted from hierarchical clustering: • Genes in clusters 1–3 were downregulated (cluster 1- genes involved in the biosynthesis and metabolic processes of lipids, organic acids, oxoacids, steroids, and fatty acids; and no GO terms were enriched in clusters 2 and 3) • Genes in clusters 4–6 were upregulated in *P. gingivalis* mice compared with the other groups (cluster 4- genes involved in the cell cycle, cell death, nuclear division, DNA replication, responses to oxidative and endoplasmic reticulum stress, and regulation of intrinsic apoptosis; and cluster 5- genes involved in the

				inflammatory response, such as in the regulation of leukocyte migration, response to LPS, cellular response to inflammatory cytokines, and NFkB pathways) • Cluster 7 included genes, the expression levels of which were higher in *P. gingivalis* mice than those in RC-fed mice, but lower compared with those in Sham and *P. intermedia* mice (cluster 7- genes involved in the biological processes for circadian regulation of gene expression) Progression from simple steatosis to steatohepatitis, fibrosis, and hepatocellular carcinoma was mediated by multiple parallel factors, including inflammation, endoplasmic reticulum stress, lipotoxicity, and altered circadian rhythms; GO terms and KEGG pathways implicated in these events were found to be significantly enriched in the clusters 1, 2, and 4 (pathways for steroid hormones, retinol, primary bile acids, arachidonic acid, amino sugars, and nucleotide sugars) <u>DNA microarray analysis for representative genes involved in the pathological mechanisms of NAFLD:</u> • Genes involved in the inflammatory responses were upregulated by HFD feeding, irrespective of the bacterial administration • Expression of *Tsc22d3* (mediates the anti-inflammatory response) was only elevated in *P. gingivalis* mice - weaker elevation of inflammatory genes in this group • Fibrosis- and endoplasmic reticulum stress -related genes were enriched and classified in cluster 4 • *Col1a1* and *Timp1* were upregulated by HFD feeding • *Ctgf* was upregulated specifically by *P. gingivalis* administration • endoplasmic reticulum stress-related genes *Chop/Ddit3* and *Ddit4* were elevated by *P. gingivalis* • *Fgf21* and *Trib3* (induced by endoplasmic reticulum stress and elevated in NAFLD) were significantly upregulated in *P. gingivalis* mice • GO terms associated with the cell cycle process (potentially implicated in carcinogenesis and end-stage NAFLD) were enriched in cluster 4 • Expression of *Hnf6* (negatively associated with hepatocellular carcinoma malignancy) and *Hhex* (*Hhex* into a hepatoma cell line decrease the expression of several proto-oncogenes and increases the expression of some tumor suppressor genes) were upregulated in *P. intermedia* mice • GO terms associated with controlling the circadian rhythm were enriched (cluster 7) • Fluctuations in the circadian rhythm affect metabolism and alter the expression of liver clock genes in NAFLD pathology. In this connection, the • *Per1* (clock gene) was significantly elevated in *P. gingivalis* mice; *P. gingivalis* and *P. intermedia* mice demonstrated contrasting expression patterns of *Bmal1* and *Dbp* • Gene expression of endoplasmic reticulum stress-related genes in HepG2 cells stimulated with LPS from *P. intermedia*, *P. gingivalis*, and *E. coli* was different from that in the liver of each experimental group

Legend: †, Phase 2 of the study selection process (full-text screening); §, handsearch; NA, data not available; *P. gingivalis*, *Porphyromonas gingivalis*; PCR, polymerase chain reaction; NS, *p*-value not significant; *C. rectus*, *Campylobacter rectus*; CFU, colony forming unit; CEJ, cemento-enamel junction; PMNs, polymorphonuclear; TNF-α, tumor necrosis factor-alpha; TUNEL, terminal deoxynucleotidyl transferase (TdT)-mediated deoxyuridine triphosphate (dUTP)-biotin nick-end labeling; 8-OHdG, 8-hydroxydeoxyguanosine; CRP, C-reactive protein; H_2O_2, hydrogen peroxide; *C. pneumoniae*, *Chlamydia pneumoniae*; *A. actinomycetemcomitans*, *Aggregatibacter actinomycetemcomitans*; SFA, saturated fatty acids; MUFA, monosaturated fatty acids; PUFA, polyunsaturated fatty acids; DGLA, dihomo-γ-linolenic acid; GLA, γ-linolenic acid (DGLA precursor); ARA, arachidonic acid; RNA, ribonucleic acid; IL-1β, interleukin 1-beta; CD68, cluster of differentiation 68;

Saa, serum amyloid A; *mgl*, monoacylglycerol; CD, chow-diet; HFD, high-fat diet; DNA, deoxyribonucleic acid; MCP-1, monocyte chemoattractant protein-1; IL-17, interleukin 17; NASH, nonalcoholic steatohepatitis; Galectin-3/Mac2, β-galactoside-binding lectin that is highly expressed in and secreted by monocytes/macrophages; α-SMA (α-smooth muscle actin), monoclonal antibody used for immunohistochemical detection of hepatic myofibroblasts; TLR2, Toll-like receptor 2; mRNA, messenger ribonucleic acid; IFN-γ, interferon gamma; IL-6, interleukin 6; IL-10, interleukin 10; IL-12, interleukin 12; *Tjp1*, tight junction protein 1; *Ocln*, occluding; *Plin2*, perilipin 2; *Acox*, Acyl-CoA Oxidase 1; *G6pc*, glucose-6- phosphatase; *Irs1*, insulin receptor substrate 1; *Tnfα*, tumor necrosis factor-alpha; *Il1β*, interleukin 1-beta; *Il6*, interleukin 6; *Il10*, interleukin 10; *Fitm2*, fat storage-inducing transmembrane protein 2; *Plin2*, perilipin 2; *Acaca*, acetyl-coenzyme A carboxylase alpha; *G6pc*, glucose-6- phosphatase; *Glut2*, glucose transporter 2; *G6p*, glucose-6-phosphate; *Glck*, glucokinase; *Acc1*, acetyl-CoA carboxylase; *Tgfβ1*, transforming growth factor beta 1; DEGs, differentially expressed genes; GO, gene ontology; qPCR, quantitative polymerase-chain reaction; *Acot1*, Acyl-CoA thioesterase 1; *Acot2*, Acyl-CoA thioesterase 2; *Acot3*, Acyl-CoA thioesterase 3; *Acot4*, Acyl-CoA thioesterase 4; *Aldh3a2*, aldehyde dehydrogenase 3 family member a2; *Cpt1b*, carnitine palmitoyltransferase 1b; *Cyp4a10*, cytochrome P450, family 4, subfamily a, polypeptide 10; *Cyp4a14*, cytochrome P450, family 4, subfamily a, polypeptide 14; *Cyp4a31*, cytochrome P450, family 4, subfamily a, polypeptide 31; *Ehhadh*, enoyl-CoA hydratase and 3-hydroxyacyl CoA dehydrogenase; NFκB, nuclear factor kappa-light-chain-enhancer of activated B cells; FDR*q*, false discovery rate-adjusted *p*-value; Gal-3, galectin-3; TGF-β1, transforming growth factor beta 1; *F. nucleatum*, *Fusobacterium nucleatum*; *Tsc22d3*, TSC22 domain family member 3; *Lipin1*, phosphatidate phosphatase-1; *Ddit4*, DNA-damage-inducible transcript 4; *Bmal1*, brain and muscle ARNT-Like 1; AZM, azithromycin; AST, aspartate aminotransferase; ALT, alanine aminotransferase; NAS, NAFLD activity score; pSmad2, phosphorylated Smad2; *A. naeslundii*, *Actinomyces naeslundii*; *V. rogosae*, *Veillonella rogosae*; CDAHFD60 diet, CDAHFD60, choline-deficient, l- amino acid-defined, high-fat diet with 60 kcal % fat and 0.1 % methionine; RC, regular chow; *P. intermedia*, *Prevotella intermedia*; KEGG, Kyoto encyclopedia of genes and genomes; NAFLD, nonalcoholic fatty liver diseases; *Col1a1*, collagen type I alpha 1 chain; *Timp1*, TIMP metallopeptidase Inhibitor 1; *Ctgf*, connective tissue growth factor; *Chop*, C/EBP homologous protein, *Ddit3*, DNA damage inducible transcript 3; *Fgf21*, fibroblast growth factor 21; *Trib3*, tribbles pseudokinase 3; *Hnf6*, hepatocyte nuclear factor 6; *Hhex*, hematopoietically expressed homeobox; *Per1*, period circadian regulator 1; *Dbp*, D-box Binding PAR bZIP Transcription Factor; HepG2 cell, cell line exhibiting epithelial-like morphology that was isolated from a hepatocellular carcinoma; *E. coli*, *Escherichia coli*.

TABLE 4

Mechanistic insights (*in vitro* experiments) into the impacts of endotoxemia and/or bacteremia by periodontal pathogens on the hepatocytes (complementary data)

Study | Design	Bacteremia/Endotoxemia	*In vitro* design	Molecular insights
†Furusho et al., 2013[74] Laboratory study	Immunolocalization of *P. gingivalis*: • Detected in 21:40 biopsy specimens (52.5 %) • *P. gingivalis* was identified as single and aggregated brown particles in hepatocytes *P. gingivalis*-positive cases showed significantly higher fibrosis scores	Immortalized human fetal hepatocytes were maintained in hepatocyte basal medium[A,B] containing 0.4 mM palmitate for 18 h to induce accumulation of lipids. Palmitate-treated cells and control cells were incubated in fresh medium with or without *P. gingivalis*-LPS (1μg/mL)	Palmitate induced marked accumulation of cytoplasmic lipid droplets in human hepatocytes (LX-2 steatotic hepatocyte model) Human hepatocyte constitutively showed strong expression of TLR4, and palmitate treatment induced upregulation of TLR2 expression <u>Steatotic hepatocytes:</u> • mRNA expressions of IL-1β, IL-6 and TNF-α were slightly upregulated • Stimulation of *P. gingivalis*-LPS upregulated mRNA expression of inflammasomes including NLRP3 and Casp-1, in addition to proinflammatory cytokines including IL-1β, IL-6, IL-8 and TNF-α in steatotic hepatocytes

	than the *P. gingivalis*-negative cases: i) perisinusoidal fibrosis score ($p = 0.018$); ii) periportal fibrosis score ($p = 0.049$); and total fibrosis score ($p = 0.007$) Serum LPS levels in CD-*P. gingivalis*(+) and HFD-*P. gingivalis*(+) were significantly higher than those in CD-*P. gingivalis*(-) and HFD-*P. gingivalis*(-) ($p < 0.05$) There was no significant difference in LPS levels between the CD-*P. gingivalis*(+) and the HFD-*P. gingivalis*(+)	and the cells were harvested 6 h after stimulation	During *in vitro* study, palmitate treatment induced upregulation of TLR2 expression in hepatocytes
§Nagasaki et al., 2021[82] Laboratory study	Immunocolocalization: *P. gingivalis* was detected in hepatocytes with *P. gingivalis*-odontogenic infection	To clarify the mechanism of pathological progression of NASH, LX-2 human hepatic stellate cell line and immortalized human fetal hepatocytes (Hc3716-hTERT cells)[A] were exposed to palmitate to induce accumulation of lipids mimicking a fatty liver[B,C] The cells were incubated in fresh medium without or with *P. gingivalis* infection at MOI 100, along with *P. gingivalis*-LPS/lipoprotein (1 μg/mL). KYT-1 and KYT-36 (3 μM) were used for gingipain inhibition [RgpA, RgpB (arginine-specific cysteine proteinase) and Kgp (lysine-specific proteinase), respectively][D-F] TGF-β receptor I inhibitor (1 μg/mL) was added to media before 24 hours from	*P. gingivalis*-infection and LPS-PG (*P. gingivalis*-LPS/lipoprotein) stimulation induce hepatic stellate cells activation: • Palmitate (free fatty acids upregulated in serum of NASH patient) treatment significantly upregulated PAR2 and TLR2 levels in human hepatic stellate cell line (LX-2 cells) • *P. gingivalis*-infection significantly promoted proliferation of LX-2 cells with/without palmitate treatment ($p < 0.01$) *In LX-2 cells with/without palmitate, α-SMA and type I collagen (markers of myofibroblastic differentiation of hepatic stellate cell line) were prominently upregulated by both P. gingivalis-infection and LPS-PG stimulation* Stimulation of PAR2-TGF-β1 pathway caused by *P. gingivalis*-infection induced hepatic stellate cells activation: • *P. gingivalis*-infection induced hepatic stellate cells activation through Smad2/3 and ERK1/2 pathways similar to direct stimulation with TGF-β1 • LX-2 cells significantly produced TGF-β1 after *P. gingivalis* infection ($p < 0.01$); TGF-β1 from palmitate-treated LX-2 cells was significantly increased than from non-treated cells [approximately 39.7 % ($p < 0.05$] • Gingipain inhibitors significantly inhibited TGF-β1 production from LX-2 cells ($p < 0.01$) • TGF-β receptor I, which directly phosphorylates TGF-β1 signaling molecules, inhibited completely suppressed phosphorylation of Smad2 and Smad3 caused by *P. gingivalis*-infection • In LX-2 cells with LPS-PG stimulation, Smad2, Smad3, and ERK1/2 were prominently activated as well as *P. gingivalis*-infection *ERK pathway was highly activated in palmitate-treated LX-2 cells, in which expression level of TLR2 was markedly upregulated*

		P. gingivalis infection or TGF-β1 stimulation. hepatic stellate cells were cultured with *P. gingivalis* (MOI 100) or TGF-β1 (1 ng/mL) in the media for 24 hours. Protein levels of TGF-β1 in the supernatant were analyzed by using a human TGF-β1 immunoassay (ELISA) kit	Gal-3 production caused by *P. gingivalis*-infection and -LPS stimulation enhanced myofibroblastic differentiation of hepatic stellate cells through upregulation of TGF-β receptor II expression: • LX-2 cells markedly induced Gal-3 production by LPS-PG • Gal-3 expression was also upregulated by *P. gingivalis* infection • Gal-3 upregulated α-SMA expression in LX-2 cells through Smad and ERK pathways as well as TGF-β1 • Gal-3 upregulated TGF-β receptor II expression of LX-2 with/without palmitate treatment *Gal-3 promoted hepatic stellate cells activation via upregulation of TGF-β receptor II expression resulting in increasing the sensitivity for TGF-β1* TGF-β1 and Gal-3 production from hepatocytes by *P. gingivalis*-infection and -LPS stimulation contributed to hepatic stellate cell activation in paracrine manner: • Expression of TLR2 in immortalized human fetal hepatocytes (Hc3716-hTERT cells) was significantly increased by palmitate treatment for 18 hours • TGF-β1 from Hc3716-hTERT cells with/without palmitate was also significantly up-regulated by *P. gingivalis*-infection, but not by LPS-PG • Upregulation of Gal-3 production in Hc3716-hTERT cells was prominently caused by *P. gingivalis*-infection and LPS-PG stimulation *TGF-β1 and Gal-3 produced from hepatocytes additionally promoted myofibroblastic differentiation of hepatic stellate cells in paracrine manner*

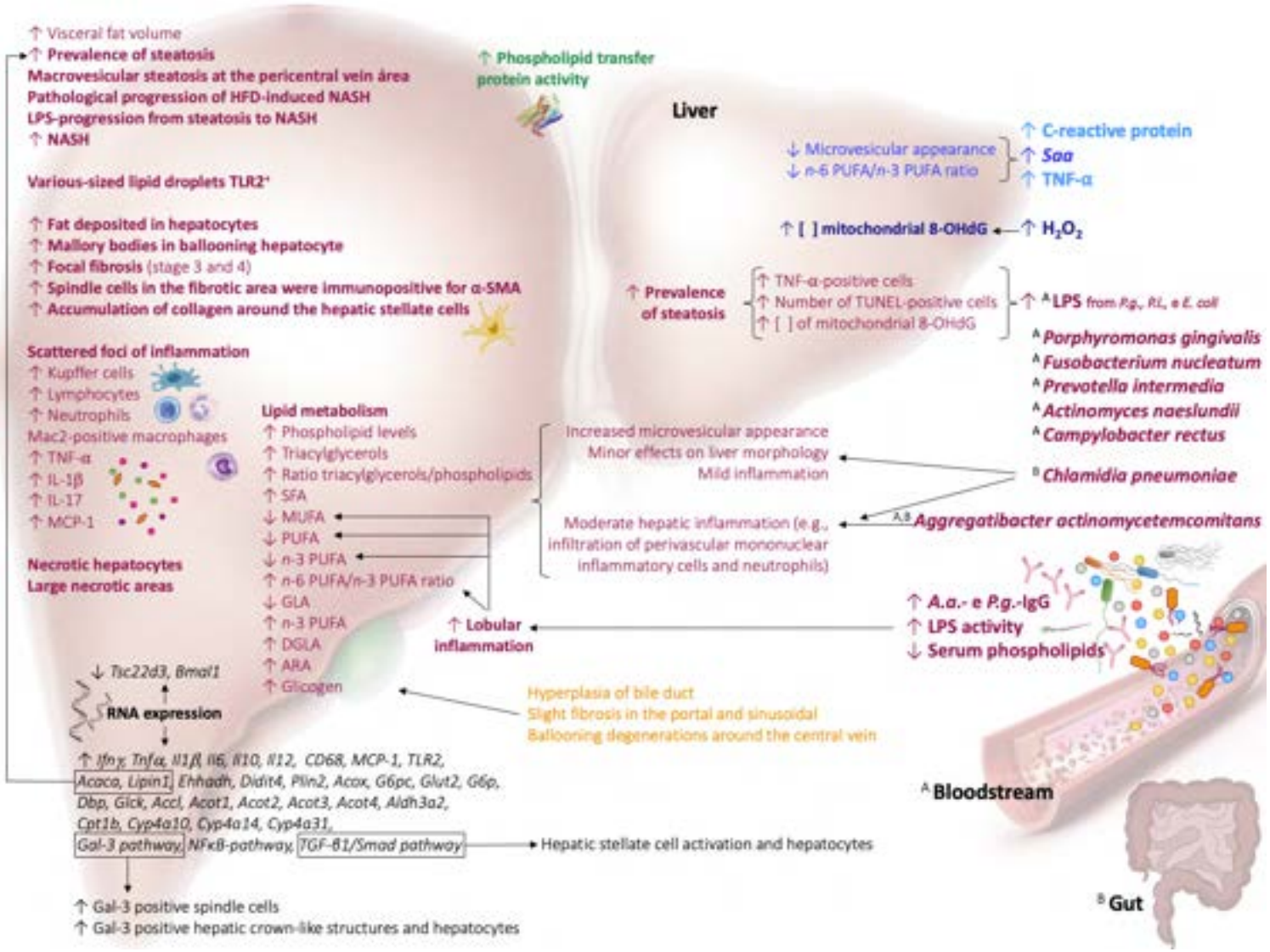
Legend: †, Phase 2 of the study selection process (full-text screening); §, handsearch; *P. gingivalis*, *Porphyromonas gingivalis*; LPS, lipopolysaccharide; CD, chow-diet; HFD, high-fat diet; LX-2, human hepatic stellate cell line; TLR2/4, toll-like receptor 2/4; IL-1β, interleukin 1-beta; IL-6, interleukin 6; TNF-α, tumor necrosis factor-alpha; NLRP3, Nod-like receptor 3; Casp-1, caspase-1; NASH, nonalcoholic steatohepatitis; Hc3716-hTERT cells, immortalized human fetal hepatocytes; MOI, multiplicity of infection; KYT-1, gingipain inhibitor [RgpA, RgpB (arginine-specific cysteine proteinase)]; KYT-36, gingipain inhibitor [Kgp (lysine-specific proteinase)]; TGF-β1, transforming growth factor beta 1; ELISA, enzyme-linked immunosorbent assay; PAR2, protease-activated receptor 2; TLR2, Toll-like receptor 2; α-SMA (α-smooth muscle actin), monoclonal antibody used for immunohistochemical detection of hepatic myofibroblasts; ERK1/2, extracellular signal-regulated kinase 1/2; Gal-3, galectin-3.

References: [A], Waki K, Anno K, Ono T, Ide T, Chayama K, Tahara H. Establishment of functional telomerase immortalized human hepatocytes and a hepatic stellate cell line for telomere-targeting anticancer drug development. Cancer Sci. 2010 Jul;101(7):1678-85. doi: 10.1111/j.1349-7006.2010.01576.x; [B], Wobser H, Dorn C, Weiss TS, Amann T, Bollheimer C, Büttner R, Schölmerich J, Hellerbrand C. Lipid accumulation in hepatocytes induces fibrogenic activation of hepatic stellate cells. Cell Res. 2009 Aug;19(8):996-1005. doi: 10.1038/cr.2009.73; [C], Furusho H, Miyauchi M, Hyogo H, Inubushi T, Ao M, Ouhara K, Hisatune J, Kurihara H, Sugai M, Hayes CN, Nakahara T, Aikata H, Takahashi S, Chayama K, Takata T. Dental infection of *Porphyromonas gingivalis* exacerbates high fat diet-induced steatohepatitis in mice. J Gastroenterol. 2013 Nov;48(11):1259-70. doi: 10.1007/s00535-012-0738-1; [D], Kadowaki T, Baba A, Abe N, Takii R, Hashimoto M, Tsukuba T, Okazaki S, Suda Y, Asao T, Yamamoto K. Suppression of pathogenicity of *Porphyromonas gingivalis* by newly developed gingipain inhibitors. Mol Pharmacol. 2004 Dec;66(6):1599-606. doi: 10.1124/mol.104.004366; [E], Cao C, Ji X, Luo X, Zhong L. Gingipains from *Porphyromonas gingivalis* promote the transformation and proliferation of vascular smooth muscle cell phenotypes. Int J Clin Exp Med. 2015 Oct 15;8(10):18327-34; [F], Guevara T, Rodríguez-Banqueri A, Lasica AM, Ksiazek M, Potempa BA, Potempa J, Gomis-Rüth FX. Structural determinants of inhibition of *Porphyromonas gingivalis* gingipain K by KYT-36, a potent, selective, and bioavailable peptidase inhibitor. Sci Rep. 2019 Mar 20;9(1):4935. doi: 10.1038/s41598-019-41354-3.

Two studies presented complementary results to the *in vivo* assays, of mechanistic insights in *in vitro* experiments.[74,82] To clarify the mechanism of pathological progression of NASH, LX-2 human hepatic stellate cell line and immortalized human fetal hepatocytes were exposed to palmitate to induce accumulation of lipids mimicking a fatty liver. The cells were incubated in fresh medium without or with *P. gingivalis* infection. In LX-2 cells with/without palmitate, α-SMA and type I collagen were prominently upregulated by both *P. gingivalis*-infection and LPS-PG stimulation, inducing hepatic stellate cells activation. ERK pathway was highly activated in palmitate-treated LX-2 cells, in which expression level of TLR2 was markedly upregulated. Gal-3 promoted hepatic stellate cells activation via upregulation of TGF-β receptor II expression resulting in increasing the sensitivity for TGF-β1. In addition, TGF-β1 and Gal-3 produced from hepatocytes additionally promote myofibroblastic differentiation of hepatic stellate cells in paracrine manner.[82] In the other study,[74] palmitate induced marked accumulation of cytoplasmic lipid droplets in human hepatocytes (LX-2 steatotic hepatocyte model). Human hepatocyte constitutively showed strong expression of TLR4, and palmitate treatment induced upregulation of TLR2 expression. The mRNA expressions of TNF-α, IL-1β and IL-6 were slightly upregulated in steatotic hepatocytes. Stimulation of *P. gingivalis*-LPS upregulated mRNA expression of inflammasomes including NLRP3 (Nod-like receptor 3) and Casp-1 (caspase-1), in addition to proinflammatory cytokines including TNF-α, IL-1β, IL-6 and IL-8 in steatotic hepatocytes (Table 4).

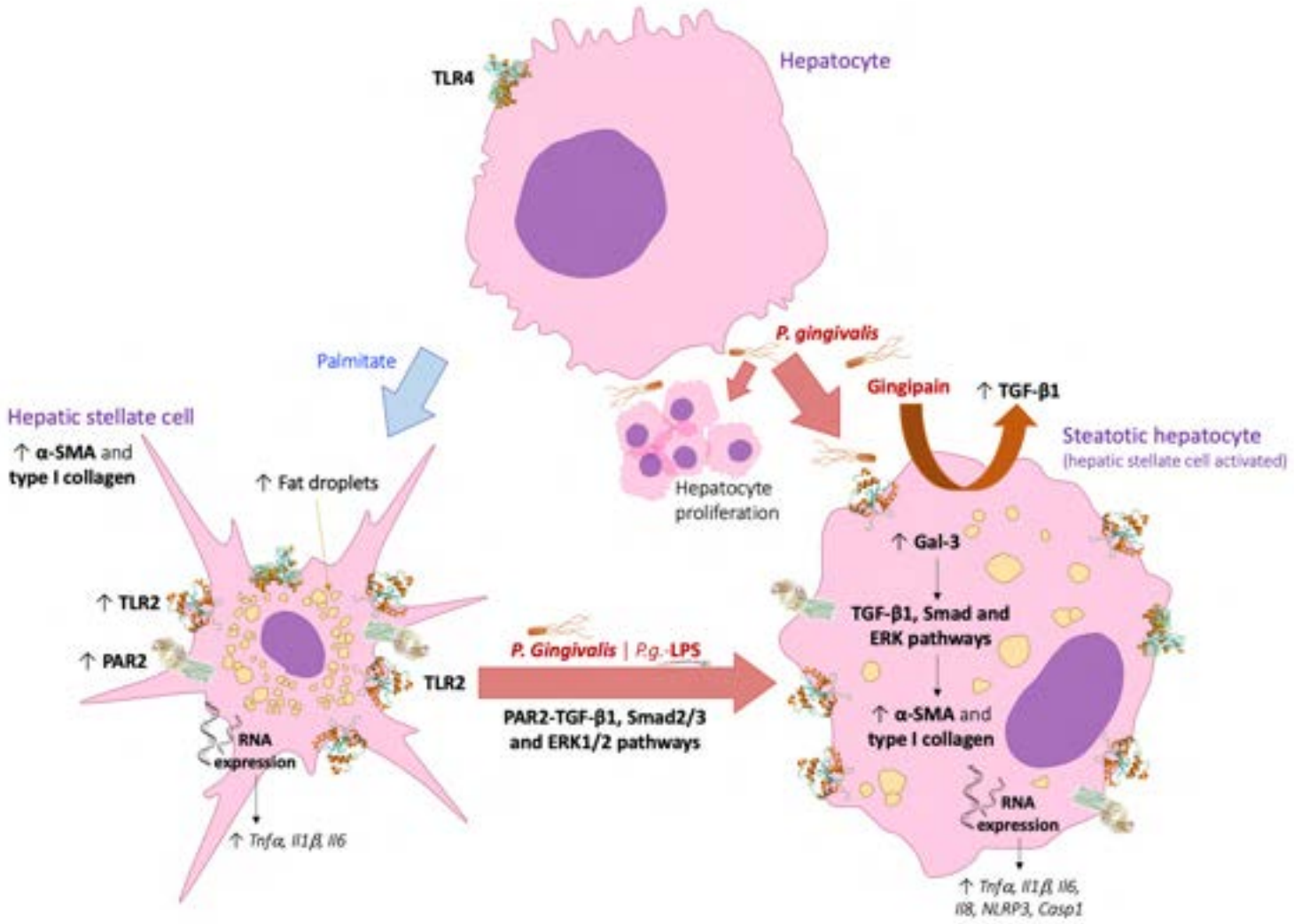
The synthesis of results of the 14 experimental studies gave rise to a biological mechanism for the intersection between endotoxemia and bacteremia by periodontal pathogens and liver abnormalities, proposed in Figures 9 and 10.

FIGURE 9. Mechanistic insights into the impacts of endotoxemia and bacteremia by periodontal pathogens on the liver from *in vivo* studies



Legend: Up arrow, level/expression increase; down arrow, level/expression reduction. The legend of the minemonic terms cited in the figure is shared in Table 2.

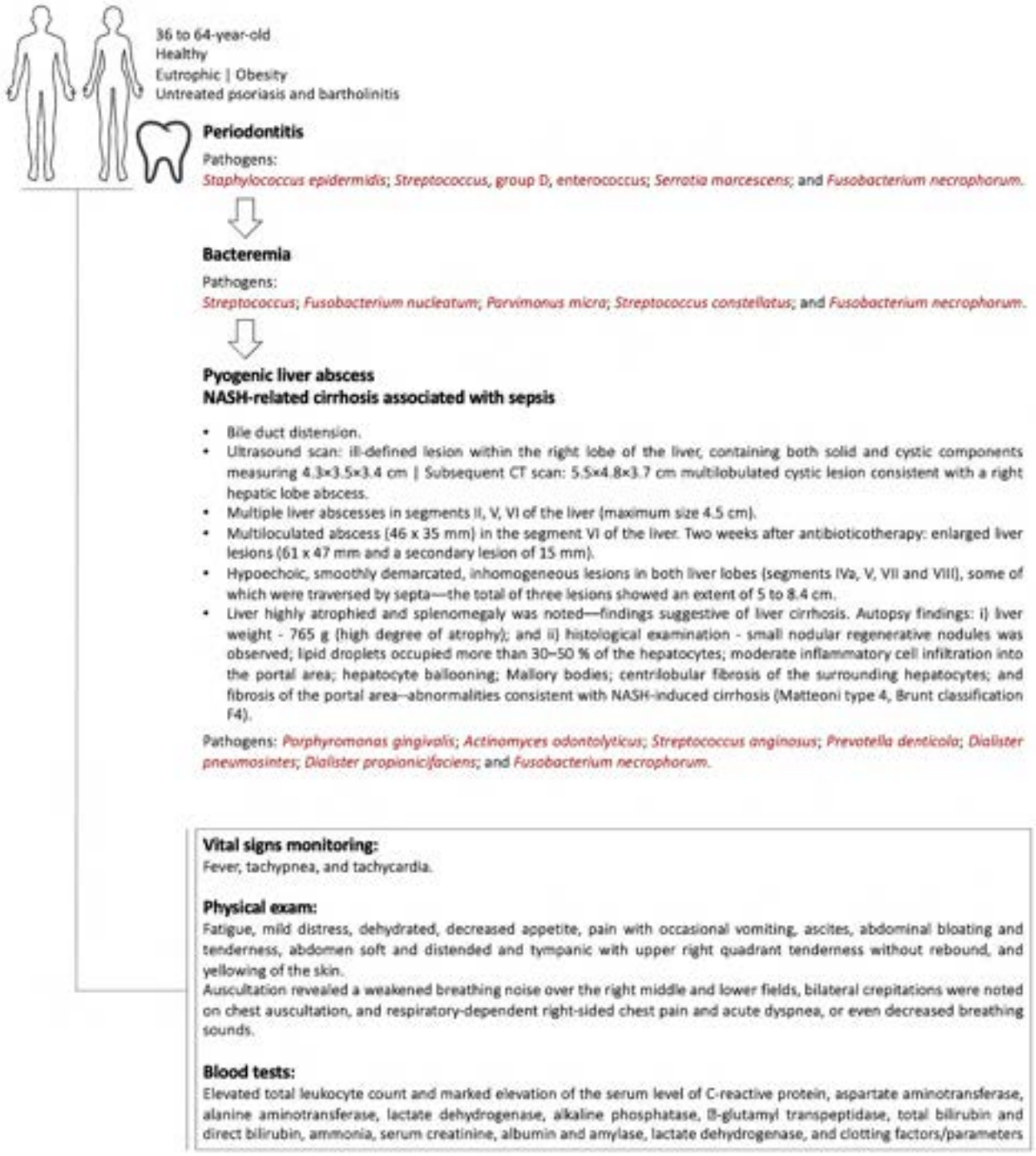
FIGURE 10. Mechanistic insights into the impacts of endotoxemia and/or bacteremia by periodontal pathogens on hepatocytes from *in vitro* studies



Legend: Up arrow, level/expression increase. The legend of the minemonic terms cited in the figure is shared in Table 4.

Case report. Six studies reported cases of pyogenic liver abscess[84,85,87-89] and NASH-related cirrhosis associated with sepsis[86] caused by bacteremia from oral pathogens in individuals with periodontitis[84-86,88,89] or undergoing closed periodontal treatment and tooth extraction.[87] The oral pathogens detected in the bloodstream and liver were: i) *Streptococcus*, *F. nucleatum*, *Parvimonus micra*, *Streptococcus constellatus*, and *Fusobacterium necrophorum*; and ii) *P. gingivalis*, *Actinomyces odontolyticus*; *Streptococcus anginosus*, *Prevotella denticola*, *Dialister pneumosintes*, *Dialister propionicifaciens*, and *Fusobacterium necrophorum*, respectively. Liver abnormalities reported in cases of pyogenic abscess were bile duct distension, ill-defined lesion within the right lobe of the liver, containing both solid and cystic components, multilobulated cystic lesion consistent with a right hepatic lobe abscess in segments II, V, VI of the liver. Hypoechoic, smoothly demarcated, inhomogeneous lesions in both liver lobes (segments IVa, V, VII and VIII), some of which were traversed by septa, have also been described. [84,85,87-89] Autopsy findings of NASH-related cirrhosis associated with sepsis: i) liver weight - 765 g (high degree of atrophy); and ii) histological examination - small nodular regenerative nodules, lipid droplets occupying more than 30–50 % of the hepatocytes, moderate inflammatory cell infiltration into the portal area, hepatocyte ballooning, Mallory bodies, centrilobular fibrosis of the surrounding hepatocytes, and fibrosis of the portal area.[86] Unlike in vivo experiments, patients with liver disease associated with bacteremia by oral pathogens showed alterations of routine blood tests, including CRP and liver biomarkers. A graphical synthesis of results of the six case report studies is available in Figure 11.

FIGURE 11. Clinical characterization of bacteremia-related liver diseases in individuals with periodontitis



For details on case reports, see Table 5.

TABLE 5

Case report studies				
Study | Case reported	**Population | General health**	**Liver abnormalities**	**Periodontal assessment**	**Bacteremia | Endotoxemia**
§Farsakian and Bronny, 1986[84] Liver abscess secondary to dental disease	63-year-old white male patient with pyogenic liver abscess that was thought to be secondary to dental infection 1-week history of decreased appetite, abdominal bloating, and pain with occasional vomiting; patient had no fever or chills Vital signs monitoring: • Body temperature: > 39.2°C Physical exam: well-developed white male in mild distress who appeared minimally dehydrated. His abdomen was soft, distended, and tympanic with upper right quadrant tenderness without rebound; bowel sounds were normal Examination findings were normal except for poor oral health Blood tests: serum creatinine, 1.5 mgm/dL; alkaline phosphatase, 167 µm/L; total bilirubin, 1.1 mg/dL; serum SGOT, 507 µm/L; LDH, 726 µm/L; albumin, 3.4 g/dL; red blood cell, 4.49 x 10^6/mm^3; hemoglobin, 13.3 g/dL; hematocrit, 39.3 %; platelet, 190/mm^3; leukocytes, 19.2 x 10^3/mm^3; 56 % segmented neutrophils; 3 % lymphocytes; 9 % monocytes; 32 % bands; prothrombin time, 13.5 seconds; partial thromboplastin time, 22.4 seconds; and serum amylase, 17 iµ/L When admitted, the patient was hydrated and given antibiotics intravenously Before the second CT scan, the patient used large doses of antibiotics, including metronidazole, ampicillin, and gentamicin	Pyogenic liver abscess On the first day, an ultrasound of the gallbladder showed the organ to be normal without stones but with some bile duct distension On the second day a CT scan of the liver showed multiple hepatic abscesses On the seventh day the liver abscesses were drained The culture of the abscess sample was negative, while the blood cultures again produced *Streptococcus* The patient recovered and the drains were removed after 1 week	Patient was in no acute distress, but had persistent bad breath It was speculated that poor oral health may have been the source of the infection—foci of oral infection: • Periodontal examination showed red, swollen, and inflamed mucosa; blunted papilla; and tissue recession of 2 to 3 mm. Periodontal pockets of 3 to 7 mm were measured around all teeth with 4 to 5 mm being the average pocket depth. A hemorrhagic exudate was noticed within the sulcus on probing. Maxillary anterior teeth had 1 + mobility, whereas the mandibular anterior teeth had a mobility of 1. Large deposits of calculus and heavy dental plaque were evident • The radiographic examination confirmed the presence of infrabony pockets and horizontal bone loss consistent with chronic generalized advanced periodontitis. Periapical radiolucent areas were noted in association with the maxillary right first and second premolars On the 15th day, the maxillary right first and second premolars were extracted	Blood cultures produced *Streptococcus*

			and a swab culture of the apex of the extraction socket was taken: growth of *Staphylococcus epidermidis*; *Streptococcus*, group D, enterococcus; and *Serratia marcescens* Scaling and curettage were also initiated Patient fully recovered and was discharged on the 30th day	
§Yoneda et al., 2011[85] Liver abscess caused by periodontal bacterial infection with *Fusobacterium necrophorum*	36-year-old man. With regard to the etiology, immunodeficiency, diabetes and HIV infection were excluded Vital signs monitoring: • Body temperature: > 40°C Blood tests: elevated total leukocyte count and marked elevation of the serum level of CRP, AST, ALT, LDH, alkaline phosphatase, GGT, total bilirubin and direct bilirubin	Abdominal contrast-enhanced computed tomography revealed multiple liver abscesses in segments II, V, VI of the liver (maximum size 4.5 cm, segment VI) and splenomegaly Liver abscesses were drained and antibiotic therapy with ceftriaxone sodium at 2 g/day was started Cultures of samples of aspirate from the liver abscess revealed growth of *F. necrophorum*, which was thus considered the pathogenic agent After the results of sensitivity testing for different antibiotics, the antibiotic was changed to ampicillin/sulbactam at the dose of 12 g/day	Because *F. necrophorum* is commonly found in the oropharyngeal flora, the patient was referred to the department of oral and maxillofacial surgery for identification of the focus and treatment of the supposed oral infection: • A panoramic radiograph revealed several periodontal lesions near the upper right and left molars, and the left lower molars • Intraoral examination revealed many teeth affected by caries (27 teeth) and a generalized aggressive periodontitis with bleeding on probing and expression of putrid fluid from the pockets • Pocket probing depth was up to 5 mm • *F. necrophorum* was detected in smears of the fluid obtained from the pockets After drainage and focal remediation, the patient showed a dramatic improvement of the general status: total leukocyte count, CRP, AST, ALT, LDH, alkaline phosphatase, GGT, total bilirubin and direct bilirubin were within the reference ranges after treatment	Cultures of blood samples revealed growth of *F. necrophorum*, which was thus considered the pathogenic agent

			A second contrast-enhanced abdominal CT revealed disappearance of the liver abscesses	
†Omura et al., 2016[86] Morbidly obese patient with non-alcoholic steatohepatitis-related cirrhosis who died from sepsis caused by dental infection of *Porphyromonas gingivalis*	54-year-old woman with obesity (body height: 168 cm; bodyweight: 132.4 kg; and BMI: 48.5 kg/m^2) Past medical history was unremarkable for chronic conditions (patient had no history of examination) History of ethanol consumption and smoking was excluded Vital signs monitoring: • Heart rate: 129 b.p.m. (blood pressure was not measured) • Respiratory rate: 28 breaths/minute • Body temperature: 38.4°C Level of consciousness: III-200 on the Japan Coma Scale score and E1V1M4 on the Glasgow Coma Scale score Physical exam: decreased breathing sounds, abdominal distention, yellowing of the skin, no peripheral coldness and marked lower leg edema were found. Blood tests: leukocytosis with neutrophil predominance, high liver enzyme levels, elevated bilirubin and ammonia levels, and decreased prothrombin time were found on blood tests at admission 13-point/grade C Child–Pugh classification: large amount of ascites; total bilirubin level: 9.3 mg/dL; albumin level: 1.7 g/dL; and prothrombin time activity: 17.8 % (international normalized ratio, 2.31) Cirrhosis investigation: • Hepatitis C virus antibody and hepatitis B surface antigen were negative (no viral infection) • Hepatitis B surface antibody was positive, but hepatitis B core antibody was low positive (existing infection pattern--hepatitis B virus was unlikely to have caused the cirrhosis) • IgG level was high; antinuclear antibody level was less than ×40 elevated • Autoimmune diseases were negative • Alcohol-related factors were excluded Diagnosis: NASH-related cirrhosis associated with sepsis	Contrast computed tomography: liver was highly atrophied and splenomegaly was noted—findings suggestive of liver cirrhosis Autopsy findings: • Liver weight: 765 g (high degree of atrophy) • Histological examination: small nodular regenerative nodules was observed; lipid droplets occupied more than 30–50 % of the hepatocytes; moderate inflammatory cell infiltration into the portal area; hepatocyte ballooning; Mallory bodies; centrilobular fibrosis of the surrounding hepatocytes; and fibrosis of the portal area--abnormalities consistent with NASH-induced cirrhosis (Matteoni type 4, Brunt classification F4) • *P. gingivalis* was found in the hepatocytes on immunohistochemical staining (immunolocalization)	Chronic periodontitis Severe periodontal disease with an apparent bleeding tendency, because of which the patient's front teeth fell out easily during intubation Bleeding continued for several days, requiring suture and coagulation of gingiva Tonsillitis was also observed	Although it was unlikely to have been caused by phlogogenic bacteria, the oral flora *P. micra* (periodontal pathogen) was detected in venous blood *P. gingivalis* was not detected by popular culture at that time Because the patient developed a high fever, tachycardia, tachypnea and increased inflammatory response, the diagnosis was likely sepsis, although the focus of infection was not specified

§Schimmel et al., 2019[87] Polymicrobial liver abscesses and pleural empyema in a 40-year-old male after tooth extraction and closed periodontal treatment	40-year-old patient (body height: 182 cm; bodyweight: 73 kg; and BMI: 22 kg/m^2) Only tetrahydrocannabinol and amphetamine abuse has been reported, but this was several years ago Vital signs monitoring: • Heart rate: tachycardic—140 b.p.m. (blood pressure was not measured). ECG: tachycardic steep type, regular R progression with R/S transition in V4/V5, no significant disturbances in repolarization, no block picture, no extrasystoles • Body temperature: pyrexic—39.4°C Physical exam: fever, tenderness in the right upper abdomen, respiratory-dependent right-sided chest pain and acute dyspnea. Auscultation revealed a weakened breathing noise over the right middle and lower fields Blood tests: • Blood count: leukocytes, 35.5 × 10^9/L (3.5 – 9.8 × 10^9/L); monocytes, 2.91 × 10^9/L (0.2 - 0.6 × 10^9/L); immature granulocytes, 0.38 x 10^9/L (0–0.03 x 10^9/L); neutrophils, 29.69 x 10^9/L (1.6 – 7.1 × 10^9/L); rod cells, 9.1 % (3 – 5 %); segmental cells, 75.3 % (40 – 75 %); lymphocytes, 5.8 % (18 – 48 %); platelets, 415 × 10^9/L (140 – 360 × 10^9/L) • Inflammation parameters: C-reactive protein, 238.58 mg/L (< 5 mg/L); IL-6, 891.0 pg/mL (< 7 pg/mL); procalcitonin, 3.20 ng/mL (< 0.05 ng/mL) • Electrolytes: sodium, 129.4 mmol/L (135 – 145 mmol/L); potassium, 4.74 mmol/L (3.49 – 4.63 mmol/L) • Blood coagulation: quick value 50 % (> 70 %) • Venous blood gas analysis: pH, 7.503 (7.37 – 7.45); Na, • 126 mmol/L (135 – 145 mmol/L); Ca, 1.08 mmol/L (1.15 – 1.35 mmol/L); glucose, 8.2 mmol/L (4.11 – 5.89 mmol/L) Patient stated that 16 weeks ago a tooth extraction of the 3rd molar (18, 28, 38, 48) and a 1st molar (46) and subsequent systematic closed periodontitis treatment of all quadrants Serological and molecular analysis revealed no evidence of protozoal disease or tuberculosis. After the microbiological test results, the antimicrobial therapy could be de-escalated to penicillin G (4 × 5 million IU/d i.v.) and continued for a further 14 days	Chest X-ray: Pronounced shadowing of the lower right half of the chest and a mediastinal shift to the left; an ipsilateral broncho pneumogram was described Thoracic CT scan with i.v. contrast agent: • Inflammatory mediastinal and pleural focal findings in terms of a most likely reactive lymphadenopathy and multiple abscesses with a maximum diameter of 4.6 cm • Massive, protein-rich pleural effusion on the right with subsequent total atelectasis in the sense of a pleural empyema • Four subcapsular fluid collections in the liver segments IVa (4.8 × 4.4 cm), V (8.3 × 6.7 cm), VII (5.3 × 2.7 cm) and VIII (3.5 × 2 cm) with partial septation and thickened wall • Minimal perihepatic fluid accumulation Abdominal ultrasonography: Hypoechoic, smoothly demarcated, inhomogeneous lesions in both liver lobes (segments IVa, V, VII and VIII), some of which were traversed by septa, which were compatible with an abscess; the total of three lesions showed an extent of 5 to 8.4 cm	Closed periodontal treatment and tooth extraction	*S. constellatus* was cultured with massive growth in the pleura puncture None of the blood cultures obtained showed any growth even after seven days of incubation *A. odontolyticus* was detected in the abscess aspirate sent from the right lobe of the liver Massive growth of *S. anginosus* was found in the aspirate from the left lobe of the liver *P. denticola* was isolated from the intraoperative swabs of the video-assisted thoracoscopy In total, four different species of the physiological microbiota of the oral cavity were identified

	Pain was treated with piritramide, novaminsulfone and pregabalin, later exclusively with oral tilidine Control sonographies of the abdomen and the pleura on both sides showed a complete regression of the abscesses without any indication of recurrence or other pathological findings—patient could be discharged on the 42nd day of the inpatient stay with an overall delayed convalescence due to the necessary continuous rinsing of the empyema			
§Soeiro et al., 2019[88] Hepatic abscess due to *Dialister pneumosintes*	51-year-old woman, with a history of untreated psoriasis and bartholinitis <u>Vital signs monitoring:</u> • Body temperature: acute fever, 40°C The patient presented fatigue; however, physical examination and blood tests were normal Serological investigations were negative for amoebiasis and echinococcosis Patient was instructed to take amoxicillin-acid clavulanic orally and was discharged home; she returned to the same hospital the next day with a persistent high-grade fever and a mild pain of the right upper quadrant of the abdomen – antibiotic treatment was switched to ceftriaxone and metronidazole	CT scan of the abdomen showed a multiloculated abscess (46 x 35 mm) in the segment VI of the liver; MRI of the liver and biliary tract showed no further abnormalities Two weeks after ceftriaxone and metronidazole, fever had not abated, and a repeat MRI showed enlarged liver lesions (61 x 47 mm and a secondary lesion of 15 mm) Patient was submitted to drainage of the liver abscess Because of worsening pain in the right upper abdominal quadrant, persistent fever, and elevated serum C-reactive protein two days after the abscess drainage, a CT scan was repeated and showed pleural and peritoneal effusions leading to a change in the antibiotic therapy to piperacillin/tazobactam Because pleural effusion worsened and was complicated with respiratory failure, a pleural drain was placed 5 days after admission for a total of 3 days; pleural fluid was consistent with an exudate Patient's condition improved and the abdominal tube was removed 6 days after insertion	After diagnosing unusual bacterial species in the liver (*D. pneumosintes* and *D. propionicifaciens*), the authors repeated the history taking and physical examination, focusing on patient's dental and oral hygiene: • One month before she first presented to the hospital, the patient confessed to have self-treated a dental abscess with non-steroidal anti-inflammatory drugs • Physical examination identified periodontitis with bone loss in four teeth, which were extracted after 17 days of treatment with piperacillin/tazobactam Based on these findings, the authors considered that the dental infection had thus caused the liver abscess	All pairs of aerobic and anaerobic blood cultures obtained at admission, day 4, day 8, day 12 and day 15 remained sterile after 7 days of incubation; microbiological analysis of the liver abscess pus and the pleural fluid were negative (Gram-staining) Cultures remained negative after 7 days of incubation on various media Presence of bacterial DNA in the liver pus sample was investigated by using a broad-range bacterial 16S rRNA gene PCR:[A] the 628-bp consensus sequence obtained shared 99.5 %

				identities with the sequence of *D. pneumosintes* JCM 10004T and 91.6 % with *D. propionicifaciens* JCM 17568T—taxonomic affiliation to the species *D. pneumosintes* was performed using CLSI interpretive criteria[B]
[§]Collins and Diamond, 2021[89] *Fusobacterium nucleatum* causing a pyogenic liver abscess: a rare complication of periodontal disease that occurred during the COVID-19 pandemic	64-year-old woman with a 6-day history of lethargy, fever, shortness of breath and mild abdominal pain. Regarding the etiology, HIV infection was excluded The patient was resuscitated, and broad-spectrum intravenous antibiotics were commenced in line with local trust policy (tazocin and gentamicin) Provisional diagnoses: COVID-19 or sepsis of unknown origin—two negative COVID-19 PCR tests Patient had no relevant medical history and was an ex-smoker Vital signs monitoring: • Heart rate: tachycardic—106 b.p.m. (blood pressure was not measured) • Respiratory rate: tachypnoeic—30 breaths/minute, and oxygen saturations of 99 % on high flow nasal oxygen (60 L/minute at 90 %) • Body temperature: pyrexic—38.3°C Physical exam: bilateral crepitations were noted on chest auscultation, and abdominal examination showed mild generalized tenderness Blood tests: marked inflammatory response, deranged liver function tests and a metabolic acidosis, with a lactate of 7.1 Transthoracic echocardiogram and ultrasound Doppler scan excluded Lemierre syndrome, an infectious thrombophlebitis of the internal jugular veins secondary to *F. nucleatum* oropharyngeal infection[C,D]	Purulent abscess fluid of the pyogenic liver abscesses was drained and sent for culture and sensitivity testing. No growth was detected from this aspirate. Antibiotics were rationalized to intravenous Ceftriaxone and oral Metronidazole in accordance with microbiology advice following the identification of *F. nucleatum* on blood culture analysis Ultrasound scan of the abdomen on day 2 of admission: ill-defined lesion within the right lobe of the liver, containing both solid and cystic components measuring 4.3×3.5×3.4 cm Subsequent CT scan to further characterize the ultrasound findings: 5.5×4.8×3.7 cm multilobulated cystic lesion consistent with a right hepatic lobe abscess	Patient had received oral antibiotics from her general dental practitioner in preceding weeks for a troublesome periodontal abscess associated with an upper left posterior tooth Patient had experienced ongoing pain from a mobile tooth in the upper left quadrant and was previously diagnosed with generalized moderate periodontal disease with localized severe disease in the upper left quadrant Intraoral periapical radiograph demonstrated the severe bone loss in the upper left quadrant (most notably interproximally between the 27 and 28 teeth An area of periapical pathology can also be seen associated with the 28 tooth The 28 tooth was grade 2 mobile and symptomatic Both 27 and 28 teeth were of poor prognosis Due to the patient recent upper left quadrant pain arising during the	Blood cultures identified a *F. nucleatum* bacteraemia

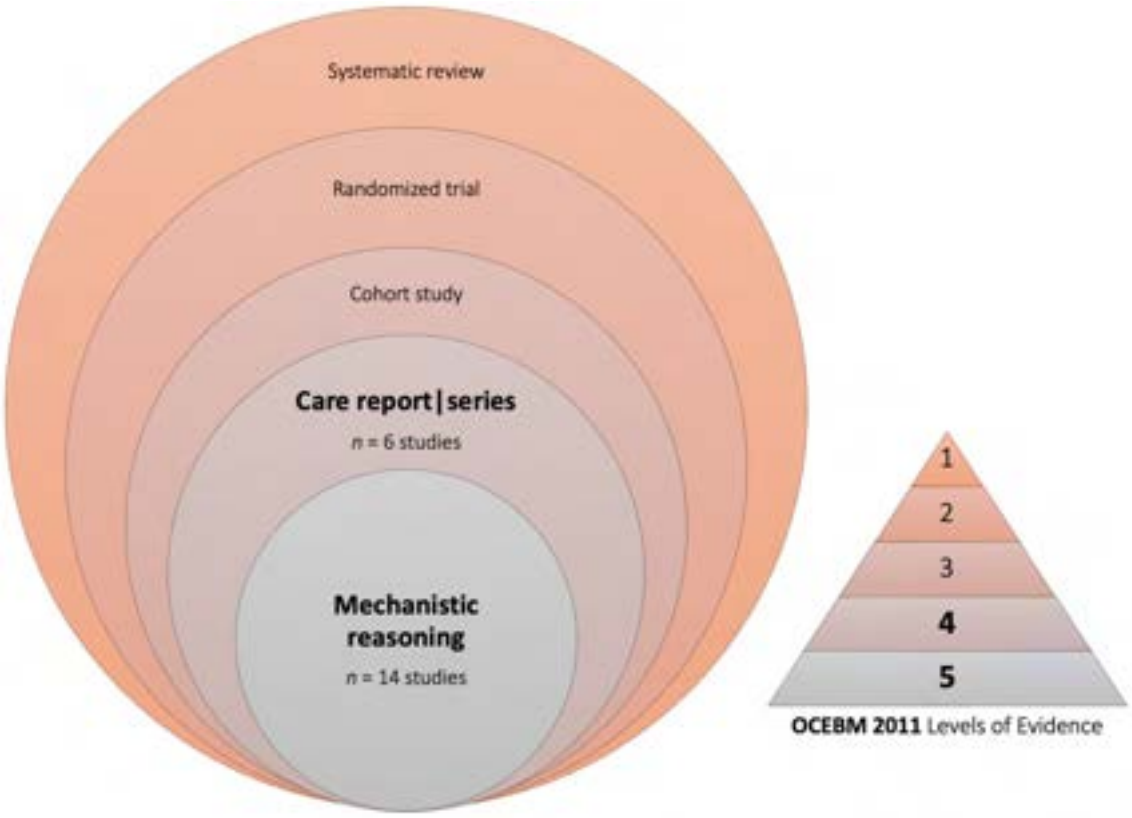
			COVID-19 pandemic, she received advice, analgesia and antimicrobials from her general dental practioner via phone consultation, as per guidelines at the time.[E] She received three separate courses of antibiotics in the form of Amoxicillin for 5 days, followed by a further course of Amoxicillin for 7 days and finally a course of Metronidazole for 5 days In the absence of signs, symptoms, or evidence of any other pathology and with blood cultures positive for *F. nucleatum*, the periodontium was considered to be the source of infection in this case	

Legend: [†], Phase 2 of the study selection process (full-text screening); [§], handsearch; SGOT, glutamic-oxaloacetic transaminase test; LDH, lactate dehydrogenase; CRP, C-reactive protein; ALT, alanine aminotransferase; AST, aspartate aminotransferase; GGT, γ-glutamyl transpeptidase; CT scan, computed tomography scan; *F. necrophorum*, *Fusobacterium necrophorum*; BMI, body-mass index; b.p.m., beats per minute; IgG, immunoglobulin G; NASH, nonalcoholic steatohepatitis; *P. gingivalis*, *Porphyromonas gingivalis*; *P. micra*, *Parvimonus micra*; i.v., intravenously; NA, data not available; *S. constellatus*, *Streptococcus constellatus*; *A. odontolyticus*, *Actinomyces odontolyticus*; *S. anginosus*, *Streptococcus anginosus*; *P. denticola*, *Prevotella denticola*; MRI, magnetic resonance imaging; *D. pneumosintes*, *Dialister pneumosintes*; *D. propionicifaciens*, *Dialister propionicifaciens*; DNA, deoxyribonucleic acid; CLSI, clinical and laboratory standards institute; COVID-19, coronavirus disease 2019; PCR, polymerase chain reaction; *F. nucleatum*, *Fusobacterium nucleatum*.

References: [A], Ferrand J, Bonnet I, Alauzet C, Lozniewski A. Evaluation of the Vitek MS and the MALDI Biotyper systems for the identification of less commonly isolated but clinically relevant anaerobes and facultative anaerobes. Anaerobe. 2018 Dec;54:210-216. doi: 10.1016/j.anaerobe.2018.05.014; [B], Petti CA, Bosshard PP, Brandt ME, Clarridge JE, Feldblyum TV, Foxall P, et al. Interpretive criteria for identification of bacteria and fungi by DNA target sequencing; Approved Guideline. 28:7; [C], Han YW. *Fusobacterium nucleatum*: a commensal-turned pathogen. Curr Opin Microbiol. 2015 Feb;23:141-7. doi: 10.1016/j.mib.2014.11.013; [D], Johnson King O, Sharma V. Lemierre syndrome leading to ankylosis of the temporomandibular joint. Br J Oral Maxillofac Surg. 2019 Dec;57(10):1153-1155. doi: 10.1016/j.bjoms.2019.10.306; [E], Scottish Dental Clinical Effectiveness Programme. Acute Dental Problems - COVID-19 - SDCEP, 2020. Available: https://www.sdcep.org.uk/published-guidance/acute-dental-problems-covid-19/ [Accessed 28 Aug 2020].

Additional analyses. The literature that relates endotoxemia and bacteremia by periodontal pathogens with liver abnormalities, according to the eligibility criteria established in this scoping review, is restricted to OECBM 2011 levels of evidence 4 and 5 (Figure 10).

FIGURE 10. Levels of evidence from primary studies



Legend: *n*, absolute frequency.

DISCUSSION

In response to the focused question of this scoping review, the authors synthesized the mechanistic insights reported in the laboratory studies and proposed a biological mechanism for the intersection between endotoxemia and bacteremia by periodontal pathogens and liver abnormalities. Despite weak evidence available to guide clinical decision-making, mechanistic reasoning studies and case reports provide important insights on the intersections between endotoxemia and bacteremia by periodontal pathogens and liver abnormalities, including NAFL and NASH, pyogenic abscess, and death from NASH-related cirrhosis associated with sepsis.

Research related to periodontal disease and liver disease initially suggested a bidirectional association between poor oral hygiene and the presence of periodontal disease and chronic hepatitis and cirrhosis.[90-93] The effects of periodontitis on the development of NAFLD emerged from in vitro-based basic research and continue to be discussed today.[49,74,94]

If more than 5% of the hepatocytes are fatty, then it is diagnosed as fatty liver or steatosis. The spectrum of NAFLD ranges from NAFL to NASH, which can progress to end-stage liver disease. In addition to fat deposition in the liver, NASH is characterized by necroinflammation, hepatocellular damage, and faster fibrosis progression.[27-32,49-56] The same histological findings were associated with LPS endotoxemia and *P. gingivalis*, *C. pneumoniae*, and *A. actinomycetemcomitans* bacteremia in this scoping review.[72-74,78-80,82,83] These three periodontal pathogens accelerated the progression from NAFL to NASH,[78,80,82] and the degree of fibrosis was progressively exacerbated with increasing bacterial burden.[83] *P. gingivalis*-odontogenic infection exacerbated pathological progression of NASH through Gal-3 (galectin-3) and TGF-β1/Smad pathway.[80] This *P.gingivalis*-LPS-TLR2-mediated signaling pathway, also involving ERK1/2 pathways, leads to activation of hepatic stellate cells, involving the transition from a quiescent to a proliferative, migratory, and fibrogenic (e.g., myofibroblast) phenotype, which is characteristic of hepatic fibrogenesis.[74,82] The partial and transient benefits of AZM for liver parameters altered by *P. gingivalis* suggest limited effects of the use of this antibiotic on liver abnormalities resulting from bacteremia.[82]

Serum levels of acute phase proteins CRP[72,75] and *Saa*[73] were significantly increased by LPS endotoxemia[72] and *A. actinomycetemcomitans*-[75] and *A. actinomycetemcomitans* plus *C. pneumoniae*-bacteremia.[73] Although ALT and AST did not vary between groups in laboratory studies, blood test changes in reported cases included CRP, AST, ALT, and other hematologic parameters. Although commonly referred to collectively as liver function tests, serum aminotransferase concentrations are an indicator not of hepatocellular dysfunction but of hepatocellular damage. ALT and AST enzymes are present in high concentration in hepatocytes and catalyze the production of pyruvic acid and oxaloacetic acid, respectively. These enzymes leak into the circulation when hepatocytes or their cell membranes are damaged.[95] Therefore, it is possible that the liver damage in animal models exposed to endotoxemia and bacteremia was not sufficient for significant variations in liver enzymes in these groups.[72,82,83] Possibly, the hepatic impairment caused by the high-fat diet in infected and uninfected animals underestimated the effects of *P. gingivalis* bacteremia on these biomarkers.[82] The increase in ALT and AST in pyogenic liver abscess and NASH-related cirrhosis associated with sepsis was expected due to the intense hepatocellular damage in these cases.

Chen et al. reviewed the role of oxidative stress in the pathogenesis of NAFLD.[96] Oxidative stress reflects the imbalance between the production of reactive oxygen species (ROS) and the scavenging capacity of the antioxidant system in favor of the former.[97] ROS, including H_2O_2, are continuously produced intracellularly as byproducts energetic metabolism in different types of liver cells.[98] Hepatic lipid overload induces overproduction of oxidants, affecting several ROS-generating mechanisms. At high concentrations, ROS cause oxidative changes in cellular macromolecules, inducing liver damage.[99,100] Furthermore, ROS signaling promotes metabolic dysfunction and inflammatory response,[101,102] and is considered the main contributor to liver injury and disease progression in NAFLD.[97,103] Oxidative stress was associated with LPS endotoxemia[72] and bacteremia by *P. intermedia* and *P. gingivalis*,[83] with increased serum levels of H_2O_2, TUNEL-positive cells, 8-OHdG and upregulated genes in the liver. Proinflammatory genes were also expressed in livers exposed to endotoxemia and bacteremia,[83] increasing levels of TNF-α, TGF-β1, IL-1β, IL-6, IL-10, IL-12, IL-17, IFN-γ, MCP-1, and CD68.[72-75,77,80,82] These features have been described in the blood and/or liver from animals,[72-74,78,79,80,82] and seem to be associated with increased NAS in odontogenic infection by *P. gingivalis*.[78,82] Complementary data from *in vitro* experiments confirmed the activation of TLR2-PAR2-Gal-3-TGF-B1-Smad2/3 and ERK1/2 pathways in hepatic stellate cells and steatotic hepatocytes stimulated by *P. gingivalis* or *P. gingivalis*-LPS. In addition to increasing α-SMA and type I collagen, *P. gingivalis*-LPS increased mRNA expression of inflammasomes such as NLRP3 and Casp-1, in addition to the aforementioned proinflammatory cytokines, including IL-8.[74,82] As we know, oxidative stress, inflammatory mediators and inflammasomes can influence the progression from NAFL to NASH[26,27-32,49-56] and also participate in the pathogenesis of periodontal disease.[104-108]

Omura et al.[86] reported a fatal case of NASH-related cirrhosis associated with sepsis in a 54-year-old woman with obesity (BMI: 48.5kg/m^2). Histological examination of autopsied biopsies described small nodular regenerative nodules, lipid droplets occupying more than 30–50% of the hepatocytes, moderate inflammatory cell infiltration into the portal area, hepatocyte ballooning, Mallory bodies, centrilobular fibrosis of the surrounding hepatocytes, and fibrosis of the portal area—abnormalities consistent with NASH-induced cirrhosis (Matteoni type 4, Brunt classification F4). The authors related the case to severe periodontitis with an apparent tendency to bleeding and to immunocolocalization of *P. gingivalis* in hepatocytes, as no other cause was identified. Another five cases reported bacteremia by oral pathogens in patients with periodontitis as a cause of pyogenic liver abscess.[84,85,87-89] although it is not possible to establish a causal relationship in case report designs and these results are still inconclusive, they support the hypothesis of an intersection between endotoxemia and bacteremia by periodontal pathogens and liver abnormalities.

Inflammation is essential for the tissue remodeling and maintenance of homeostasis and normal liver physiology. However, constant exposure to dietary and microbial products favors the potentially prolonged immune activation and unresolved inflammation in susceptible host.[109] All studies included in this scoping review exposed the liver to LPS endotoxemia and periodontal pathogen bacteremia, of which two studies added a high-fat diet to *P. gingivalis* infection.[80,82] Two laboratory studies used gavage with P. gingivalis,[76,77] one used gavage with *P. gingivalis*, *F. nucleatum* and *F. alocis* (pathogens),[81] and one used gavage with *P. gingivalis*, *P. intermedia*, *A. naeslundii* and *V. rogosae*.[83] Two of these studies reported NAFLD.[77,83] Nakajima et al.[76] demonstrated a significant impact of *P. gingivalis* administration on the composition and diversity of the hepatic microbiota, and Yamazaki et al.[81] reported gene expression profiles in the liver related to inflammation and lipid metabolism, stimulated by *F. nucleatum*. There was a robust effect of high-fat diet feeding on the liver. However, the administration of *P. intermedia* and *P. gingivalis* induced additional and substantial changes in the expression profile of genes related to biosynthesis and metabolic processes, cell cycle process potentially implicated in carcinogenesis and end-stage NAFLD, tumor suppressor genes, responses to oxidative and endoplasmic reticulum stress, regulation of intrinsic apoptosis, inflammatory response, response to LPS, and others. In these studies, the intersection between periodontal pathogen bacteremia and liver abnormalities involved the oral-gut-liver axis, where gut microbiota, high-fat diet exposure, and microbial challenge overcame the adaptive capacity of the liver.[50,55,76,79,83,109,110] More recently, the concept of the gut-liver axis and gut dysbiosis has been proposed as another potential route linking the oral cavity and the liver in a bidirectional crosstalk.[50,76,109] Endotoxemia and bacteremia in the other inoculation models and experimental periodontitis occurred through the bloodstream. No different patterns of liver abnormalities were identified comparing studies that used naive animals[70-72,74,76-78,81,83] and those that used high-fat diet model,[80,82] apoE-deficient mice,[73] LFKO$^{-/-}$,[75] and germ-free mice.[79] The same was observed for the endotoxemia/bacteremia intervention.

Currently, an updated theory called the “multiple-hit" hypothesis involves a number of factors that may act in parallel in the pathogenesis of NAFLD.[96,103] Among the many factors that contribute to “multiple hits” is oxidative stress, which is considered the main contributor to liver damage and disease progression in NAFLD.[97] In this context, the results of this scoping review suggest endotoxemia and bacteremia by periodontal pathogens as a possible "multi-hit" factor associated with the pathogenesis of NAFLD. This makes sense because epithelial ulceration of the gingival sulcus or periodontal pocket exposes a highly vascularized connective tissue to pathogenic microorganisms, allowing them and their toxins to enter the bloodstream.[35-40] It is noteworthy that all bacteria inoculated or identified in the blood and liver of the included studies were previously described as periodontal pathogens.[111-118]

According to Kuraji et al.,[26] further research is needed to elucidate the mechanism by which periodontal pathogens, LPS, and proinflammatory mediators translocate to the liver and the precise role of periodontal disease in the pathogenesis of NAFLD. It is reasonable to think that bacterial and immunoinflammatory stimuli from the periodontal pocket[3,119-121] have the potential to induce liver abnormalities and accelerate the progress of NAFLD,[26,27-32,49-56] as an inflammatory comorbidity. In addition, endotoxemia and bacteremia involved in periodontitis-related NAFLD have been described both via hematogenous dissemination and oral-gut-liver axis.[73,75,79,80,82]

Limitations. Scoping reviews are exploratory and address a broad issue, not a specific question. This type of study assesses the extent of available evidence, organizes it, synthesizes it, qualifies it or not, highlights gaps and proposes conceptual hypotheses for future research. This scoping review answered the following question: "What associations between endotoxemia and bacteremia by periodontal pathogens and liver abnormalities have been reported?" It was not possible to explore a causal relationship between periodontitis and liver abnormalities. However, the methodology used ensured a broad and precise search for articles on the subject, gathering the available evidence. The OCEBM2011 rating level of the included studies was low (4 and 5). Fourteen of the 20 studies (70%) were classified as mechanistic reasoning and the remaining 30% were case reports. The requirement for confirmation of endotoxemia and bacteremia established in the eligibility criteria excluded many studies, as reported in the article. No bias could be attributed to these variables. Laboratory studies presented methodological limitations, according to the SYRCLE's tool. Unreported data on random outcome assessment, allocation concealment, and blinding compromised the quality of these studies. This seems to be a methodological limitation to be improved in future research. Despite the design of the studies, the results were overwhelming. Periodontal pathogens reached the liver via the bloodstream and oral-gut-liver axis and were associated with liver abnormalities and pathological progression of NASH. In humans, odontogenic infection of the liver was correlated with pyogenic abscess and NASH-related cirrhosis associated with sepsis. One of the reported cases died. At this time of understanding the mechanisms of pathogenesis of liver diseases and the risk factors associated with disease progression, this scoping review makes an important contribution in this regard. Further studies on the crosstalk between periodontium and liver should be encouraged. For the authors, there is minimal but sufficient evidence to propose a conceptual hypothesis of an association between endotoxemia and bacteremia by periodontal pathogens and liver abnormalities, to be investigated.

Conclusions. This scoping review provides important findings to consider when investigating the role of periodontal disease in causing or aggravating liver diseases. Recognizing

the limitations of this study, experimental evidence and clinical observations suggest direct effects of periodontal pathogens on the pathogenesis of NAFLD. Live pathogens and their virulence factors, especially LPS, have been associated with liver abnormalities, NAFL, NASH, pyogenic liver abscess, and NASH-related cirrhosis associated with sepsis. Although hematogenous dissemination is the most studied, endotoxemia and bacteremia through the oral-gut-liver axis also appear to be associated with the pathogenesis of NAFLD. Thus, we synthesized data from the literature on the subject into biological models and clinical record that describe the mechanisms through which endotoxemia and bacteremia by periodontal pathogens increase NAFLD risk.

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Conflict of interest

None of the authors has any type of conflict of interest related to the study, as well as related to the peer review process of the manuscript. None of the universities and public agencies that support research in Brazil represents a conflict of interest in this study.

Contribution statement

All authors made substantial contributions to the study and were equally responsible for its design, execution, and content, and agreed to its submission for publication.

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DISCUSSÃO

A pandemia de COVID-19 impactou profundamente as atividades de ensino em todos os níveis, incluindo a Pós-graduação e as atividades de pesquisa em desenvolvimento naquele momento. Assim como as atividades de ensino e extensão precisaram ser revisadas e se adaptar àquela realidade, grande parte dos projetos de pesquisa e planos de trabalho também foram reformulados, e esse foi o nosso caso. O projeto inicial de avaliação da condição hepática em indivíduos com obesidade, correlacionando estas variáveis e a periodontite com níveis séricos de PCR, citocinas inflamatórias e outros biomarcadores, foi inviabilizado pela pandemia. A partir deste momento, tendo nos apropriado da literatura relacionada ao tema, identificamos as principais limitações de evidência e as recomendações de mais estudos sobre a relação entre obesidade e periodontite, PCR enquanto biomarcador de risco sistêmico e critério de diagnóstico da periodontite, e mecanismos de patogênese das NAFLD até então pouco estudada no contexto da Medicina Periodontal. Considerando o número e a qualidade dos estudos existentes e o nível de evidência estabelecido para cada tema, nós delineamos estudos de natureza exploratória nos quais propomos hipóteses conceituais originais e estabelecemos o melhor nível de evidência para questões clínicas relevantes sobre obesidade e periodontite, PCR e periodontite, e endotoxemia/bacteremia por patógenos periodontais e NAFLD. Ainda neste contexto, nós publicamos dois ensaios teóricos sobre a importância da pandemia de COVID-19 para a Medicina Periodontal, que compõem o primeiro objetivo específico e o primeiro capítulo da Tese.

Desta forma, formulamos uma hipótese conceitual sobre a importância da patogênese da COVID-19 para a pesquisa em Medicina Periodontal, revisamos os mecanismos biológicos envolvidos na relação bidirecional entre obesidade e periodontite e realizar uma síntese de evidências de nível 1 acerca dessa associação, baseada em estudos de meta-análise, realizamos uma síntese de evidências científicas sobre os benefícios sistêmicos do tratamento periodontal em pacientes com obesidade e periodontite a partir de ensaios clínicos, estabelecemos o efeito do tratamento periodontal nos níveis séricos de proteína C-reativa em diferentes condições/doenças sistêmicas a partir de revisões sistemáticas de estudos de intervenção, e realizamos uma síntese de evidências disponíveis sobre os efeitos da endotoxemia e da bacteremia por patógenos

periodontais no fígado, avaliamos a qualidade e o nível das evidências disponíveis, e propusemos um modelo de patogênese das doenças hepáticas a partir dessa exposição.

Estamos vivendo a "terceira era" da construção do conhecimento científico em Periodontia, de progressos consideráveis no entendimento de possíveis associações entre doenças periodontais e certas condições/doenças sistêmicas (Genco e Sanz, 2020). A Medicina Periodontal é compreendida como uma disciplina ou subárea da Periodontia, como proposto por Steven Offenbacher no ano de 1996. Nesta publicação, Dr. Offenbacher descreve que "[...] dados sobre os efeitos sistêmicos das doenças periodontais começaram a definir uma nova disciplina de medicina periodontal, que certamente está em sua 'infância', mas tem um futuro brilhante." A Medicina Periodontal é um termo coletivo usado para descrever como a infecção/inflamação periodontal pode afetar a saúde em outros sistemas do corpo humano (Beck et al., 2019).

Já nesta publicação, o autor descreve e faz uma revisão crítica a respeito da patogênese das doenças periodontais, onde a participação de mediadores inflamatórios, patógenos periodontais e suas toxinas, mais especificamente o LPS, são amplamente discutidas (Offenbacker, 1996). Os mesmos fatores envolvidos na patogênese das doenças periodontais descritos por Offenbacker foram revisitados e atualizados em novos estudos que também consideravam sua etiologia multifatorial, o compartilhamento de fatores de risco e de mecanismos biológicos envolvidos com outras condições/doenças.

A periodontite é uma doença inflamatória crônica multifatorial associada a biofilme disbiótico, e caracterizada pela destruição progressiva do aparato de suporte dentário (Papapanou et al., 2018). Mais recentemente, ela vem sendo descrita como uma doença crônica não transmissível (DCNT) e uma comorbidade do diabetes *mellitus* (Polak e Shapira, 2018; ADA, 2019; Loos e Van Dyke, 2020; Polak et al., 2020; Sanz et al., 2020; Van Dyke e Sima, 2020). A relação entre o desafio bacteriano e a resposta do hospedeiro é um mecanismo biológico plausível que liga a periodontite a vários distúrbios, incluindo doenças cardiometabólicas, neurodegenerativas cognitivas e autoimunes, infecções respiratórias e certos tipos de câncer (Hajishengallis, 2022).

A periodontite compartilha várias características com a COVID-19, incluindo sua as comorbidades relacionadas e seus efeitos na inflamação sistêmica. Alguns estudos iniciais identificaram uma possível associação entre a periodontite e o risco de infecção

e complicações da doença. Corroborando os resultados do nosso ensaio teórico, Tamimi et al. (2022) descreveram as semelhanças entre COVID-19 e periodontite em relação às comorbidades associadas, aos biomarcadores inflamatórios elevados, biomarcadores de coagulação, à atividade de células do sistema imunológico, e aos biomarcadores de dano tecidual elevados.

Até o momento, nossa publicação parece ser o primeiro estudo sobre este tema, e apenas o nosso trabalho descreve este cenário como um desafio para a pesquisa em Medicina Periodontal (Barbirato et al., 2021a,b). Se de fato estas duas doenças compartilham elementos importantes de sua patogênese, acreditamos ser possível que eventos biológicos relacionados ao início, progressão, interações sistêmicas e resposta ao tratamento em pacientes com periodontite possa apresentar um comportamento diferente do que conhecemos do período pré-pandemia. Segundo os próprios autores, mais pesquisas são necessárias para confirmar a hipótese de associação entre COVID-19 e periodontite (Tamimi et al., 2022).

Apesar das diferentes vacinas e abordagens preventivas e terapêuticas a que grande parte da população mundial foi exposta, estes indivíduos, assim como aqueles que não foram vacinados para a COVID-19 ou desenvolveram sintomas, complicações ou sequelas da doença, representam um novo desafio para a compreensão da patogênese de DCNT, assim como a periodontite e suas interações sistêmicas. Outro ponto importante a se considerar, são os impactos da pandemia no diagnóstico, manejo e suporte dos pacientes com DCNT. A redução de atendimentos presenciais e de procedimentos de triagem, atrasos no diagnóstico e tratamento, bem como políticas de distanciamento social levaram, de forma unânime, a impactos indesejáveis na saúde física e psicológica destes pacientes. É esperado que isso possa contribuir para mais mortes, segundo Mak et al. (2022). No contexto do nosso trabalho, consideramos o distanciamento social, a mudança do estilo de vida, o uso de múltiplas drogas e as sequelas da COVID-19, componentes adicionais à patogênese compartilhada entre essa doença e as doenças periodontais, capaz de influenciar o que sabemos sobre os fatores de risco e as interações sistêmicas da periodontite. Segundo os autores, o impacto da pandemia de COVID-19 em pacientes com DCNT está apenas começando a se desvendar.

A reflexão sobre os efeitos da pandemia de COVID-19 na Periodontia talvez tivesse sido descrita na seção “The research-based future of periodontology” do artigo de Slots, publicado em 2017, cujo título foi *Periodontitis: facts, fallacies and the future* (Slots, 2017). O artigo que reporta um mapeamento sistemático dos registros de ensaios clínicos em Medicina Periodontal, e o Editorial sobre o trabalho em progresso nessa mesma área, publicados no periódico *Journal of Clinical Periodontology* em 2016 (Monsarrat et al., 2016; e Loos, 2016, respectivamente), certamente teriam mencionado as pesquisas sobre COVID-19 e NAFLD realizadas nos últimos anos, e a construção contínua de conhecimento e de evidências científicas a esse respeito.

Larvin et al. (2021) descreveram efeitos aditivos da periodontite e da obesidade nos desfechos da COVID-19. A taxa de mortalidade foi aproximadamente três vezes maior entre pessoas com obesidade que foram diagnosticadas com periodontite, do que naqueles sem periodontite. A obesidade também foi associada a maiores taxas de hospitalização e mortalidade, e a periodontite parece exacerbar esse efeito. A obesidade *per se* aumenta a susceptibilidade às formas graves de COVID-19 (Cai et al., 2020; Gao et al., 2020; Petrilli et al., 2020; Price-Haywood et al., 2020; Simonnet et al., 2020; Stefan et al., 2021). Embora o mecanismo fisiopatológico seja desconhecido, existem evidências moderadas da associação entre obesidade e periodontite (Jepsen et al., 2017).

No artigo publicado por Azevedo et al. (2020), descrevemos os principais eventos biológicos envolvidos na relação entre obesidade e periodontite. A obesidade parece atuar sobre a periodontite pelo estado hiperinflamatório sistêmico e comprometimento do metabolismo da glicose destes pacientes, tendo como principais fatores biológicos associados as citocinas pró-inflamatórias IL-1β, IL-6 e TNF-α, perda da homeostasia de leptina e adiponectina, aumento dos níveis de ácidos graxos livres e de espécies reativas de oxigênio, acúmulo de AGEs, aumento da colagenólise e dos níveis de PCR e angiotensinogênio, e pelas complicações vasculares. Possivelmente a evidência moderada de associação entre estas duas doenças esteja relacionada ao componente multifatorial e às comorbidades associadas a ambas. Neste sentido, Genco et al. (2005) sugerem que o estado hiperinflamatório na obesidade deva ser resultado do aumento da resistência insulínica e da predisposição ao diabetes mellitus, os quais, então, aumentariam o risco para doenças periodontais.

Em uma síntese da melhor evidência acerca da relação entre obesidade e

periodontite em seus efeitos bidirecionais, baseada em resultados apresentados em artigos de revisão sistemática com meta-análise, demonstramos a existência de associação entre obesidade e parâmetros clínicos periodontais, resistina e IL-1β no fluido crevicular gengival (FCG), mas não para a adiponectina, leptina, TNF-α, IL-6 e IL-8. Não existem evidências até o momento para efeitos da obesidade sobre a resposta ao tratamento da periodontite, e para benefícios da cirurgia bariátrica para os tecidos periodontais (Capítulo 3, dados não publicados).

Entendemos que a divergência de resultados observada entre estudos observacionais e de intervenção pode estar relacionada com a progressão de DCNT ao longo do tempo. No caso de diagnóstico tardio ou não alcance de metas terapêuticas (descompensação), as injúrias em diferentes tecidos e órgãos acumuladas ao longo do tempo podem representar sequelas que não sejam significativamente reversíveis. Neste contexto, o tratamento da periodontite ou da obesidade poderia ser insuficiente para gerar benefícios estatisticamente significativos e de magnitude de efeito clínico relevante. Os resultados desta *umbrela review* refletem o melhor nível de evidência sobre o tema, dão luz às lacunas da literatura e à necessidade de novos estudos para a investigação dos efeitos mútuos da obesidade e da periodontite. Ainda assim, se faz necessário reconhecer as limitações metodológicas existentes nos estudos primários e secundários que subsidiaram esta síntese, uma vez que fatores de confusão como tabagismo, parâmetros e condições sistêmicas, tempo de evolução e gravidade de ambas as doenças devem ser mais bem considerados nas meta-análises e interpretações dos resultados.

Pouco se sabe sobre os benefícios sistêmicos do tratamento periodontal em pacientes com obesidade. A maioria dos estudos investiga os efeitos da obesidade nos tecidos periodontais, mesmo entre os estudos de tratamento da periodontite. Apesar do tratamento periodontal levar à redução da inflamação local e sistêmica em pacientes com periodontite e diabetes (Artese et al., 2015), persistia uma questão: Quais são os benefícios do tratamento periodontal em pacientes com obesidade, considerando índice hematológico e bioquímico do sangue, biomarcadores de inflamação e estresse oxidativo, qualidade de vida e contagem de patógenos periodontais como variáveis? A revisão sistemática que conduzimos sobre o tema reuniu três ensaios clínicos randomizados e dados de efeito pré- pós-tratamento da periodontite reportado em 15 ensaios clínicos. Os achados atuais sugerem a melhora da pressão arterial, níveis séricos de colesterol total,

LDL, triglicerídeos, HbA1c, resistência insulínica, PCR ultra-sensível, IL-1β, TNF-α e C3, níveis de TNF-α, adipocitocinas (quemerina, vaspina, omentina-1, visfatina) e biomarcador de estresse oxidativo (8-OHdG) no FCG, e redução da contagem de *Porphyromonas gingivalis* (*P.g.*), *Aggregatibacter actinomycetemcomitans* (*A.a.*), *Tannerella forsythia* (*T.f.*), *Treponema denticola* (*T.d.*) e *Prevotella intermedia* (*P.i.*) na bolsa periodontal (Capítulo 4, dados não publicados).

Adicionalmente, dadas as limitações metodológicas de estudos secundários sobre os efeitos do tratamento da periodontite em biomarcadores de inflamação sistêmica em pacientes com diabetes, desenvolvemos um estudo de revisão sistemática e meta-análises de ensaios clínicos randomizados sobre esta condição. Nossos resultados demonstraram evidência moderada para efeitos significativos do tratamento da periodontite na redução gradual dos níveis séricos de PCR em pacientes com diabetes tipo 2 que fumam, durante os primeiros seis meses de acompanhamento, mesmo sem o uso de antibióticos. No total, 14 ensaios clínicos foram incluídos no estudo e 18 biomarcadores de inflamação ou estresse oxidativo foram considerados na análise dos dados. Dentre as limitações deste estudo, destacamos o número limitado de trabalhos e a heterogeneidade metodológica (Apêndice 1, dados não publicados).

As DNCT devem ser diagnosticadas e tratadas com brevidade, e biomarcadores basais devem ser estabelecidos para predição de risco dessas doenças (Tonetti et al., 2018; Furman et al., 2019; Sanz et al., 2020).

A PCR ultra-sensível representa um somatório da inflamação sistêmica geral do paciente que pode, em parte, ser influenciada pela periodontite. Embora os biomarcadores inflamatórios devam ser interpretados no contexto clínico e nenhum valor único deva ser usado para determinar ou descartar um diagnóstico específico, a PCR ultra-sensível reflete a carga inflamatória e o risco de impacto sistêmico da periodontite, relacionado ao grau de progressão da doença. Na atual classificação das doenças periodontais, Tonetti et al. (2018) preveem que no futuro será possível vincular o grau de periodontite ao potencial impacto sistêmico da doença, e que biomarcadores devem ser investigados para este fim. Entretanto, de acordo com esses mesmos autores, a avaliação do risco de impacto sistêmico da periodontite com base nos níveis de PCR e biomarcadores ainda carece de evidências específicas.

Assim, desenvolvemos uma *umbrella review* que teve como objetivo sumarizar as evidências sobre o efeito do tratamento da periodontite nos níveis séricos de PCR, considerando as condições/doenças sistêmicas na inclusão e síntese dos dados, a partir de revisões sistemáticas de ensaios clínicos. Reunimos as evidências de três revisões sistemáticas qualitativas e nove estudos de meta-análise. As condições sistêmicas reportadas nas revisões foram as doenças cardiovasculares e história familiar de doenças cardiovasculares, pré-hipertensão e hipertensão arterial, desordens metabólicas, diabetes mellitus, pacientes em hemodiálise e/ou diálise peritoneal, artrite reumatóide e gestantes. Demonstramos neste estudo, que as evidências atuais sugerem a redução dos níveis séricos de PCR após o tratamento da periodontite em pacientes com diabetes tipo 2, pré-hipertensão e hipertensão arterial, e insuficiência renal submetidos a hemodiálise e/ou diálise peritoneal (Capítulo 5, dados não publicados). A melhora de PCR em pacientes com diabetes tipo 2 que receberam tratamento da periodontite foi o único parâmetro inflamatório sistêmico com resultado significativo na nossa meta-análise.

A PCR é uma proteína plasmática de fase aguda sintetizada no fígado, cuja concentração se eleva na presença de processos inflamatórios ou infecciosos. Além de quebrar os nutrientes absorvidos pelo intestino, o fígado remove bactérias e outras substâncias estranhas do sangue que entram na veia porta, desempenhando um importante papel fisiológico na desintoxicação do LPS (Munford, 2005; Meyle e Chapple, 2015). As ulcerações e o aumento do número e extensão dos capilares sanguíneos na superfície interna do sulco gengival ou da bolsa periodontal inflamada, favorecem a endotoxemia (LPS) e a disseminação hematogênica (Bacteremia) de patógenos periodontais (Schwartz et al., 1972; Sconyers et al., 1973; Carroll et al., 1980; Beck et al., 1999; D'Aiuto et al., 2004; Forner et al., 2006).

Segundo Younossi et al., nós estamos apenas começando a compreender os mecanismos de patogênese das doenças hepáticas e a contribuição de fatores ambientais e genéticos para o risco de desenvolver um curso progressivo da doença. Ao mesmo tempo em que se busca estas respostas na Medicina, tem havido um intenso debate sobre periodontite como fator de risco para o início e progressão da NAFLD na Odontologia (Kuraji, et al., 2021), mais uma vez integrando essas duas áreas através da Medicina Periodontal.

É possível que exista uma associação entre a periodontite e NAFLD (Kuraki et al., 2021), e que o fígado exerça um papel na patogênese das doenças periodontais além da síntese de PCR. A teoria chamada de hipótese “multiple-hit” envolve uma série de fatores que podem atuar paralelamente na patogênese da NAFLD (Nakajima et al., 2015; Friedman et al., 2018). Em uma revisão publicada recentemente, Kuraji et al. (2021) descrevem que mais pesquisas são necessárias para elucidar o mecanismo pelo qual patógenos periodontais, LPS e mediadores pró-inflamatórios translocam para o fígado, e o papel preciso da doença periodontal na patogênese da NAFLD. Segundo os autores, poucos trabalhos até o momento abordaram a relação entre as doenças periodontais e os órgãos do sistema digestivo.

Nós estabelecemos uma hipótese conceitual de que a translocação hematogênica de patógenos periodontais e suas toxinas podem influenciar a saúde hepática e os níveis séricos de PCR, e reunimos as evidências disponíveis a esse respeito em uma revisão de escopo. Descrevemos as anormalidades hepáticas reportadas neste contexto, descrevemos casos clínicos de patologias hepáticas que foram associadas à bacteremia e infectadas localmente por patógenos bucais, realizamos uma síntese destes dados, e propomos um modelo de plausibilidade biológica que descreve os mecanismos de patogênese envolvidos (Capítulo 6, dados não publicados).

Os estudos experimentais evidenciaram efeitos diretos de patógenos periodontais na patogênese da NAFLD. Patógenos vivos e seus fatores de virulência, especialmente LPS, foram associados às anormalidades hepáticas, esteatose hepática não alcoólica (NAFL) e esteatohepatite não alcoólica (NASH). Aa análises histológicas de NAFL demonstraram a presença de necroinflamação, dano hepatocelular e progressão mais rápida da fibrose hepática associados à endotoxemia por LPS e bacteremia por *P.g.*, *A.a.* e *Chlamydia pneumoniae* (*C.p.*) (Tomofuji et al., 2007; Hyvärinen, 2009; Furusho et al., 2013; Fujita et al., 2018; Sasaki et al., 2018; Nagasaki et al., 2020,2021; Yamazaki et al., 2021). O grau de fibrose foi progressivamente exacerbado com o aumento da carga bacteriana (*P.g.* e *P.i.*) (Yamazaki et al., 2021).

O estresse oxidativo no fígado e no sangue foi associado à endotoxemia por LPS (Tomofuji et al., 2007) e bacteremia por *P.g.* e *P.i.* (Yamazaki et al., 2021). Os genes pró-inflamatórios também foram expressos em fígados expostos à endotoxemia e bacteremia (Yamazaki et al., 2021), aumentando os níveis de TNF-α, TGF-β1, IL-1β, IL-6, IL-10,

IL-12, IL-17, IFN-γ , MCP-1 e CD68 (Tomofuji et al., 2007; Hyvärinen et al., 2009; Furusho et al., 2013; Velusamy et al., 2014; Fujita et al., 2018; Sasaki et al., 2018; Nagasaki et al., 2020,2021). Este perfil inflamatório parece estar associado ao aumento de NAS na infecção odontogênica por *P.g.* (Fujita et al., 2018; Nagasaki et al., 2021). Os níveis séricos de PCR e *Saa* (Hyvärinen, 2009) foram significativamente aumentados por LPS (Tomofuji et al., 2007) e bacteremia, onde *A.a.* (Velusamy et al., 2014) e *C.p.* foram translocadas até o fígado (Hyvärinen, 2009).

Os modelos de infecção por patógenos periodontais através de gavagem não resultaram em periodontite, porém, a bacteremia foi confirmada em todos esses estudos seja no sangue ou no fígado. Nakajima et al. (2015) demonstraram um impacto significativo da administração de *P.g.* na composição e diversidade da microbiota hepática, e Yamazaki et al. (2020) descreveram perfis de expressão gênica no fígado relacionados à inflamação e metabolismo lipídico, estimulados por *Fusobacterium nucleatum* (*F.n.*).

A administração de *P.g.* e *P.i.* induziu alterações adicionais e substanciais à esteatose hepática induzida por dieta hipercalórica no perfil de expressão de genes relacionados à biossíntese e processos metabólicos, processo do ciclo celular potencialmente implicado na carcinogênese e NAFLD em estágio final, genes supressores de tumor, respostas a reações oxidativas e estresse do retículo endoplasmático, regulação intrínseca de apoptose, resposta inflamatória, resposta ao LPS, entre outros. Nestes estudos, a interseção entre a bacteremia e as anormalidades hepáticas envolveu o eixo boca-intestino-fígado, onde a microbiota intestinal, a exposição à dieta rica em gordura e o desafio microbiano superaram a capacidade adaptativa do fígado (Arimatsu et al., 2014; Nakajima et al., 2015; Sasaki et al., 2018; Yamazaki et al., 2021; Albuquerque-Souza e Sahingur, 2022; Wang et al., 2022).

No início do nosso estudo, pensamos nos efeitos diretos da bacteremia por patógenos periodontais no fígado, através da disseminação hematogênica apenas. Os resultados da nossa revisão de escopo demonstram que isso é de fato possível e esse é o modelo mais estudado, porém, a translocação de patógenos periodontais até esse órgão também foi reportada a partir do intestino. De fato, o conceito de eixo intestino-fígado e disbiose intestinal tem sido proposto como outra via potencial ligando a cavidade bucal

ao o fígado em um *crosstalk* bidirecional (Arimatsu et al., 2014; Nakajima et al., 2015; Albuquerque-Souza e Sahingur, 2022).

Os registros clínicos dos casos reportados na de NAFLD associada à bacteremia a partir de periodontite, incluídos na revisão de escopo, também foram sumarizados em uma figura, informando os principais achados. Omura et al. (2016) relataram um caso fatal de cirrose relacionada à NASH associada à sepse em uma mulher de 54 anos com obesidade (IMC: 48,5kg/m2). As análises de biópsias feitas durante a autópsia revelaram anormalidades consistentes com cirrose induzida por NASH, e imunocolocalização de *P.g.* nos hepatócitos. Os autores relacionaram o caso à periodontite grave com aparente tendência ao sangramento, pois nenhuma outra causa foi identificada. Outros cinco casos relataram bacteremia por patógenos bucais em pacientes com periodontite como causa de abscesso hepático piogênico. Apesar dos estudos de caso não apresentarem força de evidência suficiente para afirmar uma relação de causalidade, a identificação de patógenos periodontais no fígado destes pacientes sugere que a bacteremia associada à periodontite pode alcançar este órgão e ser identificado em condições patológicas.

Na meta-análise de Chan et al. (2022), os reportaram uma prevalência de 38,77% (IC95% = 32,94-44,95) de MAFLD em uma amostra de 3.320.108 indivíduos. Destes, 5,37% (IC95% = 4,36-6,59) eram magros, e 29,78% (IC95% = 26,06-33,79) não-obesos, e complicações metabólicas como hipertensão e diabetes foram considerados fatores significativamente associados à MAFLD nestes pacientes. Apesar da NAFLD ser considerada um problema de saúde pública intimamente ligado às epidemias de obesidade e diabetes *mellitus* tipo 2 (Cusi et al., 2022), indivíduos magros e não obesos também apresentam alterações hepáticas (*the so-called non-obese* NAFLD). Neste contexto, tomando como referência os resultados da nossa revisão de escopo, acreditamos ser possível que alguns casos de NAFLD sem condição ou fator de risco evidente para esta condição, possam estar associadas à periodontite e efeitos diretos de patógenos ou seus fatores de virulência no fígado por disseminação hematogênica ou pelo eixo boca-intestino-fígado.

Em 2017, Kumar publicou uma revisão com o objetivo de examinar a força das evidências atuais no estabelecimento de uma ligação causal entre patobiontes orais e doenças sistêmicas. Neste trabalho intitulado *From focal sepsis to periodontal medicine: a century of exploring the role of the oral microbiome in systemic disease*, a autora afirma

que embora várias linhas de evidência estejam surgindo e sugerindo que a periodontite pode estar ligada a certas doenças, há pouca evidência neste momento de que as bactérias da boca ou vias bacterianas desempenhem um papel em todas essas ligações. No entanto, as associações sistêmicas da periodontite podem, em parte, ser causais, mas a potencial conexão de causa e efeito entre periodontite e comorbidades é corroborada por estudos em modelos pré-clínicos de doença, que também fornecem *insights* mecanicistas sobre essas associações (Hajishengallis, 2022). As observações feitas por Hajishengallis (2022) e Kumar (2017), somadas às referências que descrevem a necessidade de mais estudos sobre os pontos que abordamos, demonstram a importância dos resultados apresentados nesta Tese, apesar das limitações que todo estudo apresenta.

A presente tese i) sugere a COVID-19 como um fator de confundimento a ser considerado nas pesquisas em Medicina Periodontal; ii) descreve os principais eventos biológicos envolvidos na relação entre obesidade e periodontite; iii) demonstra a existência de evidências científicas para a associação entre obesidade e parâmetros clínicos periodontais, resistina e IL-1β no FCG, iv) e que a o tratamento da periodontite pode resultar em melhora da pressão arterial, níveis séricos de colesterol total, LDL, triglicerídeos, HbA1c, resistência insulínica, PCR ultra-sensível, IL-1β, TNF-α e C3, níveis de TNF-α, adipocitocinas (quemerina, vaspina, omentina-1, visfatina) e biomarcador de estresse oxidativo (8-OHdG) no FCG, e reduzir da contagem de *P.g.*, *A.a.*, *T.f.*, *T.d.* e *P.i.* na bolsa periodontal; v) reúne evidências atuais que confirmam a redução dos níveis séricos de PCR após o tratamento da periodontite em pacientes com diabetes tipo 2, pré-hipertensão e hipertensão arterial, e insuficiência renal submetidos a hemodiálise e/ou diálise peritoneal; e vi) propõe uma hipótese conceitual com fortes evidências experimentais de que a translocação de patógenos periodontais e suas toxinas por disseminação hematogênica ou via eixo boca-intestino-fígado podem estar associadas à patogênese de NAFLD e aumento dos níveis de PCR, tanto na NAFL quanto em NASH.

CONCLUSÃO

A partir da síntese dos capítulos que compõem esta Tese, foi possível conclur que a obesidade e a avaliação hepática devem ser consideradas em novas pesquisas e na prática clínica em Medicina Periodontal, tanto pela evidência de associação entre a obesidade e periodontite, quanto pelas injúrias hepáticas por efeito direto de patógenos periodontais e LPS observadas em modelos experimentais *in vivo*. A evidência de associação entre a periodontite e níveis séricos de PCR em algumas DCNT reforça a importância deste biomarcador para avaliação de impacto sistêmico da periodontite, e os efeitos da COVID-19 na patogênese das doenças periodontais e sistêmicas devem ser considerados.

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APÉNDICES

Periodontitis-therapy for systemic improvement of inflammation and oxidative stress biomarkers in patients with type 2 diabetes mellitus: A systematic review and meta-analysis of randomized controlled trials

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ABSTRACT

Background. Hyperglycemia, immune system dysregulation, changes in cytokine levels and oxidative stress are central to the pathogenesis of both diseases, although evidence on the systemic impacts of periodontitis in patients with diabetes is still limited. This systematic review aimed to evaluate the impact of periodontal therapy on systemic biomarkers of inflammation and oxidative stress in patients with type 2 diabetes mellitus and periodontitis.

Types of studies reviewed. The authors included randomized controlled trials comparing periodontitis-therapy and absence of subgingival instrumentation. Pairs of reviewers independently conducted the selection of studies from six databases, gray literature, manual search and contact of experts until August 2021, data extraction, risk of bias and certainty of evidence using RoB2 and GRADE, respectively.

Results. Of 1,062 records screened, the authors determined that 14 studies enrolling 1223 participants proved eligible. Moderate-quality evidence suggested a positive effect of

periodontitis-therapy on serum levels of c-reactive protein [0.39 (CI 95% 0.27 to 0.5)], even without the use of antibiotics [0.34 (CI 95% 0.22 to 0.46)], in patients with type 2 diabetes mellitus. The significant reduction in c-reactive protein in smokers in favor of periodontitis-therapy was greatest at six months of follow-up.

Conclusions and Practical implications. Available evidence suggests that non-surgical periodontal therapy with or without antibiotics as an adjunct to scaling and root planing affects short-term biomarkers of systemic inflammation in patients with type 2 diabetes mellitus, with moderate evidence of improvement in serum hs-CRP levels.

Protocol record: PROSPERO [CRD42020206295].

Key Words. Diabetes mellitus; periodontitis; therapy [Subheading]; root planning; systematic review [Publication Type]; meta-analysis [Publication Type].

INTRODUCTION

The worldwide epidemic of type 2 diabetes mellitus (T2DM) is one of the main causes of disability and premature mortality.[1] The pro-inflammatory state affects glycemic control and is implicated in the main complications of T2DM, such as atherosclerosis, chronic kidney disease, peripheral vascular problems and periodontitis.[2] According to Löe (1993)[3] periodontitis is the sixth complication of diabetes mellitus. Periodontitis is a dysbiotic biofilm-induced chronic inflammatory disease that affects the supporting structures of the teeth and impacts systemic health.[4] Microbial dysbiosis and systemic inflammatory burden in patients with periodontitis have been associated with an increased risk of potentially fatal chronic diseases, including diabetes, cardiovascular disease, and kidney failure.[5]

Although the biological mechanism of the association between T2DM and periodontitis is still unclear, previous investigations have shown that hyperglycemia caused by the DM, dysregulation of the immune system, changes in cytokine levels and oxidative stress are central to the pathogenesis of both diseases, exerting bidirectional effects.[6-8]

Animal and clinical studies have found elevated levels of interleukin- (IL-) 1β, tumor necrosis factor-alpha (TNF-α), IL-6, RANKL/OPG and oxygen metabolites in the gingival tissue of individuals with poorly controlled T2DM. Furthermore, elevated levels of IL-1β, IL-2, IL-6, IL-7, IL-8, IL-12, IL-17, IL-21, IL-23, interferon gamma (IFN-γ), TNF-α, macrophage inflammatory protein-1alpha (MIP-1α), granulocyte macrophage-CSF (GM-CSF), c-reactive

protein and oxidative stress mediators in the serum of individuals with T2DM and periodontitis have been reported in the literature. Periodontal therapy is expected to reduce the levels of these systemic biomarkers, improve metabolic control and reduce the risk of systemic complications in individuals with T2DM.[7,9]

To date, there is no robust evidence on the impact of periodontitis combined with hyperglycemia and/or smoking on systemic inflammatory state, nor the effect of periodontal therapy.[10-15] Therefore, the aim of this systematic review was to investigate the effects of periodontal therapy on systemic biomarkers of inflammation and oxidative stress in patients with T2DM and periodontitis.

METHODS

***Protocol and Registration*.** This study was conducted according to The Enhancing the QUAlity and Transparency Of health Research (EQUATOR network) recommendations, including the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA 2020);[16] The review protocol was registered in the PROSPERO database (http://www.crd.york.ac.uk/PROSPERO) under the number CRD42020206295.

***Focused question*.** Based on the PICOs principle—the Population: patients with T2DM and periodontitis; the Intervention: periodontal therapy with subgingival approach; the appropriate Control (or comparator): non-periodontal therapy or periodontal therapy without subgingival approach; the Outcomes of interest and the Study design: systemic parameters related to inflammation or oxidative stress in biological samples of serum, saliva and gingival crevicular fluid in randomized controlled trials (RCT)—the following focused question was proposed: What are the effects of periodontal therapy on systemic biomarkers of inflammation and oxidative stress in patients with type 2 diabetes mellitus and periodontitis?

***Types of periodontal interventions*.** We did not restrict the search by type of periodontal therapy. Periodontal interventions were based on scaling and root planning (SRP) sections (i.e, non-surgical periodontal therapy), one-stage/intensive full mouth SRP, full-mouth disinfection and surgical procedures (e.g, periodontal flap surgery), for supra- and subgingival biofilm and calculus removal [Intervention (I)]. Mechanical therapy plus local or systemic drug use (i.e, antimicrobial, anti-inflammatory or others), or associated with photodynamic therapy/laser therapy, were also included. Periodontal interventions in patients with T2DM were compared with the passive option [control (C)]: without periodontal treatment or supragingival approach alone.

Study selection criteria

1. Inclusion criteria: i- RCT; and ii- studies that evaluated the systemic effect of therapeutic interventions for periodontitis in patients with T2DM on parameters related to inflammation or oxidative stress in samples of serum, saliva and gingival crevicular fluid.
2. Exclusion criteria: i- trials in which no confirmation or diagnosis criteria for T2DM and/or periodontitis were not reported and could not be retrieved after contacting the original authors; ii- trials in which outcomes of interest were not available for analysis and the original values could not be retrieved after contacting the original authors; and iii- unavailability of full paper copy.
3. No data or language restrictions were applied.

The retrieved articles were exported to rayyan™ reference manager (https://www.rayyan.ai) and duplicates were removed by the program and manually. Authors of studies that were not retrieved in full text were contacted by e-mail up to five attempts. The selection process was conducted in two phases: Phase 1, two researchers (NSN, DSB) independently examined the titles and abstracts of all identified references, applying the including process (blind process); and Phase 2, the same two reviewers independently applied the exclusion criteria to the other studies, based on reading the full text (blind process). Inter-reviewer reliability in the study selection process was determined by the Cohen κ test, assuming an acceptable threshold value of 0.8.[17] The disagreement at any stage was resolved by discussion and mutual decision (consensus meeting) with a third reviewer (CS). The final decision/selection was always based on reading the full text of the publication.

***Search Strategy*.** Search strategies were customized for each database from the MeSH terms, entry terms and free keywords used for PubMed, Web of Science, Cochrane Library, other sources (gray literature), protocol registration databases, and manual search. We considered DeCS/MeSH terms, Emtree terms and Index terms for electronic searches in LILACS, Embase and Scopus databases. All terms were combined by the Boolean operators "OR" and "AND", without applying filters from the databases: ((diabetes mellitus, type 2 OR diabetes mellitus) AND (periodontal diseases OR periodontitis)) AND (periodontal debridement OR subgingival curettage OR dental scaling OR root planing OR dental prophylaxis OR debridement* OR curettage* OR scaling OR periodontal therapy OR periodontal treatment OR planing* OR scaling and root planing OR full-mouth therapy) AND (inflammatory markers OR acute-phase proteins OR intercellular signaling peptides and proteins OR oxidative stress). The electronic search was be performed in August 2021. Databases alerts were created to identify studies published after the time of the search, until the manuscript submission process.

Searches were performed in the MEDLINE using the PubMed search engine (http://www.ncbi.nlm.nih.gov/sites/pubmed), Web of Science (https://www.webofknowledge.com) accessed through the Clarivate Analytics (https://clarivate.com), Cochrane Library (https://www.cochranelibrary.com), Embase (https://www.embase.com) through Elsevier (https://www.elsevier.com), Scopus (http://www.scopus.com) and LILACS via VHL (https://bvsalud.org). Other sources _ gray literature _ were consulted through Google Scholar (https://scholar.google.com.br) and System for Information on Grey Literature in Europe (SIGLE) through OpenGrey (www.opengrey.eu) databases. The protocol registration databases included PROSPERO (https://www.crd.york.ac.uk/prospero/) and Open Science Framework – OSF (https://osf.io/). Hand-searches were also performed in specialized periodicals (*Journal of Clinical Periodontology; Journal of Dental Research; The Journal of The American Dental Association; Journal of Periodontology; Journal of Periodontal Research; Periodontology 2000; The International Journal of Periodontics & Restorative Dentistry; Journal of Applied Oral Science; Journal of Periodontal & Implant Science; Journal of Oral Pathology & Medicine;* and *Oral Surgery, Oral Medicine, Oral Pathology and Oral Radiology*), and in reference lists of selected articles. To keep the search strategy updated, alerts were established for each database. Experts were identified using expertscape.com (https://expertscape.com) and contacted for other data sources.

Data extraction and data synthesis. Data were independently extracted by the three reviewers (NSN, DSB, CS [blinded process]) using a standardized sheet, as recommended by the Cochrane Collaboration's handbook for systematic review.[18] From the selected articles the following data were extracted: A) descriptive data on medical condition (study, eligibility criteria, participants, diagnostic criteria for T2DM, and object of investigation); B) descriptive data on periodontal diagnosis, therapy and evaluation [study, diagnostic criteria for periodontitis, intervention group (periodontal therapy), comparative group, supportive periodontal care, and follow-up]; C) quantitative parameters evaluated in serum samples; and D) quantitative parameters evaluated in plasma samples. Extracted data were presented in tables in the order of the PICO strategy, and qualitative synthesis were presented in the form of text and figure. Longitudinal data from groups with subgingival debridement at periodontal support visits were described but not considered in the analyses.

Quantitative measures were described as absolute frequency and mean ± standard deviation or median [inferior quartile (25 %) and superior quartile (75 %)] interquartile range. Biomarker measurements were stratified by sample origin and standardized to a single unit of measure per biomarker. Longitudinal data were analyzed considering the mean difference ±

standard deviation between each follow-up and the initial measurements (Δ, follow-up periods minus baseline). When not available, the differences between the standard deviations were estimated using the formula: $\sigma BV = \sqrt[2]{(\sigma Control^2 + \sigma Test^2) - (2.R.\sigma Control.\sigma Test)}$.

In cases of missing data or data available only in graphs, the corresponding authors were contacted via e-mail and/or social media. Data available only in graphs were extracted by the digital program WebPlotDigitizer™ version 4.4 (https://automeris.io/WebPlotDigitizer/), if necessary.

Summary measures and synthesis of the results. Standard paired meta-analyses of direct comparisons were performed using inverse variance and a fixed effects model. Effect measures were presented as mean difference and 95% relative confidence interval of the variations of each biomarker between baseline and follow-up periods. Heterogeneity was assessed by using the Chi square (χ^2) based Q-statistic method [if homogeneous studies, the null hypothesis is confirmed at the 10% significance level ($p \geq 0.1$)] and inconsistency measurement (I^2); the value of I^2 ranged 0 to 100, with larger values (≥ 75%) suggesting high heterogeneity.[19] Meta-analyses with χ^2 p-value < 0.1 and $I^2 \geq 75\%$ were discarded. Meta-analysis was performed using RevMan™ 5.4 software (Review Manager, version 5.4, Nordic Cochrane Centre, Cochrane Collaboration, September 2020) and exported as forest plots and funnel plots. The presence of publication bias was also investigated for the outcomes of interest based on visual detection/analysis of the funnel plot.

Analysis of subgroups or subsets. The effects of periodontal therapy on biomarkers of inflammation and oxidative stress were stratified by smoking and the use of antibiotic adjuvant to NSPT for TNF-α at three months follow-up and hs-CRP at three and six months follow-up.

Risk of bias and quality assessment. The Revised Cochrane risk-of-bias tool for randomized trials (RoB2) and Delphi List were used to assess the risk of bias and methodological quality of the RCT, respectively.[20,21] Both tools assess parameters which may be related to effect sizes, which implies a restriction on internal validity. The risk of bias of the studies was classified according to the RoB 2 algorithm into “low risk of bias”, “some concerns” and “high risk of bias”. The answer options used in the 8-points Delphi list were a "Yes"/”Probably yes”/"No"/"Don’t know"/”NA” (NA, not applicable) answer format (descriptive analysis within studies). The studies were independently evaluated by two authors (NSN, DSB), and agreement was reached in a consensual meeting with a third reviewer (CS), as needed (Appendix 1 and 2, respectively).

Grading the body of evidence. Furthermore, the quality of responses in this systematic review was accessed through the Grading of Recommendations Assessment, Development and Evaluation (GRADE) system. The system classifies the quality of evidence into high, moderate, low and very low, according to factors that consider study design, risk of bias in reported outcomes, inconsistency of outcomes among studies, indirectness of reported outcomes, imprecision of reported outcomes and potential publication bias. The strength of the recommendation is graded into strong or weak.[22,23]. The studies were independently evaluated by two authors (NSN, DSB), and agreement was reached in a consensual meeting with a third reviewer (CS), as needed. Three different strength of evidence were considered:

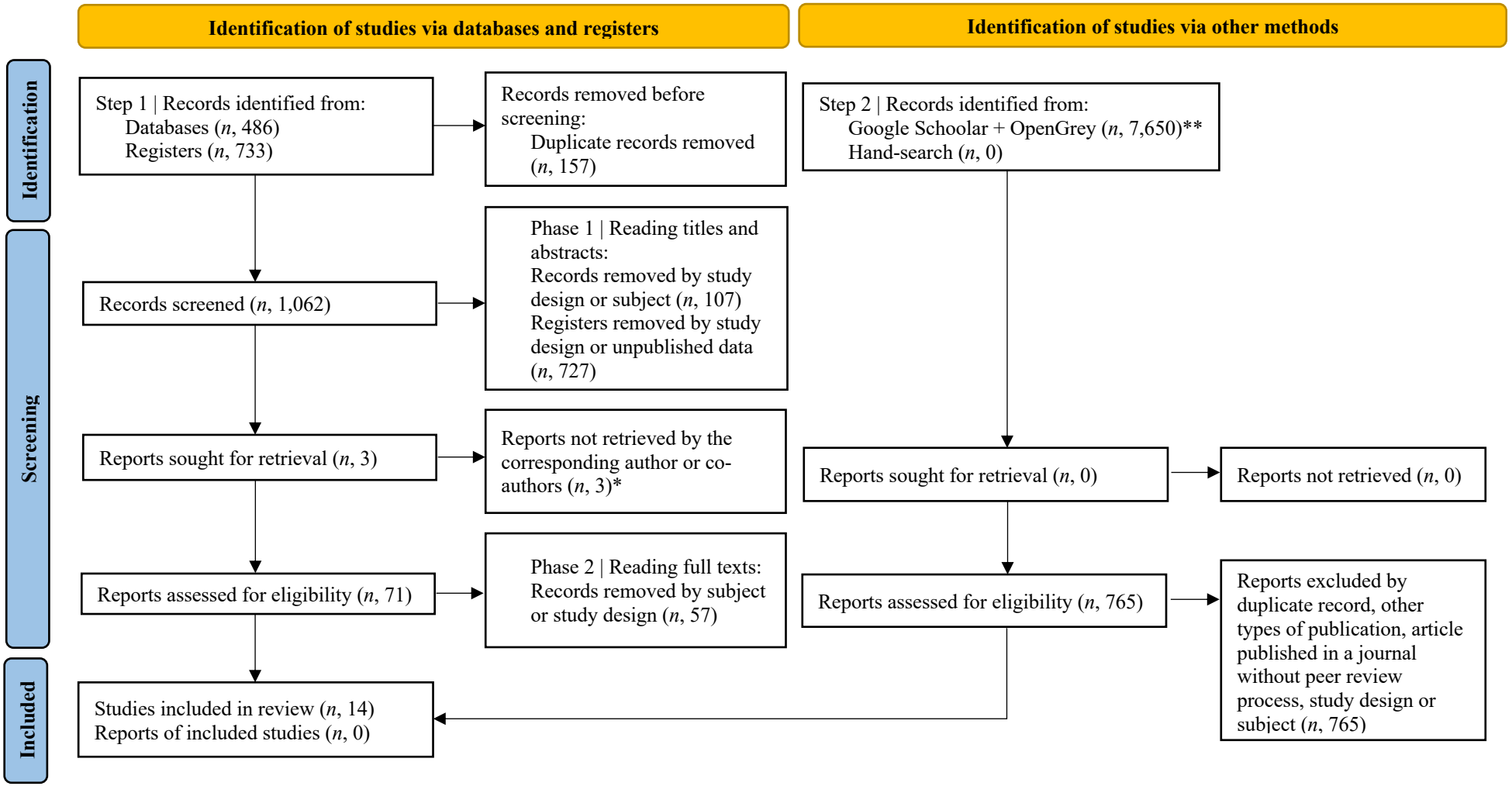
- High: "The authors have a lot of confidence that the true effect is similar to the estimated effect".
- Moderate: "The authors believe that the true effect is probably close to the estimated effect".
- Low: "The true effect might be markedly different from the estimated effect".
- Very low: "The true effect is probably markedly different from the estimated effect".

Grade of recommendation considered recommendation to do [I, strong (benefits >>> risk & burdens; IIa, moderate (benefits >> risk & burdens); and IIb weak (weak)] and recommendation not to do [III (no benefit / potentially harm)].

RESULTS

Study selection. One thousand sixty-two abstracts and articles were found in the databases and registers; seven hundred and sixty-five results from other sources were also evaluated. After checking the titles and abstracts, only 71 articles potentially qualified. Fifty-seven articles were excluded by subject or study design (Figure 1). Fourteen studies enrolling 1,223 participants were finally selected[24-37] and nine data sets were included in the meta-analyses.[26-30,32,34,35,37] The kappa coefficients for the agreement in study selection between the two reviewers (NSN, DDB) were ≥ 0.9 for all databases.

FIGURE 1. Article screening process depicted in the PRISMA Flow Diagram



From: Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ 2021;372:n71. doi: 10.1136/bmj.n71. For more information, visit: http://www.prisma-statement.org/

Legend: *, studies were not excluded, as data available only in graphics were extracted by the WebPlotDigitizer version 4.4 program; **, the first 10 % of Google Schoolar search results were accessed for the eligibility criteria.

TABLE 1

Design and quality analysis of primary studies

Study	Participants	Periodontal therapy	Comparative group	Supportive periodontal care	Follow-up	Object of investigation	RoB2 risk-of-bias	Delphi methodological quality
Mizuno et al., 2017	Periodontitis + Type 2 DM	NSPT	OHI + Supra-gingival plaque/calculus removal	Yes	3 and 6 months after the baseline visit	Serum: oxidative stress balance (oxidative index) and hs-CRP	Low	Yes
Wang et al., 2017	Periodontitis + Type 2 DM	NSPT	No intervention	NR	3 months after the baseline visit	Serum: IL-6, TNF-α, APN and FGF-21	Low	Yes
Geisinger et al., 2016	Periodontitis + Type 2 DM	NSPT	NR	Yes	3 and 6 months after the baseline visit	Serum: IL-6, IL-10, TNF-α and sE-selectin Plasma: IL-8, hs-CRP and sICAM-1	Low	Yes
Kapellas et al., 2016	Periodontitis + Type 2 DM	NSPT	OHI	Unclear	3 months after the baseline visit	Serum: hs-CRP Plasma: IL-6	Low	Yes
Artese et al., 2015a	Periodontitis + Type 2 DM	NSPT	OHI + Supra-gingival plaque/calculus removal	Yes	6 months after the baseline visit	Serum: IL-6, IL-8, IL-17, TNF-α and MCP-1	Low	Yes
Kumar et al., 2015	Chronic generalized periodontitis + Type 2 DM	NSPT + Doxycycline	No intervention	Yes	3 months after the baseline visit	Serum: TNF-α	Low	Yes

Wu et al., 2015	Periodontitis + Type 2 DM	NSPT	OHI	Yes	3 and 6 months after the baseline visit	Serum: visfatin GCF: visfatin	Low	Yes
Raman et al., 2014	Moderate to advanced chronic periodontitis + Type 2 DM	NSPT + 0.12 % Chlorhexidine mouthrinse	OHI	NR	Baseline, 2 months and 3 months 15 ml of venous blood was collected from each patient at baseline, prior to treatment and at 3 months after assigned treatments (levels of HbA1c and hs-CRP were assessed)	Serum: hs-CRP	Low	Yes
Bharti et al., 2013	Mild to moderate periodontitis + Type 2 DM	NSPT + Minocycline topic	No intervention	Yes	Baseline, 2 months and 6 months	Serum: IL-6, TNF-α, hs-CRP, APN, leptin and resistin	Low	Yes
Chen et al., 2012	Chronic periodontitis + Type 2 DM	NSPT	No intervention	Yes	1.5, 3 and 6 months after completion of the initial periodontal therapy	Serum: TNF-α and hs-CRP	Low	Yes
Koromantzos et al., 2012	Periodontitis + Type 2 DM	NSPT	OHI + Supra-gingival plaque/calculus removal	Yes	1, 3 and 6 months after the baseline visit	Plasma: hs-CRP, MMP-2, MMP-9 and OxS marker *d*-8-iso	Low	Yes
Sun et al., 2011	Periodontitis + Type 2 DM	NSPT + Tinidazole and Ampicillin	NR	NR	3 months after the baseline visit	Serum: IL-6, TNF-α and hs-CRP	Low	Yes
Sun et al., 2010	Periodontitis + Type 2 DM	NSPT + Tinidazole and Ampicillin	NR	NR	3 months after the baseline visit	Serum: IL-6, TNF-α, hs-CRP and APN	Low	Yes

Katagiri et al., 2009	Mild to severe periodontitis + Type 2 DM	NSPT + Minocycline topic	OHI	Yes	1, 3 and 6 months after the baseline visit	Serum: hs-CRP	Low	Yes

Legend: DM, diabetes mellitus; NSPT, non-surgical periodontal therapy; NR, not reported; ICAM, intercellular cell adhesion molecule; VCAM, vascular cell adhesion molecule, TNF-a, tumor necrosis factor-alpha, IL-, interleukin-; MMP-, matrix metalloproteinase-; FGF-21, fibroblast growth factor-21; MCP-1, monocyte chemoattractant protein-1; APN, apolipoprotein; hs-CRP, high sensitivity-C-reactive protein.

Study characteristics. All selected studies were RCT and included ≥ 18 years old patients with T2DM (HbA1c 5.8 to 11%) and moderate/severe periodontitis. All studies tested NSPT versus non-periodontal therapy or periodontal therapy without subgingival approach. Four and three out of fourteen studies had included smokers[27,28,36,37] and alcohol consumption,[27,36,37] respectively; whereas the rest of the selected articles either did not include smokers or did not mention in the study.[24-26,29-35] Sun et al. (2010, 2011)[25,26] and Kumar et al. (2015)[32] used systemic antibiotics adjuvant to NSPT (doxycycline and tinidazole + ampicillin, respectively). Furthermore, Katagiri et al. (2009)[24] and Bharti et al. (2013)[29] used topical administration of minocycline during subgingival SRP—Table 1 and Appendix 3 and 4.

All RCT studies reported improvement in clinical parameters after periodontal therapy at one month,[24,28] one and a half month,[27] two months,[29,30] three months[24-28,30,32-37], and six months follow-up.[24,27-29,31,33,35,36] Only Kapellas et al. (2016)[34] reported no improvement in PPD and CAL, despite improvement in GBI; this study included aboriginal Australian participants with fewer remaining teeth, periodontal evaluation at four sites on each tooth excluding third molars using a PCP2 periodontal probe, and reported no clear supportive periodontal care (Appendix 5).

Biomarkers of inflammation and oxidative stress were evaluated in serum [E-selectin, intercellular cell adhesion molecule (ICAM), vascular cell adhesion molecule (VCAM), TNF-α, IL-6, IL-8, IL-10, IL-17, matrix metalloproteinase 2 (MMP-2), MMP-9, fibroblast growth factor-21 (FGF-21), monocyte chemoattractant protein-1 (MCP-1), apolipoprotein (APN), visfatin, leptin, resistin, OxS marker *d*-8-iso, oxidative index and high sensitivity-C-reactive protein (hs-CRP)], plasma (ICAM, IL-6, IL-8 and hs-CRP) and gingival crevicular fluid (visfatin) for up to six months of follow-up (post-NSPT) —Appendix 6. The included studies reported two or more clinical periodontal parameters, including visible plaque index (VPI), gingival bleeding index (GBI), periodontal probing depth (PPD), clinical attachment level/loss (CAL), and bleeding on probing (BOP) (Table 1, Appendix 4 and 5). All selected patients had chronic periodontitis, but the extent and severity of the disease were not consistent.

Quality assessment and heterogeneity evaluation. The evidence level of each study following the RoB2 (Appendix 1) and Delphi list (Appendix 2) tools revealed a low risk of bias and a methodological quality of the primary studies. The kappa coefficients for the agreement in these two assessments between the two reviewers (N.S.N, D.S.B) were > 0.9.

Methodological heterogeneity was mainly related to the use of antibiotics adjuvant to NSPT[24-26,29,32] and the inclusion of smokers[27,28,36,37] and alcohol consumption[27,36,37] in the eligibility criteria of the included RCT (Table 1, and Appendix 3). Koromantzos et al. (2015)[28]

and Mizuno et al. (2017)[36] did not describe the absence of significant systemic effects of periodontal therapy on matrix metalloproteinases or oxidative parameters (Appendix 6 and 7).

Five out of twelve data sets considered for meta-analyses and subgroup analyses had considerable heterogeneity (Figure 2A, C, E, J and K). There was no statistical heterogeneity (χ^2 p-value ≥ 0.1 and $I^2 < 75\%$) for: i- three months follow-up – TNF-α [subset analysis (antibiotic + smokers)], hs-CRP [pooled meta-analysis (no antibiotic + antibiotic + non-smokers + smokers)], hs-CRP [subset analysis (no antibiotic + non-smoker + smokers)], hs-CRP [subset analysis (no antibiotic + non-smokers)] and hs-CRP [subset analysis (no antibiotic + smokers)]; and ii- six months follow-up – IL-6 [meta-analysis (no antibiotic + non-smokers)] and hs-CRP [subset analysis (no antibiotic + smokers)] (Figure 2B, D, F, G, H, I, L, respectively).

Synthesis of results

Qualitative analysis. According to data from primary studies, NSPT reduced serum levels of E-selectin,[35] TNF-α,[26] IL-6,[26] and visfatin[33] six months after treatment. Sun et al. (2011),[26] Raman et al. (2014)[30] and Kapellas et al. (2016)[34] reported a reduction in serum levels of hs-CRP at the three months follow-up. Instead, some authors reported an increase in serum levels of VCAM,[35] APN[29] and hs-CRP[35] six months after NSPT, and an increase in serum levels of FGF-21 three months after NSPT.[37] Geisinger et al. (2016)[35] reported no difference between CG and IG for TNF-α and Bharti et al. (2013)[29] reported no difference between CG and IG for IL-6, hs-CRP, APN, leptin and resistin in the serum six months after NSPT. The effects of periodontal treatment on serum levels of TNF-α and hs-CRP were greater in the studies using antibiotics as an adjuvant to NSPT[27,32] and in smokers[27,37] (Appendix 6).

There was no benefit of periodontitis treatment for plasma levels of ICAM, IL-6 and IL-8 and hs-CRP (Appendix 7).

Visfatin levels in gingival crevicular fluid of CG varied over time:[33] i- baseline (83.5 ng/mL ± 37.02); ii- three months follow-up [74.97ng/mL ± 37.92 (Δ, -8.62ng/mL ± 37.48)]; and iii- six months follow-up [79.92ng/mL ± 38.3 (Δ, -3.67ng/mL ± 37.68)]. The authors described a reduction in visfatin in the gingival crevicular fluid after NSPT: i- baseline (80.65 ± 36.17); ii- three months follow-up [26.55 ± 18.67 ng/mL (Δ, -54.1ng/mL ± 31.33)]; and iii- six months follow-up [29.3ng/mL ± 19.69 (Δ, -51.35ng/mL ± 31.37)].

Meta-analysis. Pooled difference of hs-CRP between baseline and three months follow-up pointed out a significant benefit of periodontal therapy [mean treatment effect, 0.39 (CI 95% 0.27 to 0.5); Figure 2F], even without the use of antibiotics [mean treatment effect, 0.34 (CI 95%

0.22 to 0.46); Figure 2G]. The meta-analysis suggested the absence of a late effect of NSPT with or without adjuvant antibiotic for IL-6 in non-smoking patients; however, this result was not significant [mean treatment effect, -0.04 (CI 95% -0.37 to 0.3); Figure 2D].

Subgroup analysis. Serum hs-CRP levels decreased after NSPT in smokers and this effect was greater at six months of follow-up [mean treatment effect, 1.14 (CI 95% 1.03 to 1.26); Figure 2L] than at three months of follow-up [mean treatment effect, 0.34 (CI 95% 0.22 to 0.46); Figure 2I]. Although the improvement in hs-CRP three months after NSPT was greater in non-smoking patients (Figure 2H) compared to smokers (Figure 2I), the sample size and standard deviation seem to have limited the statistical significance of the result [mean treatment effect, 0.96 (CI 95% -2.12 to 4.05); Figure 2H].

There was an important reduction in TNF-α three months after NSPT, but this result was not significant [mean treatment effect, 3.37 (CI 95% -0.46 to 7.19); Figure 2B].

Publication bias. The funnel plots generally demonstrated symmetric distribution of the data sets. Due to the limited number of included studies, publication bias could not be completely ruled out (Figure 2).

Quality of evidence. Based on GRADE guidelines,[22] the effect of periodontal therapy on systemic biomarkers of inflammation and oxidative stress in patients with T2DM and periodontitis showed moderate-quality evidence; there was a strong recommendation to perform periodontal therapy for the outcomes of interest, considering the absence of adverse effects/complications reported in the studies, as well as the need for mechanical periodontal therapy for the treatment of periodontitis and its expected local and systemic benefits.

Occurrence of adverse effects/complications associated with periodontal therapy. None of included studies reported the occurrence of adverse effects/complications.

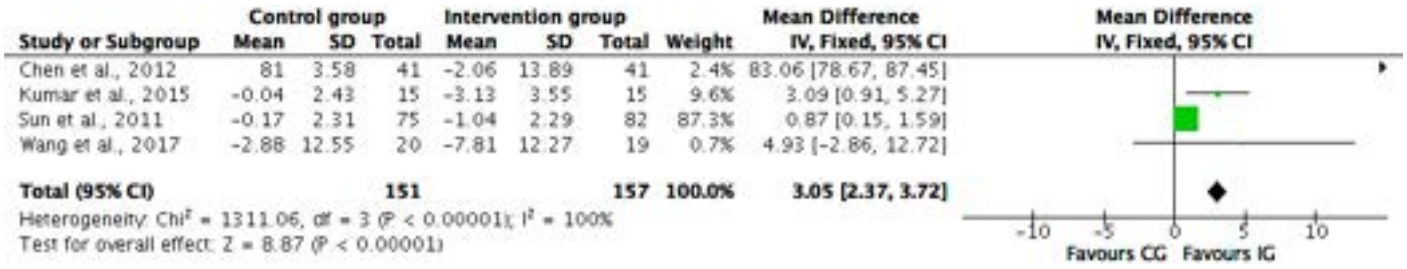
FIGURE 2

Pooled difference of longitudinal variations of serum TNF-α, IL-6, APN and hs-CRP between CG and IG (figures A, D, E, F and J). Subgroup analysis for the effects of smoking and antibiotic adjunct to NSPT on biomarkers variation at 3 and 6 months of follow-up (figures B, C, G, H, I, K and L)

Forrest plot | **Funnel plot**

TNF-α| 3 months follow-up

A

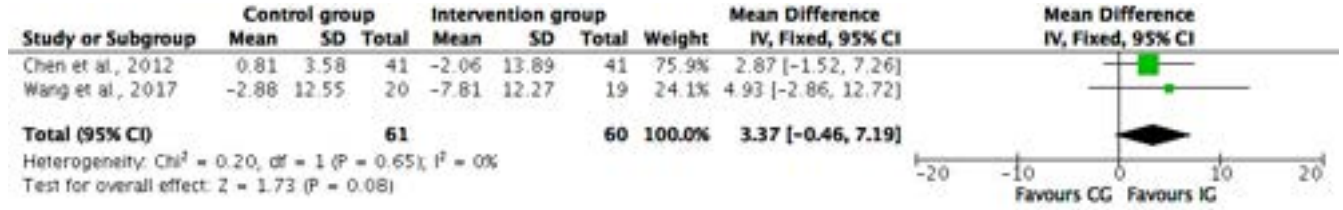


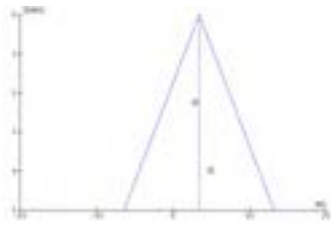
Kumar et al., (2015) and Sun et al. (2011) included antibiotic | Wang et al. (2017) and Chen et al. (2012) included smokers

Analysis of subgroups or subsets

No antibiotic and smokers

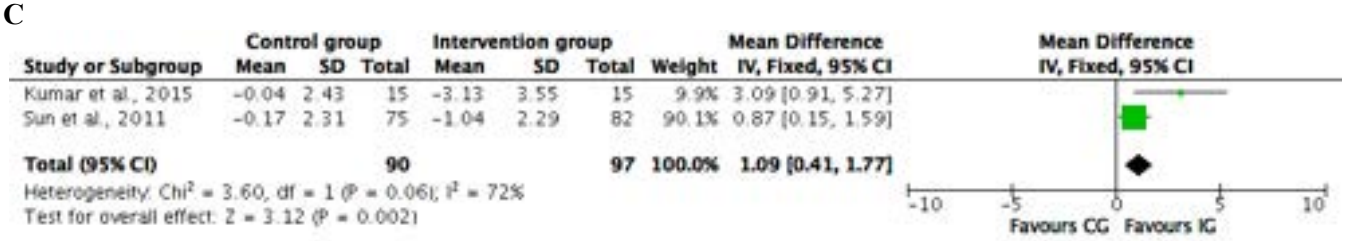
B

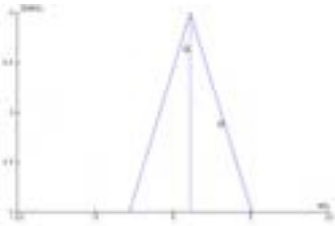




Antibiotic and non-smokers

C



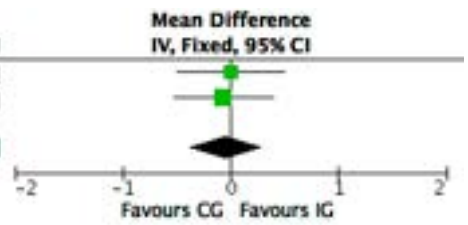


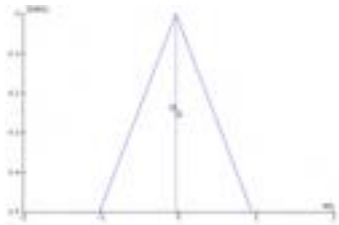
IL-6 | 6 months follow-up

D

Study or Subgroup	Control group Mean	SD	Total	Intervention group Mean	SD	Total	Weight	Mean Difference IV, Fixed, 95% CI
Barthi et al., 2013	0.2	0.61	8	0.2	0.6	21	46.6%	0.00 [-0.49, 0.49]
Geisinger et al., 2016	-0.1	2.78	235	-0.03	2.33	240	53.4%	-0.07 [-0.53, 0.39]
Total (95% CI)			**243**			**261**	**100.0%**	**-0.04 [-0.37, 0.30]**

Heterogeneity: Chi² = 0.04, df = 1 (P = 0.84); I² = 0%
Test for overall effect: Z = 0.22 (P = 0.83)





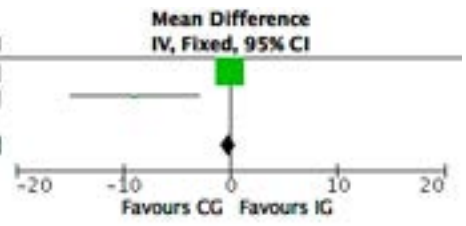
Barthi et al. (2013) included antibiotic

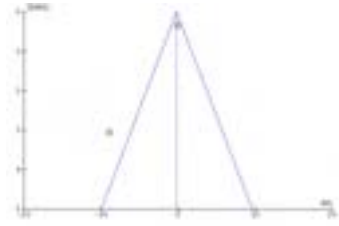
APN | 6 months follow-up

E

Study or Subgroup	Control group Mean	SD	Total	Intervention group Mean	SD	Total	Weight	Mean Difference IV, Fixed, 95% CI
Sun et al., 2011	0.03	2.12	75	0.11	2.22	82	98.7%	-0.08 [-0.76, 0.60]
Wang et al., 2017	0.28	8.15	20	9.18	10.65	19	1.3%	-8.90 [-14.87, -2.93]
Total (95% CI)			**95**			**101**	**100.0%**	**-0.19 [-0.87, 0.48]**

Heterogeneity: Chi² = 8.27, df = 1 (P = 0.004); I² = 88%
Test for overall effect: Z = 0.56 (P = 0.58)





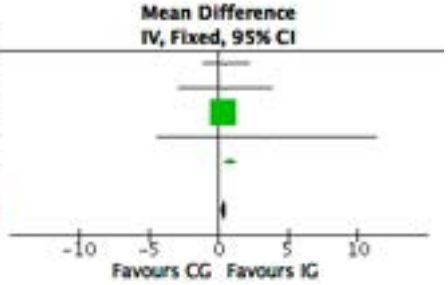
Sun et al. (2011) included antibiotic | Wang et al. (2017) included smokers

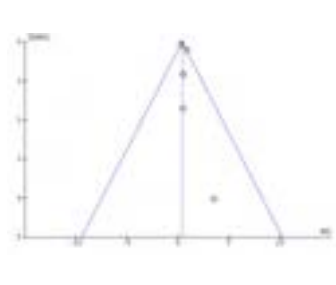
hs-CRP | 3 months follow-up

F

Study or Subgroup	Control group Mean	SD	Total	Intervention group Mean	SD	Total	Weight	Mean Difference IV, Fixed, 95% CI
Chen et al., 2012	-0.57	3.51	41	-1.13	4.03	41	0.5%	0.56 [-1.08, 2.20]
Kapellas et al., 2016	-1.5	5.79	20	-2	5.48	24	0.1%	0.50 [-2.85, 3.85]
Koromantzos et al., 2012	0.14	0.24	30	-0.2	0.23	30	90.9%	0.34 [0.22, 0.46]
Raman et al., 2014	0	5.25	17	-3.5	14.75	15	0.0%	3.50 [-4.37, 11.37]
Sun et al., 2011	0.06	1.26	75	-0.81	1.23	82	8.5%	0.87 [0.48, 1.26]
Total (95% CI)			**183**			**192**	**100.0%**	**0.39 [0.27, 0.50]**

Heterogeneity: Chi² = 7.14, df = 4 (P = 0.13); I² = 44%
Test for overall effect: Z = 6.68 (P < 0.00001)



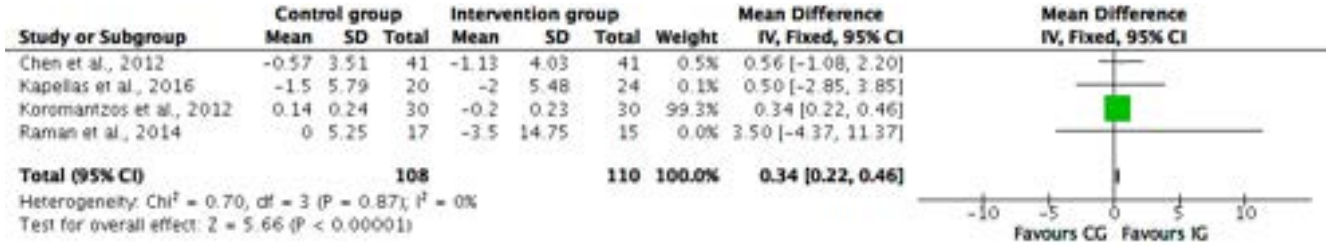


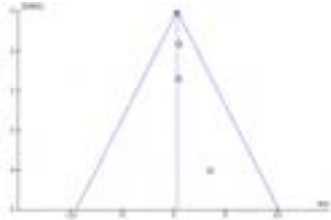
Sun et al. (2011) included antibiotic | Chen et al. (2012) and Koromantzos et al. (2012) included smokers

Analysis of subgroup or subset

No antibiotic

G

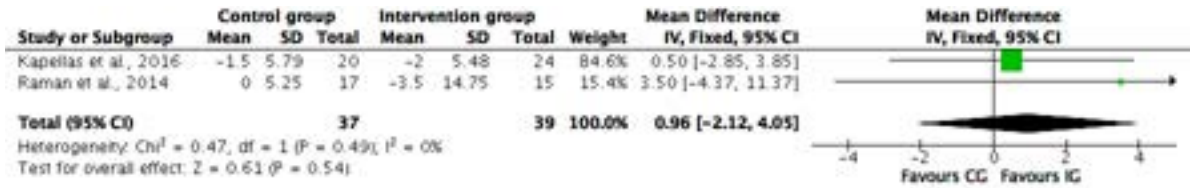




Chen et al. (2012) and Koromantzos et al. (2012) included smokers

Non-smokers

H

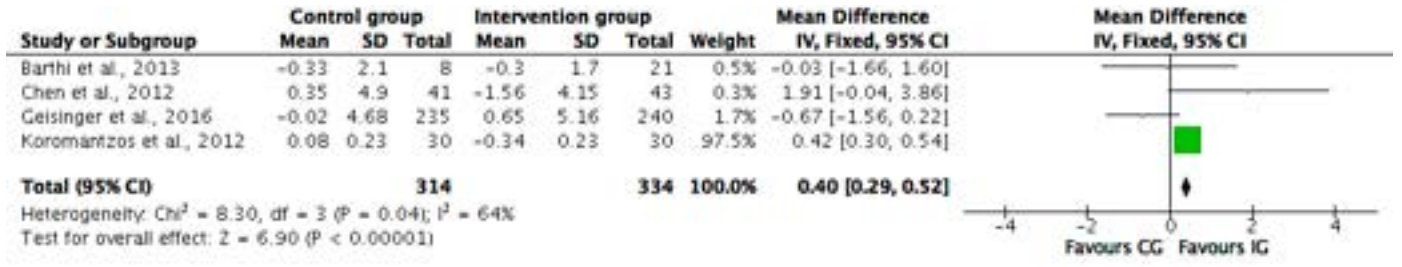


Smokers

I

hs-CRP | 6 months follow-up

J

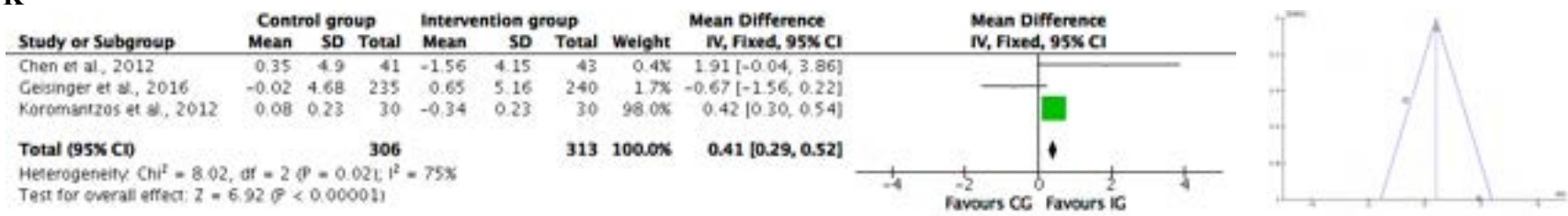


Barthi et al. (2013) included antibiotic | Chen et al. (2012) and Koromantzos et al. (2012) included smokers

Analysis of subgroup or subset

No antibiotic

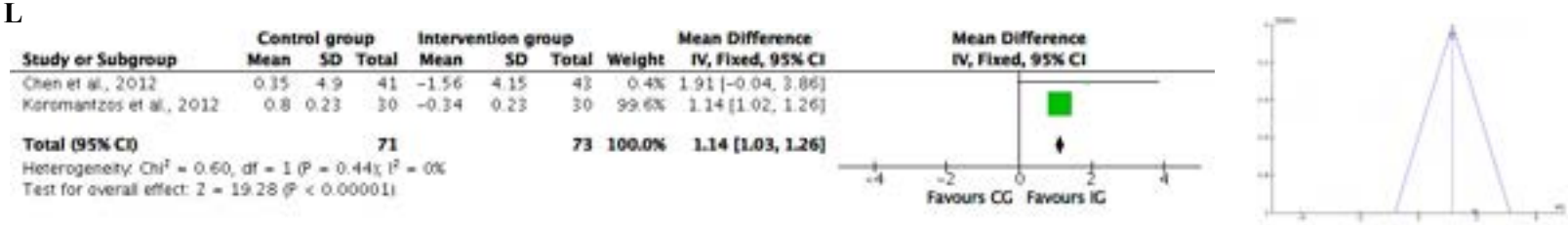
K



Chen et al. (2012) and Koromantzos et al. (2012) included smokers

L

Smokers



DISCUSSION

This study assessed the effect of periodontal therapy on systemic biomarkers of inflammation and oxidative stress in patients with T2DM and periodontitis, compared with non-periodontal therapy or periodontal therapy without a subgingival approach. The overall results indicated that NSPT has the potential to improve the systemic pro-inflammatory profile, except for oxidative stress biomarkers. According to the subgroup analyses, the NSPT can induce a significant and gradual reduction in serum hs-CRP levels in smokers with T2DM during a follow-up of three and six months, even without the use of antibiotics.

Type 2 diabetes mellitus is known to be associated with periodontitis, but the response of patients with T2DM to periodontal therapy remains unclear. Chronic periodontitis associated or not with hyperglycemia and/or smoking might contribute to a systemic inflammatory burden and increased risk of systemic complications. Miranda et al. (2019)[9] investigated the impact of chronic periodontitis associated or not with T2DM and/or smoking on the serum ratios of pro- to anti-inflammatory cytokines. The authors reported significantly higher ratios of pro-inflammatory to anti-inflammatory molecules for chronic periodontitis, non-diabetic smokers with chronic periodontitis, non-smokers with T2DM and chronic periodontitis, smokers with T2DM and chronic periodontitis, than in the control group. Non-diabetic smokers with chronic periodontitis presented higher serum ratios of TNF-α/IL-4, TNF-α/IL-5, IL-17/IL-13 and IL-6/IL-13 than the control group. Cluster analysis revealed a relevant cluster composed of IL-17, IL-23, IFN-γ, IL-12, IL-1β, IL-2, IL-21, IL-6, IL-4 and GM-CSF in the serum of non-smokers with T2DM and chronic periodontitis.

Preshaw et al. (2020)[38] performed an observational study on the effects of periodontitis-therapy on periodontal and systemic inflammation in individuals with and without diabetes. There was a significantly greater systemic inflammation in individuals with T2DM and periodontitis compared to non-diabetic controls with periodontitis, with no significant differences for oral inflammation. Serum levels of hs-CRP, IL-1β, IL-6, TNF-α, IFN-γ, leptin and adiponectin were followed for three, six and 12 months. TNF-α, IL-1β and IFN-γ significantly decreased six months after periodontal therapy, while IL-6, leptin and adiponectin remained stable, and hs-CRP showed a slight reduction during the 12-month follow-up. Furthermore, the authors recognized as a limitation of the study the fact that they did not specify any impact of smoking on the outcomes.

Some studies suggest that periodontal inflammatory conditions and subgingival bacterial species are comparable between smokers and never-smokers with T2DM[39,40] and that the combined effect of smoking and diabetes does not have a significant impact on the periodontium.[41] However, Battancs et al. (2020)[42] suggested a synergy between diabetes and smoking in terms of damage to periodontal tissues. In the study by Bastos et al. (2017),[43] the authors reported that uncontrolled T2DM can upregulate the ratio of MMP/TIMPs in sites with periodontitis more than smoking, leading to greater degradation of the extracellular matrix and commitment of periodontal tissues.

C-reactive protein increases in periodontitis,[44,45] and both smoking and periodontitis affect serum levels of this biomarker separately.[46] Therefore, periodontal therapy and/or smoking cessation has the potential to reduce serum hs-CRP levels.

A previous systematic review and meta-analysis found that periodontal therapy reduces serum TNF-α and CRP levels,[47] which are related to important implications for metabolic control and the risk of systemic complications in individuals with T2DM.[7] The main differences between our study and the systematic review by Artese et al. (2015)[47] is that we only included clinical trials comparing the effect of periodontal therapy with the absence of treatment for periodontitis (non-subgingival approach), we used a broader research strategy, we included oxidative stress biomarkers in addition to inflammatory biomarkers, we included articles published until the manuscript submission, we used updated qualitative tools and performed subgroup analyzes to control for confounding factors such as smoking and antibiotic use. Pooled difference of hs-CRP between baseline and three months follow-up pointed out a significant benefit of periodontal therapy, even without the use of antibiotics. Grouping these data sets allowed us to estimate the effects of periodontal therapy on serum levels of hs-CRP, regardless of the therapeutic protocol and tobacco exposure. However, recognizing the importance of isolating these variables, we performed subgroup analyzes that demonstrated a reduction in serum hs-CRP levels after NSPT in smokers and this effect was greater at six months of follow-up than at three months of follow-up. The improvement in hs-CRP three months after NSPT appeared to be greater in non-smokers than in smokers; as well as the reduction in TNF-α three months after NSPT, these results were not statistically significant, probably due to the sample size and standard deviation observed. The meta-analysis also suggested the absence of a late effect of NSPT with or without adjuvant antibiotic for IL-6 in non-smoking patients.

Esteves et al. (2021)[48] published a systematic review and meta-analysis on the impact of NSPT on serum TNF-α levels in individuals with T2DM. The authors considered before-and-after (pre-post treatment) data from clinical trials in the subgroup analysis, with no untreated

comparison group. Furthermore, as in the study by Artese et al. (2015)[47], Esteves et al. (2021)[48] included studies comparing the effect of the systemic condition of patients with T2DM on response to periodontal therapy, inconsistent with our eligibility criteria. There was no benefit of NSPT for serum TNF-α levels at one month, two months and three months of follow-up. Subgroup analysis showed a significant reduction of this biomarker in blood only at the six months follow-up; however, the authors included in the analysis studies with methodological heterogeneity (different comparison groups) and data from participants who did and did not use antibiotics. Therefore, there is no evidence in this regard and the effect of NSPT on serum TNF-α levels remain unanswered.

Subgroup analysis further suggests that antibiotics as an adjunct to NSPT and smoking affected serum hs-CRP levels by three months of follow-up. The use of local and systemic antimicrobials as an adjunct to NSPT may result in additional benefits for clinical periodontal parameters compared to NSPT only, especially in well-controlled patients with T2DM and deep pockets.[49,50] Cruz et al. (2021)[51] reported better clinical and microbiological outcomes five years after periodontal therapy in individuals with T2DM and periodontitis treated with metronidazole and amoxicillin adjuvant to NSPT compared to NSPT alone. This result depended on supportive periodontal care between two and five years of follow-up. The use of systemic antibiotics adjuvant to periodontitis-therapy is a controversial issue, although the literature suggests benefits in terms of reductions in mean probing depth and mean percentage of bleeding on probing for patients with T2DM.[53,54]

In addition to TNF-α and C-reactive protein, reduction in serum visfatin may also link periodontal therapy and improvement in metabolic control. Only the study by Wu et al. (2015)[33] tested the effect of periodontal therapy on visfatin levels in blood and gingival crevicular fluid. The authors reported a significant reduction in this parameter at the three- and six-month follow-up.

The increase in FGF-21 and VCAM and the decrease in MMP-9 and serum ICAM may indicate tissue repair with reduced local inflammation and endothelial function activity within six months after periodontal therapy.[55-59] The increase in leptin in the three months follow-up and its reduction in the six months follow-up suggest macrophagic activity with the presence of a pro-inflammatory profile in the first three months after periodontal therapy, and possible return to the homeostasis six months after periodontal therapy. The reduction in local and systemic visfatin reinforces this result.[60,61]

Oxidative stress can potentiate pro-inflammatory conditions related to metabolic disorders and tissue destruction.[62] Therefore, investigating the relationship of T2DM with

periodontal disease and its pro-inflammatory similarities is of great value. Smoking can increase the antioxidant activity in the periodontium as a protective and adaptive mechanism of the gingival tissue, although it is not capable of reversing the periodontal destruction related to smoking. Some authors suggest that superoxide dismutase levels are higher in the gingival tissue of smokers, but they are similar in the blood of smokers and non-smokers.[8,63-65] It is possible that the inclusion of smokers in studies that evaluated oxidative stress underestimated the effects of periodontal therapy on this outcome.

According to the Cochrane review published in 2018 by Manresa et al.,[66] there is insufficient evidence to determine the superiority of different protocols or adjunctive strategies to improve tooth maintenance during supportive periodontal care. Among the studies included in this review, five did not report supportive periodontal care or were unclear; of the other nine studies, seven claimed to have performed at least OHI in the IG as a supportive periodontal care strategy. Differences in periodontal supportive therapy between studies seem not to have influenced the results as much as smoking and antibiotic use.

The cumulative effects of hyperglycemia over the years, such as the accumulation of advanced glycation end products and the cascade of inflammatory events mediated by oxidative stress,[53,67] can cause irreversible tissue damage and compromising the magnitude of the systemic effect of periodontal therapy. Perhaps the type of study is not as important as the timing of periodontal intervention in relation to the onset and progression of T2DM, and the effects of periodontal therapy may be less effective for certain biomarkers in individuals with decompensated or long-term diabetes.

Despite the presence of 14 different studies, most of them comprised NSPT, with only four articles reporting the use of antibiotics as an adjutant to NSPT and/or including smokers, which set the primary limitation of this meta-analysis. Periodontal therapy varied between studies; although all performed NSPT, it is known that the number and duration of sessions associated with the severity, complexity, extent, and distribution of the disease can influence serum levels of biomarkers, especially in the short term. A second limitation could be identified in the qualitative results, in which the number of studies for each biomarker and the sample size compromised the comparative analyzes and the quality of evidence for clinical decision making. Also, confounding factors, such as duration of T2DM and smoking, may explain the contrasting findings in the literature. The variability in the duration of T2DM makes comparisons between studies difficult, as the amount of pro-inflammatory cytokines can increase because of multiple episodes of hypoglycemia. Thus, these results should be interpreted with caution, as further studies are needed to establish the effects of periodontal therapy on the systemic inflammatory profile of patients with T2DM and periodontitis.

There is moderate level of evidence from several controlled human studies which show that periodontal therapy may affect the levels of circulating mediators that are associated with glucose homeostasis in patients with T2DM, and there is substantial information on potential mechanistic pathways which support a close association between T2DM and periodontitis. However, there is a real need for longitudinal clinical studies using larger patient groups, integrated with studies of animal models and cells/tissues in vitro. New studies would greatly benefit from the analysis of inflammatory biomarkers in the blood, which may contribute to the understanding of the biological mechanisms involved in the pathogenesis of periodontitis and its relationship with T2DM.[6,7]

Despite the methodological quality of the primary studies included in this systematic review and the certainty of the evidence for the results explored in this study, further studies using uniform definitions and outcomes and with a longer follow-up period are required to address the objectives of this review.

CONCLUSIONS

It is acknowledged that the present systematic review and meta-analysis has several limitations, and thus, the present results must be interpreted with caution. The current findings suggest that periodontitis-therapy is able to gradually reduce serum levels of C-reactive protein in smokers with T2DM during a six months follow-up, even without the use of antibiotics, but it is difficult to determine the magnitude of the likely clinical benefit.

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Conflict of interest

None of the authors has any type of conflict of interest related to the study, as well as related to the peer review process of the manuscript. None of the universities and public agencies that support research in Brazil represents a conflict of interest in this study.

Contribution statement

All authors made substantial contributions to the study and were equally responsible for its design, execution, and content, and agreed to its submission for publication.

Supporting information (funding)

None.

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SUPPLEMENTARY MATERIAL

APPENDIX 1

Risk of bias assessment using RoB2 tool

Studies	Risk-of-bias judgment					Overall risk-of-bias judgement
	Randomization process	Intended interventions	Missing outcome data	Measurement of the outcome	Selection of the reported result	
Mizuno et al., 2017	Low	Low	Low	Low	Low	Low risk of bias
Wang et al., 2017	Low	Low	Low	Low	Low	Low risk of bias
Geisinger et al., 2016	Low	Low	Low	Low	Low	Low risk of bias
Kapellas et al., 2016	Low	Low	Low	Low	Low	Low risk of bias
Artese et al., 2015a	Low	Low	Low	Low	Low	Low risk of bias
Kumar et al., 2015	Low	Low	Low	Low	Low	Low risk of bias
Wu et al., 2015	Low	Low	Low	Low	Low	Low risk of bias
Raman et al., 2014	Low	Low	Low	Low	Low	Low risk of bias
Barthi et al., 2013	Low	Low	Low	Low	Low	Low risk of bias
Chen et al., 2012	Low	Low	Low	Low	Low	Low risk of bias
Koromantzos et al., 2012	Low	Low	Low	Low	Low	Low risk of bias
Sun et al., 2011	Low	Low	Low	Low	Low	Low risk of bias
Sun et al., 2010	Low	Low	Low	Low	Low	Low risk of bias
Katagiri et al., 2009	Low	Low	Low	Low	Low	Low risk of bias

Legend: risk-of-bias judgement—"low"/"low risk of bias", "some concerns" or "high'/"high risk of bias".

From: Higgins JPT, Savović J, Page MJ, Sterne JAC. Revised Cochrane risk-of-bias toll for randomized trials (RoB 2): TEMPLATE FOR COMPLETION. Version of 22 August 2019. For more information, visit: https://www.riskofbias.info/welcome/rob-2-0-tool/current-version-of-rob-2

APPENDIX 2

Methodological quality assessment using Delphi list tool

Studies	Delphi list								
	Q1a/b	Q2	Q3	Q4	Q5	Q6	Q7	Q8	Overall
Mizuno et al., 2017	Yes/”Don’t know”	Yes	Yes	”Probably yes”	NA	NA	Yes	No	Yes
Wang et al., 2017	Yes/”Don’t know”	Yes	Yes	”Probably yes”	NA	NA	Yes	No	Yes
Geisinger et al., 2016	Yes/”Don’t know”	Yes	Yes	”Probably yes”	NA	NA	Yes	No	Yes
Kapellas et al., 2016	Yes/”Don’t know”	Yes	Yes	”Probably yes”	NA	NA	Yes	No	Yes
Artese et al., 2015a	Yes/”Don’t know”	Yes	Yes	”Probably yes”	NA	NA	Yes	No	Yes
Kumar et al., 2015	Yes/”Don’t know”	Yes	Yes	”Probably yes”	NA	NA	Yes	No	Yes
Wu et al., 2015	Yes/”Don’t know”	Yes	Yes	”Probably yes”	NA	NA	Yes	No	Yes
Raman et al., 2014	Yes/”Don’t know”	Yes	Yes	”Probably yes”	NA	NA	Yes	No	Yes
Barthi et al., 2013	Yes/”Don’t know”	Yes	Yes	”Probably yes”	NA	NA	Yes	No	Yes
Chen et al., 2012	Yes/”Don’t know”	Yes	Yes	”Probably yes”	NA	NA	Yes	No	Yes
Koromantzos et al., 2012	Yes/”Don’t know”	Yes	Yes	”Probably yes”	NA	NA	Yes	No	Yes
Sun et al., 2011	Yes/”Don’t know”	Yes	Yes	”Probably yes”	NA	NA	Yes	No	Yes
Sun et al., 2010	Yes/”Don’t know”	Yes	Yes	”Probably yes”	NA	NA	Yes	No	Yes
Katagiri et al., 2009	Yes/”Don’t know”	Yes	Yes	”Probably yes”	NA	NA	Yes	No	Yes

Legend: Q1, treatment allocation (a, "Was a method of randomization performed?" and b "was the treatment allocation concealed?"); Q2, "Were the groups similar at baseline regarding the most important prognostic indicators?"; Q3, "Were the eligibility criteria specified?"; Q4, "Was the outcome assessor blinded?"; Q5, "Was the care providor blinded?"; Q6, "Was the patient blinded?"; Q7, "Were point estimates and measures of variability presented for the primary outcome measures?"; and Q8, "Did the analysis include an intention-to-treat analysis?". Responses: "Yes"/”Probably yes”/"No"/"Don’t know"/”NA” (NA, not applicable).

From: Verhagen AP, de Vet HC, de Bie RA, et al. The Delphi list: a criteria list for quality assessment of randomized clinical trials for conducting systematic reviews developed by Delphi consensus. J Clin Epidemiol. 1998;51(12):1235-1241. doi:10.1016/s0895-4356(98)00131-0.

APPENDIX 3

Descriptive data on medical condition				
Study	**Eligibility Criteria**	**Participants**	**Diagnostic Criteria for T2DM**	**Object of investigation**
Mizuno et al., 2017	IC: i- age ≥ 30 years; ii- physician-diagnosed with T2DM ≥ 2 months prior to the study; iii- reported being able to make hospital visits during the trial; iv- were in the care of a physician for their diabetes; and, agreed to not change their diabetes medications during the trial unless medically indicated. Patients also required a diagnosis of mild to advanced chronic periodontitis (≥ 2 interproximal sites with CAL ≥ 3 mm and ≥ 2 interproximal sites with PPD ≥ 4 mm [not on the same tooth] or one site with PD ≥ 5 mm); radiographs were used to confirm a diagnosis of chronic periodontitis EC: i- pregnancy; ii- inappropriate status for the trials; iii- limited life expectancy; iv- diabetes-related emergency; and v- receiving periodontal therapy in the prior 6 months	*n* = 37 CG: *n* = 17 and IG: *n* = 20 Smoking: CG: *n* = 5 and IG: *n* = 2 Alcohol consumption: CG and IG (*n* = 7)	"Participants enrolled between April 2014 and March 2016 at the Nephrology, Diabetology and Endocrinology Department of Okayama University Hospital were eligible if they had physician-diagnosed T2DM (diagnosed ≥ 2 months prior to the study)."	Serum: oxidative stress balance (oxidative index) and hs-CRP
Wang et al., 2017	IC/EC: i- patients diagnosed with T2DM (HbAlc, 6.5 – ≤ 10 %) over one year by a grade three hospital who volunteered for the research; ii- chronic periodontitis, iii- ≥ 15 remaining teeth; iv- more than 30 % of teeth with PPD ≥ 5 mm and CAL > 4 mm, or more than 60 % of teeth with a PPD > 4 mm and CAL ≥ 3 mm; v- BMI < 30 kg/m^2; vi- without periodontal therapy in the previous 6 months; vii- without antibiotic or non-steroidal anti-inflammatory drug administration in the 3 months; and, viii- without serious systemic diseases or complications	*n* = 39 CG: *n* = 20 and IG: *n* = 19 26 males and 13 females Mean age CG: 61.90 ± 6.75 Mean age IG: 61.58 ± 4.69 Smoking: CG [*n* = 3 (15 %)] and IG [*n* = 6 (31.58 %)]	"Patients with a diagnosis of T2DM for over one year by a grade three hospital at Xiamen Lianqian Community Health Center between June 2014 and December 2014."	Serum: IL-6, TNF-α, APN and FGF-21
Geisinger et al., 2016	IC: i- two or more tooth sites in ≥ 2 quadrants of the mouth with PPD and CAL ≥ 5 mm; ii- a minimum of 16 natural teeth; iii- no periodontal therapy in the last 6 months; and iv- T2DM (HbA1c, ≥ 7 – < 9 %) EC: participants needing treatment of extensive tooth decay, tooth abscesses, or other oral infection, such as teeth needing root canal therapy, were excluded. Additional exclusion criteria included limited life expectancy, diabetes-related emergency within 30 days, use of nonsteroidal anti-inflammatory drugs other than daily low-dose aspirin (75 – 325 mg), use of immunosuppressive medications, antibiotic use (> 7 days within 30 days of enrollment), dialysis, risk of bleeding complications, or heavy alcohol consumption (> 3 drinks/day for men and > 2 drinks/day for women)	*n* = 475 CG: *n* = 235 and IG: *n* = 240	"Duration in years and diabetes medication use. Fresh fasting blood samples were collected to determine HbA1c. Glucose and insulin levels were determined from serum. Homeostatic model assessment 2 (HOMA2 β-cell Function and HOMA2 Insulin Sensitivity) values were calculated from fasting plasma glucose and insulin levels of participants not taking insulin using the HOMA2 Calculator version 2.2."	Serum: IL-6, IL-10, TNF-α and sE-selectin Plasma: IL-8, hs-CRP and sICAM-1

Kapellas et al., 2016	IC: i- aboriginal Australian participants aged 18 years or older without a previous history of cardiovascular disease; ii- minimum of five natural teeth; and iii- moderate/severe periodontitis defined using the joint Centers for Disease Control and Prevention and American Academy of Periodontology case definition EC: i- individuals receiving treatment in the preceding 6 months; ii- those with cardiovascular disease history, rheumatic fever or any other medical condition requiring preventive antibiotic prophylaxis; iii- pregnant women; or iv- people with clinically visible endodontic or orofacial infections	Baseline: *n* = 62 CG: *n* = 27 and IG: *n* = 35 3 months follow-up: *n* = 44	NR	Serum: hs-CRP Plasma: IL-6
Artese et al., 2015a	IC: individuals ≥ 35 years of age, confirmed diagnosis of T2DM for a period of over 3 years, generalized severe chronic periodontitis (number of PPD sites ≥ 30%, CAL > 4 mm, and bleeding on probing), and ≥ 15 teeth EC: pregnant women, smokers, patients with body mass index (BMI) > 35 kg/m^2, or those who had received periodontal therapy, systemic antibiotic, or oral antiseptic therapy 6 months prior to the study	*n* = 24 CG: *n* = 12 and IG: *n* = 12	"All patients with T2DM were diagnosed according to the World Health Organization classification and remained under the supervision of an endocrinologist."	Serum: IL-6, IL-8, IL-17, TNF-α and MCP-1
Kumar et al., 2015	IC: patients > 30 years, both males and females. Chronic generalized periodontitis patients (Armitage criteria) and patients diagnosed with T2DM (HbA1c 7.5 – 11 %). No major diabetic complications. Patient willing to take part in the study and maintain appointment regularly EC: i- patients suffering from any other systemic diseases; ii- present and past smokers; iii- patients who have undergone periodontal therapy 6 months prior to the study; iv- pregnant or lactating mothers; v- patients who have received any antibiotics for the last 3 months; and less than 16 remaining natural teeth	*n* = 30 17 males and 13 females Mean age: 49.96 years "*Physician's consent and details of patient's diabetes control was obtained and no change in the medication or diet was made for the patients. None of the patients received any additional guidance in managing their diabetic status. All the multiple variables like diet, exercise and diabetic management were kept constant. After oral examination the teeth with poor prognosis were extracted. Patients requiring antibiotics post extraction were taken up for the study after the period of 3 months*"	"Patients who reported to the diabetes clinic of School of Tropical medicine, Kolkata, INDIA as well as the Department of Periodontics, Dr. R. Ahmed Dental College and Hospital, Kolkata, INDIA were included in the study."	Serum: TNF-α
Wu et al., 2015	IC: diagnosis of T2DM over 1 year with no medication changes in the last three months, without administration of non-steroidal and anti-inflammatory drugs within the previous 6 months. No history of any periodontal therapy 6 months prior to the study, with ≥ 16 teeth. Chronic periodontitis was diagnosed as having mean CAL ≥ 1mm according to the American Academy of Periodontology criteria (1999) EC: i- aggressive periodontitis; ii- current and former use of tobacco in any form; and iii- any other systemic disease (hypertension, metabolic	*n* = 46 CG: *n* = 23 and IG: *n* = 23 CG: 10 males and 13 females Mean age CG: 55.52 ± 5.22 years Mean BMI CG: 22.14 ± 0.72 kg/cm^2 IG: 12 males and 11 females	"Participants with T2DM were included on the basis of assessment of their clinical characteristics, including: (1) the diagnosis of T2DM over 1 year with no medication changes in the last three months."	Serum: visfatin GCF: visfatin

	syndrome, cardiovascular disease, immune disease, malignant tumor, etc.) that can alter the course of periodontal disease	Mean age IG: 54.09 ± 6.57 years Mean BMI IG: 22.22 ± 0.64 kg/cm^2		
Raman et al., 2014	IC: moderate to advanced chronic periodontitis, with ≥ 12 remaining teeth and with 5 or more PPD ≥ 5 mm and CAL ≥ 4 mm in ≥ 2 different quadrants which bled on probing EC: i- history of systemic antibiotic usage over the previous 4 months; ii- having NSPT within the past 6 months or surgical periodontal therapy within the past 12 months; iii- pregnancy, change of medication for diabetes during the course of the study, current smokers or history of a cerebrovascular or cardiovascular event within the past 12 months	*n* = 40 15 subjects from NSPT group and 17 from OHI group completed the study (*n* = 32)	"People with type 2 diabetes (diagnosed ≥ 1 year prior to the study) between ages of 30 to 70 were screened from the outpatient Diabetes Clinic of the University of Malaya Medical Centre."	Serum: hs-CRP
Barthi et al., 2013	IC: For medical condition: i- age 35 – 75 years; ii- HbA1c, 5.8 – 10 %; iii- absence of severe diabetic complications; iv- no evidence of systemic disease other than diabetes as a risk for periodontitis; v- no administration of systemic antibiotics during the preceding 3 months; vi- no pregnancy or lactation; vii- no allergy to tetracycline; viii- no smoking; and ix- no modifications of other anti-diabetic treatments during the preceding 2 months For dental condition: i- ≥ 10 remaining teeth; ii- ≥ 2 sites with PPD ≥ 4 mm (mild to moderate periodontal disease); and iii- no periodontal therapy during the preceding 6 months EC: Current smokers, immune disorder, T1DM and HbA1c levels above the range required by medical condition criteria	*n* = 29 CG: *n* = 8 and IG: *n* = 21	HbA1c, 5.8 – 10 % and absence of severe diabetic complications or evidence of systemic disease other than diabetes as a risk for periodontitis.	Serum: IL-6, TNF-α, hs-CRP, APN, leptin and resistin
Chen et al., 2012	IC: patients with a confirmed diagnosis of T2DM for > 1 year and no change in their diabetic treatment plan in the previous 2 months, and with no major diabetic complication, such as coronary heart disease EC: i- presence of a systemic disease other than diabetes that could influence the course of the periodontal disease; ii- systemic antibiotic administration within the previous 3 months; iii- pregnancy or lactation; and iv- refusal to provide written informed consent. Patients were also excluded if they had an active infection other than periodontitis or had received periodontal therapy in the previous 12 months	*n* = 134 CG: no treatment measure or formal OHI until the end of the study (*n* = 41) IG1 (NSPT): SRP under local anesthesia at baseline and additional subgingival debridement at the 3 months follow-up (*n* = 42) IG2 (NSPT): SRP under local anesthesia at baseline and only supragingival prophylaxis, with no intervention in deep periodontal pockets at 3 months (*n* = 43) *Current smokers were defined as patients who smoked ≥ 1 cigarette per day; those who had never smoked in their life (never smokers), and those who*	"All the patients had a confirmed diagnosis of Type 2 diabetes mellitus for > 1 year, with no change in their diabetic treatment plan in the previous 2 months and with no major diabetic complication, such as coronary heart disease."	Serum: TNF-α and hs-CRP

		had given up smoking for > 1 year (former smokers). Alcohol use was divided into drinking and not drinking, and diabetes mellitus treatment was classified as diet control, oral medication, or intravenous insulin use		
Koromantzos et al., 2012	IC: i- HbA1c, 7 – 10 %; ii- ≥ 16 remaining teeth; iii- ≥ 8 sites with PPD ≥ 6 mm; iv- four sites with CAL ≥ 5 mm distributed ≥ 2 different quadrants EC: i- history of systemic antibiotic usage over the previous 3 months; ii- NSPT during the previous 6 months; iii- surgical periodontal therapy over the previous 12 months; iv- current medication usage of calcium channel blockers, phenytoin, or cyclosporine; v- history of stroke or an acute cardiovascular event over the previous 12 months; and vi- renal or liver dysfunction (creatinine > 1.5 mg/dL or aspartate aminotransferase/alanine aminotransferase levels > 2.5 times the upper level of normal, respectively)	*n* = 60 CG: *n* = 30 and IG: *n* = 30 CG smokers: 7 current, 16 never and 7 formers IG smokers: 4 current, 13 never and 13 formers *Current smokers were defined as participants who smoked > 1 cigarette per day, never-smokers as those who had never smoked in their life, and former smokers as those who had stopped smoking >1 year previously*.	HbA1c, 7 – 10 %	Plasma: hs-CRP, MMP-2, MMP-9 and OxS marker *d*-8-iso
Sun et al., 2011	IC: i- patients diagnosed with T2DM over one year; ii- HbA1c, 7.5 – 9.5 %); iii- not older than 70 years; iv- BMI 20 kg/m^2 – 27 kg/m^2 in men and BMI 19 kg/m^2 – 26 kg/m^2 in women; iv- no medication changes during the 3 months of study; v- not smoking; and vi- without severe complications, such as diabetic nephropathy, stroke, angina, myocardial infarction and so on EC: patients with systemic inflammatory diseases (rheumatoid arthritis, etc.), blood disease, liverdamage, kidney disease or trauma	A total of 190 moderately poorly controlled (HbA1c between 7.5 % and 9.5 %) T2DM patients with periodontitis were randomly divided into two groups: CG (T2DM-NT): baseline (*n* = 75) and 3 months follow up (*n* = 75) IG (T2DM-T): baseline (*n* = 82) and 3 months follow up (*n* = 82)	Patients diagnosed with T2DM over one year with moderately poor glycemic control (HbA1c between 7.5 % and 9.5 %)	Serum: IL-6, TNF-α and hs-CRP
Sun et al., 2010	IC: i- patients diagnosed with T2DM over one year; ii- good glucose control with fasting blood glucose < 7.0 mmol/L and HbA1c, 6.5 – 7.5 %; iii- no medication changes in the last 3 months; iv- did not smoke; and v- without severe complications EC: patients with systemic inflammatory diseases (rheumatoid arthritis, etc.), blood disease, liver damage, kidney disease or trauma	CG: *n* = 30 healthy adults IGT group: *n* = 50 DM1 group (*n* = 58): T2DM without macrovascular disease DM2 group (*n* = 48): T2DM with macrovascular disease *DM2 group included 20 patients with heart disease, 12 with carotid artery atherosclerosis, 14 with lower extremity atherosclerosis, and 2 with carotid atherosclerosis and coronary heart disease* Each intervention group was randomly divided into two subgroups according to whether they performed periodontal intervention: IGT + NT (*n* = 25), IGT + T	"A total of 50 IGT and 106 T2DM patients with periodontitis were enrolled from the Department of Endocrinology and Stomatology of our Hospital from March 2008 to March 2009."	Serum: IL-6, TNF-α, hs-CRP and APN

		(*n* = 25), DM1 + NT (*n* = 29), DM1 + T (*n* = 29), DM2 + NT (*n* = 24), and DM2 + T (*n* = 24)		
Katagiri et al., 2009	IC: For medical condition: i- age of 39 – 75 years; ii- HbA1c, 6.5 – 10 %; iii- without severe diabetic complications; iv- no evidence of systemic diseases other than diabetes as a risk factor for periodontitis; v- no systemic antibiotics during the preceding 3 months; vi- no pregnancy or lactation; vii- no allergy to tetracycline; viii- no smoking; and ix- no modifications in the treatment of diabetes during the preceding 2 months For dental condition: ≥ 11 remaining teeth; ≥ two pocket sites with PPD ≥ 4 mm (indicated as mild to severe periodontitis); and no periodontal therapy during the preceding 6 months	*n* = 49 CG: *n* = 17 and IG: *n* = 32	HbA1c, 6.5 – 10 %	Serum: hs-CRP
Legend: IC, inclusion criteria; EC, exclusion criteria; T2DM, type 2 diabetes mellitus; HbAlc, hemoglobin A1c; BMI, bone mass index; PPD, periodontal probing depth; CAL, clinical attachment level/loss; *n*, sample size (absolute frequency); CG, control group; IG, intervention group; IGT, impaired glucose tolerance; NT, non-periodontal intervention; T, periodontal intervention; min, minute(s); h, hour(s); NR, not reported; ICAM, intercellular cell adhesion molecule; VCAM, vascular cell adhesion molecule, TNF-a, tumor necrosis factor-alpha, IL-, interleukin-; MMP-, matrix metalloproteinase-; FGF-21, fibroblast growth factor-21; MCP-1, monocyte chemoattractant protein-1; APN, apolipoprotein; hs-CRP, high sensitivity-C-reactive protein.				

APPENDIX 4

Descriptive data on periodontal diagnosis, therapy and evaluation

Study	Diagnostic criteria for periodontitis	Periodontal therapy (IG)	CG	Supportive periodontal care	Follow-up
Mizuno et al., 2017	PPD and CAL were determined at six sites on all teeth using a color-coded probe. The proportion of sites with BOP and the number of BOP-positive teeth were measured in each subject. Plaque control record was measured after erythrosine staining and recorded with respect to their relative location to the gingival margin at four sites (mesial, distal, buccal and lingual) around each tooth	One session of supra-gingival plaque removal and OHI + ≥ 60 min of SRP using curettes and an ultrasonic instrument during ≥ 2 sessions completed within 42 days after the baseline visit	One session of supra-gingival plaque removal + OHI	3 and 6 months follow-up: CG: only OHI IG: periodontal maintenance therapy including OHI and oral prophylaxis for approximately 1 h during a single session	3 and 6 months after the baseline visit

Wang et al., 2017	PPD and CAL were examined at six sites per tooth, and the average was calculated. A Williams periodontal probe was used for the clinical periodontal measurements	Oral hygiene (utilizing correct methods and soft-bristled toothbrushes, interdental brushes and dental floss) + full-mouth scaling (supragingival and subgingival scaling) + extraction of hopeless teeth + restoration of balanced occlusion. Periodontal interventions were completed within two weeks	No intervention	NR	3 months after the baseline visit
Geisinger et al., 2016	Participants with at least moderate periodontitis (two or more tooth sites in ≥ 2 quadrants of the mouth with PPD and CAL ≥ 5 mm), a minimum of 16 natural teeth, and no periodontal therapy in the last 6 months. Periodontal clinical parameters: GBI and the presence or absence of plaque (VPI) from six index teeth, PPD, CAL, and BOP from six sites on each tooth, excluding third molars	NSPT within 35 days of randomization or after six months. Minimum of 180 min of SRP (non-surgical mechanical cleaning of the tooth crown and root)	NR	Participants received supportive periodontal care at the 3 months visit	3 and 6 months after the baseline visit
Kapellas et al., 2016	Measurements were made at four sites (mesio-buccal, mid-buccal, disto-buccal and disto-lingual) at every tooth excluding third molars using a PCP2 periodontal probe with 2 mm markings. Gingival bleeding on probing score was collected for each tooth periodontally assessed and was scored based on the gingival index criteria	Untimed single episode of NSPT comprising supra and subgingival scaling (single episode of NSPT comprising supra- and subgingival scaling using Gracey curettes and piezoelectric ultrasonic device) + complete full-mouth dental prophylaxis using a rubber cup and Ainsworth prophylaxis paste + oral hygiene advice	Oral hygiene advice consisting of toothbrush and flossing instructions + provision of a toothbrush and toothpaste at baseline	Unclear	3 months after the baseline visit
Artese et al., 2015a	The presence of supragingival biofilm was recorded as VPI, whereas marginal gingival bleeding was recorded as GBI. BOP, PPD, and CAL were also evaluated. The North Carolina manual probe was used in this study; VPI, GBI, and BOP were recorded as (0) absent, or (1) present. Clinical examinations were performed by two blinded and calibrated examiners on six sites per tooth (excluding the third molars), at baseline and at 6 months after periodontal therapy (excluding the third molars), at baseline and at 6 months after periodontal therapy	All individuals were given OHI. The intensive therapy group [IT (*n*, 12)] received supra- and subgingival SRP, (in sites with PPD ≥ 4 mm) using an ultrasonic device and periodontal curettes. The procedures for the IT group were performed under local anesthesia (3 % prilocaine with felypressin), in two appointments lasting ~ 120 min each	Supragingival therapy group: OHI + supragingival scaling using an ultrasonic device and periodontal curettes; A single appointment lasted ~ 60 min	Professional instructions on oral hygiene every month	6 months after the baseline visit

Kumar et al., 2015	Chronic generalized periodontitis patients (Armitage criteria) [Armitage GC. Development of a classification system for periodontal diseases and conditions. Ann Periodontol 1999;4(1):1–6] A digital orthopantomogram was advised for all the patients: i- VPI according to Silness and Löe (1964); ii- GBI according to Löe and Silness (1963) and PPD and CAL. Four units of each teeth were examined and recorded	OHI and underwent full mouth SRP procedure performed under local anesthesia. SRP was performed by the principal investigator using ultrasonic scalers and hand instruments while the subjects were under local anesthesia. The schedule of the visit was once a week for 1 month. On recall visit after 3 months, supragingival plaque was removed and OHI were reinforced as required Additionally, these patients were placed on *doxycycline 100 mg, two tablets for first day, then one tablet daily for total of 14 days*	Full mouth SRP was not performed and OHI were not given. After completion of the study, these patients were given a full NSPT and supportive periodontal care if needed	CG: there was not performed SRP as well OHI were not given IG: schedule of the visit was once a week for 1 month	3 months after the baseline visit
Wu et al., 2015	Each tooth was examined with a periodontal probe to measure GBI, BOP, PPD and CAL. Participants were re-examined after 3 and 6 months of NSPT to re-assess their periodontal conditions as described above. All participants received OHI for two or three times, including the use of interproximal cleaning aids by floss and interdental brushes. For participants in IG, subgingival SRP were completed within one month from individuals' first visit. NSPT was not accompanied by any medications	Participants in IG received OHI + NSPT. During the experimental observation, all participants were required to maintain their way of life in diet and medication	OHI	Participants were re-examined after 3 and 6 months of NSPT to re-assess their periodontal conditions	3 and 6 months after the baseline visit
Raman et al., 2014	Presence of moderate to advanced chronic periodontitis; ≥ 12 remaining teeth and with ≥ 5 pockets of ≥ 5 mm and CAL ≥ 4 mm in ≥ 2 different quadrants with BOP	Plaque scores of the subjects in the NSPT group were reviewed at weekly intervals to achieve scores of 20 % or below to a maximum of 3 weeks. Subjects were re-motivated and instructed when necessary. Assigned treatment for the NSPT group was full mouth debridement, which consisted of SRP, was done in a single visit for all subjects in the NSPT group using an ultrasonic scaler and Gracey curettes Additionally, all subjects in the NSPT group were given a 0.12 % Chlorhexidine mouthrinse (rinse three times a day using 15 ml each time for a period of 14 days commencing	No interventional treatment was given to the OHI group apart from OHI and motivation. Thereafter at each monthly recall visit, participants in both groups were reviewed and re-motivated	NR	Baseline, 2 months and 3 months 15 ml of venous blood was collected from each patient at baseline, prior to treatment and at 3 months after assigned treatments (levels of HbA1c and hs-CRP were assessed)

		immediately after completion of full mouth debridement Professional prophylaxis comprising of scaling and polishing was performed only on subjects of the IG			
Bharti et al., 2013	≥ 2 sites with PPD ≥ 4 mm (mild to moderate periodontal disease) and no administration of periodontal treatments during the preceding 6 months	During initial 2 months: intensive periodontal treatments (OHI + supra- and subgingival SRP) with *topical administration of antimicrobial agents (10 mg minocycline) 4 times at every other week* (baseline); followed by 2 months' and 6 months' observation with additional supportive periodontal care i- during 2 months' intensive periodontal treatments, at first visit (baseline), the patients underwent an initial examination; ii- second and third visits: OHI + tooth brushing, interdental brushing and/or dental flossing + removed supragingival plaque and calculus using an ultrasonic scaler; and iii- fourth and fifth visits: subgingival SRP to remove plaque and calculus using the same device. *From the second visit to the fifth visit, patients were administered 10 mg of local minocycline ointment in every periodontal pocket after treatment*. After the completion of 2 months' intensive periodontal treatment, participants visited the medical and dental clinics at 2 and 6 months	NT: patients not willing to undergo intensive periodontal treatments at the clinic were allocated to the control group	2-month follow-up: supportive periodontal care including instructions for oral hygiene techniques and supra- and subgingival debridement without topical administration of antibiotics	Baseline, 2 months and 6 months
Chen et al., 2012	Clinical diagnosis of chronic periodontitis according to the American Academy of Periodontology criteria, with CAL ≥ 1 mm (including slight, moderate and severe periodontitis), with ≥ 16 teeth	IG1 received NSPT, which consisted of SRP under local anesthesia at baseline and additional subgingival debridement at the 3 months follow-up IG2 underwent NSPT at the initial visit and only supragingival prophylaxis, with no intervention in deep periodontal pockets at 3 months	No treatment measure or formal OHI until the end of the study	Reinforcement of OHI at all follow-up periods	1.5, 3 and 6 months after completion of the initial periodontal therapy

		NSPT was completed within 24 h by an experienced periodontist without the administration of antibiotics or local antimicrobials at baseline, using standard rigid periodontal curets and ultrasonic instrumentation			
Koromantzos et al., 2012	≥ 16 remaining teeth; ≥ 8 sites with PPD ≥ 6 mm and 4 four sites with CAL ≥ 5 mm, distributed ≥ 2 different quadrants	Baseline: OHI IG: NSPT in the form of full-mouth SRP in two sessions, 1 week apart	Baseline: OHI CG (minimal treatment group): supragingival cleaning at baseline with an ultrasonic scaler. SRP was performed at the completion of the study (after the 6 months visit)	All participants received OHI after each visit, whereas the IG received additional supportive SRP at each visit, if judged necessary (presence of sites with BOP and/or increased periodontal disease)	1, 3 and 6 months after the baseline visit
Sun et al., 2011	> 20 remaining teeth; PPD > 5 mm, > 30 % teeth with CAL ≥ 4 mm, or ≥ 60 % teeth with PPD > 4 mm and CAL > 3 mm Without periodontal treatment in the previous 6 months, without antibiotics or non-steroidal anti-inflammatory drugs administered in the last 3 months, and without serious systemic diseases or complications	Oral hygiene, full-mouth scaling (supragingival and subgingival scaling), root planning, periodontal flap surgery when indicated, and extraction of hopeless teeth, restore of balanced occlusion. *Antibiotics (tinidazole 1.0 g, bid, po. and ampicillin 0.25 g, qid, po.) were prescribed for 3 days before and after periodontal intervention*	NR	NR	3 months after the baseline visit
Sun et al., 2010	> 20 remaining teeth, PPD > 5 mm, > 30 % teeth with CAL > 4 mm, or > 60 % teeth with PPD > 4 mm and CAL > 3 mm Without periodontal treatment in the previous 6 months, without antibiotics or non-steroidal anti-inflammatory drugs administered in the last 3 months, and without serious systemic diseases or complications	Oral hygiene missionary, full-mouth scaling (supragingival and subgingival scaling), root planning, periodontal flap surgery when indicated, and extraction of hopeless teeth, restore of balanced occlusion. *Antibiotics (tinidazole 1.0 g, bid, po. and ampicillin 0.25 g, qid, po.) were prescribed for 3 days before and after periodontal intervention*	NR	NR	3 months after the baseline visit
Katagiri et al., 2009	≥ 11 remaining teeth; ≥ 2 pocket sites with PPD ≥ 4 mm (indicated as mild to severe periodontitis); and no periodontal treatment during the preceding 6 months	IG: mechanical debridement of the sub-gingival plaque and calculus was performed using piezoelectric ultrasonic scalers, and *10 mg of minocycline ointment was administered topically in every periodontal pocket at the end of each visit*. The intensive periodontal	OHI: instructions for brushing their teeth, including the use of inter-proximal cleaning aids, such as floss and inter-dental brushes, depending on their individual needs	IG: additional periodontal treatment including instructions for brushing, supra- and sub-gingival debridement without topical administration of antibiotics were performed, if necessary	1, 3 and 6 months after the baseline visit

		treatment was completed over the course of four visits within 2 months			

Legend: IC, inclusion criteria; EC, exclusion criteria; T2DM, type 2 diabetes mellitus; HbAlc, hemoglobin A1c; BMI, bone mass index; VPI, visible plaque index; GBI, gingival bleeding index; PPD, periodontal probing depth; CAL, clinical attachment level/loss; BOP, bleeding on probing; OHI, oral hygiene instructions; NSPT, non-surgical periodontal therapy; SRP, scaling and root planing; *n*, sample size (absolute frequency); CG, comparative group; IG, intervention group; NT, non-periodontal intervention; min, minute(s); h, hour(s); NR, not reported.

APPENDIX 5

Descriptive data on Periodontal clinical parameters, effectiveness of periodontal therapy and evaluation

Study	Periodontal clinical parameters	Effectiveness of periodontal therapy	
		$p \leq 0.05$	$p > 0.05$
Mizuno et al., 2017	PPD, PPD ≥ 4 mm, CAL, CAL ≥ 4 mm and BOP	3 months follow-up: PPD and CAL 6 months follow-up: PPD, CAL, CAL ≥ 4 mm and BOP	3 months follow-up: PPD ≥ 4 mm, CAL ≥ 4 mm and BOP 6 months follow-up: PPD ≥ 4 mm
Wang et al., 2017	PPD and CAL	3 months follow-up: PPD and CAL	-
Geisinger et al., 2016	PPD, CAL and BOP	6 months follow-up: PPD, CAL and BOP	-
Kapellas et al., 2016	GBI, PPD ≥ 4 mm and CAL ≥ 3 mm	3 months follow-up: GBI	3 months follow-up: PPD ≥ 4 mm and CAL ≥ 3 mm
Artese et al., 2015a	VPI, GBI, PPD, PPD 4-6 mm, PPD ≥ 7 mm, CAL, CAL 4-6 mm, and CAL ≥ 7 mm and BOP	6 months follow-up: VPI, GBI, PPD, CAL BOP, PPD 4-6 mm and CAL 4-6 mm	6 months follow-up: PPD ≥ 7 mm and CAL ≥ 7 mm
Kumar et al., 2015	VPI, GBI, PPD and CAL	3 months follow-up: VPI, GBI, PPD and CAL	-
Wu et al., 2015	GBI, PPD and CAL	3 months follow-up: GBI, PPD and CAL 6 months follow-up: GBI, PPD and CAL	-

Raman et al., 2014	VPI, GBI, PPD, PPD < 4 mm, PPD 4-6 mm, PPD > 6 mm, CAL, CAL < 4 mm, CAL 4-6 mm and CAL > 6 mm	2 months follow-up: VPI, GBI, PPD, PPD < 4 mm, PPD 4-6 mm, PPD > 6 mm, CAL, CAL < 4 mm, CAL 4-6 mm and CAL > 6 mm 3 months follow-up: VPI, GBI, PPD, PPD < 4 mm, PPD 4-6 mm, PPD > 6 mm, CAL, CAL < 4 mm, CAL 4-6 mm and CAL > 6 mm	-
Barthi et al., 2013	PPD and BOP	2 months follow-up: PPD and BOP 6 months follow-up: PPD and BOP	-
Chen et al., 2012	VPI, PPD, PPD 4-5 mm, PPD ≥ 6 mm, CAL and BOP	1.5 months follow-up: VPI, PPD, PPD 4-5 mm, PPD ≥ 6 mm, CAL and BOP 3 months follow-up: VPI, PPD, PPD 4-5 mm, PPD ≥ 6 mm, CAL and BOP 6 months follow-up: VPI, PPD, PPD 4-5 mm, PPD ≥ 6 mm, CAL and BOP	-
Koromantzos et al., 2012	GBI, PPD ≤ 3 mm, PPD 4-6 mm, PPD ≥ 7 mm, CAL ≤ 3 mm, CAL 4-6 mm, CAL ≥ 7 mm and BOP	6 months follow-up: GBI, PPD ≤ 3 mm, PPD 4-6 mm, PPD ≥ 7 mm, CAL ≤ 3 mm, CAL ≥ 7 mm and BOP	6 months follow-up: CAL 4-6 mm
Sun et al., 2011	VPI, GBI, PPD and CAL	3 months follow-up: VPI, GBI, PPD and CAL	-
Sun et al., 2010	VPI, GBI, PPD, CAL and BOP	3 months follow-up: VPI, GBI, PPD, CAL and BOP	-
Katagiri et al., 2009	PPD and BOP	1 month follow-up: PPD and BOP 3 months follow-up: PPD and BOP 6 months follow-up: PPD and BOP	-
Legend: VPI, visible plaque index; GBI, gingival bleeding index; PPD, periodontal probing depth; CAL, clinical attachment level/loss; BOP, bleeding on probing. PPD and CAL, mean ± standard deviation (mm); VPI, GBI, BOP, PPD ≤ 3 mm, PPD < 4 mm, PPD ≥ 4 mm, PPD 4-5 mm, PPD 4-6 mm, PPD ≥ 6 mm, PPD > 6 mm, PPD ≥ 7 mm, CAL < 4 mm, CAL ≤ 3 mm, CAL ≥ 3 mm, CAL 4-6 mm, CAL > 6 mm and CAL ≥ 7 mm, relative frequency of periodontal sites (%).			

APPENDIX 6

Quantitative parameters evaluated in serum samples															
Objective of investigation	**Follow-up**	**Mizuno et al., 2017**		**Wang et al., 2017**		**Geisinger et al., 2016**		**Kapellas et al., 2016**		**Artese et al., 2015a**		**Kumar et al., 2015**		**Wu et al., 2015**	
		CG: *n*, 14 and 13 for 3 and 6 months follow-up, respectively	**IG:** *n*, 17 and 15 for 3 and 6 months follow-up, respectively	**CG** *n*, 20	**IG** *n*, 19	**CG** *n*, 235	**IG** *n*, 240	**CG** *n*, 20	**IG** *n*, 24	**CG** *n*, 12	**IG** *n*, 12	**CG** *n*, 15	**IG** *n*, 15	**CG** *n*, 23	**IG** *n*, 23
E-Selectin (ng/mL)	Baseline	-	-	-	-	65.3 ± 36.36	63.99 ± 33.25	-	-	-	-	-	-	-	-
	6 months	-	-	-	-	Δ, -0.1 ± 19.96	Δ, -2.33 ± 16.08	-	-	-	-	-	-	-	-
ICAM (ng/mL)	Baseline	-	-	-	-	402 ± 157.5	405.4 ± 160.8	-	-	-	-	-	-	-	-
	6 months	-	-	-	-	Δ, -0.6 ± 114.3	Δ, -0.3 ± 113.1	-	-	-	-	-	-	-	-
VCAM (ng/mL)	Baseline	-	-	12.94 (10.66 to 32.56) IR, 21.9	16.49 (11.23 to 37.82) IR, 26.59	695.4 ± 352.6	676.2 ± 306	-	-	-	-	-	-	-	-
	6 months	-	-	-	-	Δ, 10.5 ± 94.5	Δ, 17.9 ± 99.5	-	-	-	-	-	-	-	-
TNF-α (pg/mL)	Baseline	-	-	21.75 ± 14.31	25.65 ± 14.13	1.81 ± 1.56	1.91 ± 2.45	-	-	-	-	10.08 ± 2.47	10.98 ± 3.63	-	-
	1.5 months	-	-	-	-	-	-	-	-	6,140 (4,560 to 6,520); IR, 1,960	6,060 (5,020 to 7,100); IR, 2,080	-	-	-	-
	3 months	-	-	18.87 ± 9.1 Δ, -2.88 ± 12.55	17.84 ± 7.9 Δ, -7.81 ± 12.27	-	-	-	-	-	-	10.04 ± 2.39 Δ, -0.04 ± 2.43	7.85 ± 2.46 Δ, -3.13 ± 3.55	-	-
	6 months	-	-	-	-	Δ, 0 ± 0.64	Δ, 0 ± 1.29	-	-	5,930 (5,230 to 7,010); IR, 1,780	6,220 (5,150 to 7,300); IR, 2,150	-	-	-	-
IL-6 (pg/mL)	Baseline	-	-	12.94 (10.66 to 32.56) IR, 21.9	16.49 (11.23 to 37.82) IR, 26.59	2.69 ± 3.51	2.67 ± 2.93	-	-	13,990 (11,390 to 17,600); IR, 6,210	13,230 (10,320 to 15,570); IR, 5,250	-	-	-	-
	3 months	-	-	12.65 (10.24 to 19.76)	8.24 (3.98 to 11.66) IR, 7.68	-	-	-	-	-	-	-	-	-	-

				IR, 9.52											
	6 months	-	-	-	-	Δ, -0.1 ± 2.78	Δ, -0.03 ± 2.33	-	-	13,290 (11,580 to 16,200); IR, 4,620	10,570 (9,620 to 12,720); IR, 3,100	-	-	-	-
IL-8 (ng/mL)	Baseline	-	-	-	-	0.006 ± 0.004	0.007 ± 0.006	-	-	4.66 (3.97 to 5.67); IR, 1.7	3.15 (2.9 to 4.41); IR, 1.51	-	-	-	-
	6 months	-	-	-	-	Δ, 0.0005 ± 0.0004	Δ, 0.0008 ± 0.004	-	-	4.98 (4.48 to 5.67); IR, 1.19	3.59 (2.58 to 4.66); IR, 2.08	-	-	-	-
IL-10 (pg/mL)	Baseline	-	-	-	-	0.32 ± 0.56	0.43 ± 1.2	-	-	-	-	-	-	-	-
	6 months	-	-	-	-	Δ, 0.04 ± 0.39	Δ, 0.01 ± 0.46	-	-	-	-	-	-	-	-
IL-17 (ng/mL)	Baseline	-	-	-	-	-	-	-	-	2.35 (2.21 to 2.84); IR, 0.63	2.95 (2.7 to 3.94); IR, 1.24	-	-	-	-
	6 months	-	-	-	-	-	-	-	-	2.38 (2.09 to 3.08); IR, 0.99	3.52 (3.09 to 4.09); IR, 1	-	-	-	-
FGF-21 (pg/mL)	Baseline	-	-	82.61 ± 54.15	78.66 ± 51.38	-	-	-	-	-	-	-	-	-	-
	3 months	-	-	88.14 ± 51.78 Δ, 5.53 ± 53	106.32 ± 70.36 Δ, 27.66 ± 63.05	-	-	-	-	-	-	-	-	-	-
MCP-1 (ng/mL)	Baseline	-	-	-	-	-	-	-	-	21 (11.94 to 29.96); IR, 18.02	21.43 (15.03 to 27.83); IR, 12.8	-	-	-	-
	6 months	-	-	-	-	-	-	-	-	15.99 (11.94 to 20.04); IR, 8.1	19.62 (12.37 to 26.76); IR, 14.39	-	-	-	-
APN (mg/L)	Baseline	-	-	14.11 ± 7.23	15.34 ± 8.31	-	-	-	-	-	-	-	-	-	-
	3 months	-	-	14.39 ± 8.83 Δ, 0.28 ± 8.15	24.52 ± 12.01 Δ, 9.18 ± 10.65	-	-	-	-	-	-	-	-	-	-
	6 months	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Visfatin (ng/mL)	Baseline	-	-	-	-	-	-	-	-	-	-	-	-	53.15 ± 35.39	51.66 ± 38.85

	3 months	-	-	-	-	-	-	-	-	-	-	-	-	51.37 ± 36.73 Δ, -1.78 ± 36.08	18.8 ± 12.34 Δ, -32.86 ± 34.38
	6 months	-	-	-	-	-	-	-	-	-	-	-	-	52.22 ± 32.98 Δ, -0.93 ± 34.25	18.47 ± 11.18 Δ, -33.19 ± 34.64
Oxidative index	Baseline	0 ± 1.7	0.1 ± 1.5	-	-	-	-	-	-	-	-	-	-	-	-
	3 months	0.2 ± 1.1 Δ, 0.2 ± 1.49	-0.9 ± 1.6 Δ, -0.8 ± 1.55	-	-	-	-	-	-	-	-	-	-	-	-
	6 months	0.2 ± 1.6 Δ, 0.2 ± 1.65	0.4 ± 1.6 Δ, 0.3 ± 1.55	-	-	-	-	-	-	-	-	-	-	-	-
hs-CRP (mg/L)	Baseline	-	-	-	-	5.09 ± 6.64	4.98 ± 5.88	6 ± 6.6	6.1 ± 6.3	-	-	-	-	-	-
	3 months	-	-	-	-	-	-	4.5 ± 4.2 Δ, -1.5 ± 5.79	4.1 ± 3.7 Δ, -2 ± 5.48	-	-	-	-	-	-
	4 months	-	-	-	-	-	-	-	-	-	-	-	-	-	-
	6 months	-	-	-	-	Δ, -0.02 ± 4.68	Δ, 0.65 ± 5.16	-	-	-	-	-	-	-	-

Legend: CG, control group; IG, intervention group; *n*, absolute frequency; mean ± standard deviation; median [inferior quartile (25%) and superior quartile (75%)]; IR - interquartile range; Δ, follow-up periods minus baseline; -, data not available.

APPENDIX 6

(Continued)

Objective of investigation	Follow-up	Raman et al., 2014		Barthi et al., 2013		Chen et al., 2012		Koromantzos et al., 2012		Sun et al., 2011		Sun et al., 2010		Katagiri et al., 2009	
		CG *n*, 17	**IG** *n*, 15	**CG** *n*, 8	**IG** *n*, 21	**CG:** *n*, 40, 41 and 41 for 1.5, 3 and 6 months follow-up, respectively	**IG:** IG1 *n*, 42 IG2 *n*, 42, 41 and 43 for 1.5, 3 and 6 months	**CG** *n*, 30	**IG** *n*, 30	**CG** *n*, 75	**IG** *n*, 82	**CG** *n*, 30	**IG:** DM1 + T *n*, 29 DM2 + T *n*, 24	**CG** *n*, 17	**IG** *n*, 32

							follow-up, respectively								
TNF-α (pg/mL)	Baseline	-	-	0.7 ± 0.6	0.8 ± 0.3	10.52 ± 3.37	IG1: 11.19 ± 3.97 IG2: 12.43 ± 15.55	-	-	11.54 ± 2.27	11.47 ± 2.3	12.59 ± 2.3	-	12.59 ± 2.3	-
	1.5 months	-	-	-	-	10.19 ± 2.81 Δ, -0.33 ± 3.13	IG1: 10.12 ± 3.3 Δ, -1.07 ± 3.68 IG2: 10.68 ± 3.63 Δ, -1.75 ± 14.09	-	-	-	-	-	-	-	-
	2 months	-	-	-	0.8 ± 0.3 Δ, 0 ± 0.3	-	-	-	-	-	-	-	-	-	-
	3 months	-	-	-	-	11.33 ± 3.75 Δ, 0.81 ± 3.58	IG1: 11.37 ± 5.18 Δ, 0.18 ± 4.69 IG2: 10.37 ± 4.39 Δ, -2.06 ± 13.89	-	-	11.37 ± 2.35 Δ, -0.17 ± 2.31	10.43 ± 2.28 Δ, -1.04 ± 2.29	-	DM1 + T: 7.34 ± 2.03 DM2 + T: 11.55 ± 2.43	-	DM1 + T: 7.34 ± 2.03 DM2 + T: 11.55 ± 2.43
	6 months	-	-	1.2 ± 1.3 Δ, 0.5 ± 1.13	0.8 ± 0.3 Δ, 0 ± 0.3	10.98 ± 2.42 Δ, 0.46 ± 3.01	IG1: 10.78 ± 2.97 Δ, -0.41 ± 3.58 IG2: 11.03 ± 3.77 Δ, -1.4 ± 14.05	-	-	-	-	-	-	-	-
IL-6 (pg/mL)	Baseline	-	-	1.1 ± 0.7	0.9 ± 0.6	-	-	-	-	10.73 ± 2.52	10.62 ± 2.44	11.68 ± 2.71	-	11.68 ± 2.71	-
	2 months	-	-	-	0.9 ± 0.6 Δ, 0 ± 0.6	-	-	-	-	-	-	-	-	-	-
	3 months	-	-	-	-	-	-	-	-	10.42 ± 2.43 Δ, -0.09 ± 2.48	9.45 ± 2.25 Δ, -1.17 ± 2.35	-	DM1 + T: 5.85 ± 1.29 DM2 + T: 10.83 ± 2.47	-	DM1 + T: 5.85 ± 1.29 DM2 + T: 10.83 ± 2.47
	6 months	-	-	1.3 ± 0.3	1.1 ± 0.6 Δ, 0.2 ± 0.6	-	-	-	-	-	-	-	-	-	-

				Δ, 0.2 ± 0.61											
MMP-2	Baseline	-	-	-	-	-	-	12.93 ± 0.06	12.79 ± 0.07	-	-	-	-	-	-
	3 months	-	-	-	-	-	-	12.95 ± 0.06 Δ, 0.02 ± 0.06	12.82 ± 0.06 Δ, 0.03 ± 0.07	-	-	-	-	-	-
	6 months	-	-	-	-	-	-	12.89 ± 0.09 Δ, -0.04 ± 0.08	12.75 ± 0.09 Δ, -0.04 ± 0.08	-	-	-	-	-	-
MMP-9	Baseline	-	-	-	-	-	-	11.62 ± 0.11	11.53 ± 0.13	-	-	-	-	-	-
	3 months	-	-	-	-	-	-	11.64 ± 0.08 Δ, 0.02 ± 0.1	11.42 ± 0.13 Δ, -0.11 ± 0.13	-	-	-	-	-	-
	6 months	-	-	-	-	-	-	11.51 ± 0.14 Δ, -0.11 ± 0.13	11.19 ± 0.15 Δ, -0.34 ± 0.14	-	-	-	-	-	-
APN (mg/L)	Baseline	-	-	8.6 ± 5.6	7.2 ± 8.3	-	-	-	-	-	7.99 ± 2.1	8.2 ± 1.87	-	8.2 ± 1.87	-
	2 months	-	-	-	8.2 ± 7.7 Δ, 1 ± 8.02	-	-	-	-	-	-	-	-	-	-
	3 months	-	-	-	-	-	-	-	-	-	8.35 ± 2.13 Δ, 0.03 ± 2.12	-	DM1 + T: 11.04 ± 2.15 DM2 + T: 8.65 ± 19.93	-	DM1 + T: 11.04 ± 2.15 DM2 + T: 8.65 ± 19.93
	6 months	-	-	6.8 ± 3.4 Δ, -1.8 ± 4.89	8.9 ± 9.8 Δ, 1.7 ± 9.14	-	-	-	-	-	-	-	-	-	-
Leptin (ng/mL)	Baseline	-	-	14.6 ± 12.4	18 ± 16.8	-	-	-	-	-	-	-	-	-	-
	2 months	-	-	-	19.4 ± 19.1 Δ, 1.4 ± 18.06	-	-	-	-	-	-	-	-	-	-
	6 months	-	-	13.2 ± 11.1 Δ, -1.4 ± 11.8	16.7 ± 14.4 Δ, -1.3 ± 15.74	-	-	-	-	-	-	-	-	-	-
	Baseline	-	-	12.6 ± 7.2	12.5 ± 10.6	-	-	-	-	-	-	-	-	-	-

Resistin (ng/mL)	2 months	-	-	-	11.2 ± 7.8 Δ, -1.3 ± 9.51	-	-	-	-	-	-	-	-	-	-
	6 months	-	-	13.8 ± 11.1 Δ, 1.2 ± 9.75	14.4 ± 13.2 Δ, 1.9 ± 12.11	-	-	-	-	-	-	-	-	-	-
OxS marker *d*-8-iso	Baseline	-	-	-	-	-	-	3.33 ± 0.09	3.29 ± 0.1	-	-	-	-	-	-
	3 months	-	-	-	-	-	-	3.32 ± 0.09 Δ, -0.01 ± 0.09	3.29 ± 0.09 Δ, 0 ± 0.1	-	-	-	-	-	-
	6 months	-	-	-	-	-	-	3.3 ± 0.08 Δ, -0.03 ± 0.09	3.22 ± 0.08 Δ, -0.07 ± 0.09	-	-	-	-	-	-
hs-CRP (mg/L)	Baseline	5.6 ± 5.2	10.5 ± 15.8	2.05 ± 2.24	1.15 ± 1.94	2.81 ± 4.05	IG1: 3.21 ± 4.45 IG2: 3.09 ± 4.64	0.29 ± 0.25	0.42 ± 0.19	5.81 ± 1.23	5.87 ± 1.26	6.42 ± 1.28	-	2.03 (0.43 to 5.11); IR, 4.68	0.74 (0.31 to 2.69); IR, 2.38
	1 month	-	-	-	-	-	-	-	-	-	-	-	-	1.45 (0.66 to 6.79); IR, 6.13	0.81 (0.38 to 2.29); IR, 1.91
	1.5 months	-	-	-	-	2.36 ± 1.94 Δ, -0.45 ± 3.51	IG1: 2.38 ± 2.88 IG2: 1.88 ± 2.83 Δ, -1.21 ± 4.05	-	-	-	-	-	-	-	-
	2 months	-	-	-	0.85 ± 0.93 Δ, -0.3 ± 1.68	-	-	-	-	-	-	-	-	-	-
	3 months	5.6 ± 5.3 Δ, 0 ± 5.25	7 ± 13.4 Δ, -3.5 ± 14.75	-	-	2.24 ± 2.06 Δ, -0.57 ± 3.51	IG1: 1.48 ± 1 IG2: 1.96 ± 1.98 Δ, -1.13 ± 4.03	0.43 ± 0.23 Δ, 0.14 ± 0.24	0.22 ± 0.26 Δ, -0.2 ± 0.23	5.51 ± 1.29 Δ, 0.06 ± 1.26	5.06 ± 1.2 Δ, -0.81 ± 1.23	-	DM1 + T: 4.2 ± 0.92 DM2 + T: 5.68 ± 1.13	0.81 (0.23 to 4.25); IR, 4.02	1.09 (0.51 to 3.25); IR, 2.74
	6 months	-	-	1.72 ± 1.91 Δ, -0.33 ± 2.1	0.85 ± 0.68 Δ, -0.3 ± 1.7	3.16 ± 5.45 Δ, 0.35 ± 4.9	IG1: 1.58 (1.31) IG2: 1.53 ± 1.27 Δ, -1.56 ± 4.15	0.37 ± 0.19 Δ, 0.08 ± 0.23	0.08 ± 0.26 Δ, -0.34 ± 0.23	-	-	-	-	1.25 (0.31 to 2.64); IR, 2.33	1.04 (0.33 to 1.83); IR, 1.5

Legend: CG, control group; IG, intervention group; *n*, absolute frequency; mean ± standard deviation; median [inferior quartile (25%) and superior quartile (75%)]; IR - interquartile range; Δ, follow-up periods minus baseline; -, data not available.

APPENDIX 7

Quantitative parameters evaluated in plasma samples					
Objective of investigation	**Follow-up**	**Geisinger et al., 2016**		**Kapellas et al., 2016**	
		CG *n*, 235	**IG** *n*, 240	**CG** *n*, 20	**IG** *n*, 24
ICAM (ng/mL)	Baseline	402 ± 158	405.4 ± 161	-	-
	6 months	Δ, -0.6 ± 114	Δ, -0.3 ± 113	-	-
IL-6 (pg/mL^{-1})	Baseline	-	-	2.9 ± 2.5	2.9 ± 2.7
	3 months	-	-	1.8 ± 2.5 Δ, -1.1 ± 2.5	3.7 ± 2.1 Δ, 0.8 ± 2.46
IL-8 (pg/mL)	Baseline	6 ± 4.18	6.51 ± 5.52	-	-
	6 months	Δ, 0.54 ± 3.45	Δ, 0.08 ± 4.25	-	-
hs-CRP (mg/L)	Baseline	5.09 ± 6.64	4.98 ± 5.88	-	-
	6 months	Δ, -0.02 ± 4.68	Δ, 0.65 ± 5.16	-	-

Legend: CG, control group; IG, intervention group; *n*, absolute frequency; mean ± standard deviation; Δ, follow-up periods minus baseline; -, data not available.

2 – ATIVIDADES ACADÊMICAS

Apenas atividades acadêmicas vinculadas à Faculdade de Odontologia da Universidade Federal do Rio de Janeiro, iniciadas e desenvolvidas ao longo do período de doutoramento foram consideradas.

A. Artigos submetidos e em revisão por pares, não relacionados à Tese:

- *Influence of sociodemographic factors on users' perception of the quality of public oral health service: a cross-sectional study*
- *Neo-osteogenesis using an intentionally exposed polypropylene membrane after tooth extraction or guided bone regeneration technique: case series and literature review*

B. Resumo publicado nos anais do SAIO/IADR Latinoamerica:

- Impacto do tratamento da periodontite no estado inflamatório em pacientes com diabetes mellitus

C. Apresentação de Poster em evento científico:

- *Potential impact of COVID-19 pathogenesis on Periodontal Medicine Research* (Apresentado no IADR Boston 2021)
- Impacto do tratamento da periodontite no estado inflamatório em pacientes com diabetes mellitus (Apresentado no SAIO/IADR Latinoamerica 2021)
- Periodontite e doença hepática gordurosa: alterações moleculares relacionadas a sobrepeso e obesidade (Apresentado pela aluna de IC em três eventos acadêmicos: i) 44º Congresso Universitário Brasileiro de Odontologia, 2020; ii) Jornada Odontológica d Instituto de Saúde de Nova Friburgo, Universidade Federal Fluminense, 2020; e iii) Jornada da Faculdade de Odontologia da UFRJ, 2020)

D. Produção técnica (vídeos educativos):

- Coorientador, disciplina de Clínica Integrada – “O que você precisa saber sobre os vírus e o novo coronavírus”.

- Coorientador, disciplina de Periodontia 2 – Dois vídeos produzidos a partir da atividade de extensão intitulada “Doenças cardiovasculares e sua relação com saúde bucal e COVID-19”.

E. Atividade em ensino:

- Treinamento em docência cursado como disciplina e atividade prática obrigatória do curso nas disciplinas de Periodontia I e II.
- Professor Substituto de Periodontia, alocado nas disciplinas de Periodontia e Clínica Odontológica Integrada, no período 2020-2022.
- Integro a equipe de trabalho da disciplina de Odontologia Baseada em Evidência, coordenada pela professora Dra Lucianne Cople Maia desde 2022/1.

F. Coorientações:

- Iniciação Científica (12 meses) – Pamella Oliveira de Azevedo (Concluído)
- Trabalho de Conclusão de Curso, Graduação FOUFRJ – Alex Rangel (Em andamento)
- Mestrado Acadêmico FOUFRJ, Periodontia – Natasha Soares Nogueira (Concluído)
- Mestrado Profissionalizante FOUFRJ, CTBMF – Leandro Torres (Em andamento)
- Mestrado Profissionalizante FOUFRJ, Periodontia – Bruno (Em andamento)

G. Atividade de extensão:

- Tutor do Projeto de Extensão intitulado “Reorientacão da formação profissional em Odontologia-UFRJ-Experiências no SUS com ênfase nos determinantes sociais de saúde e fatores de risco para as doenças periodontais” nos anos de 2020 e 2021.

H. Avaliador:

- Membro de banca de Doutorado da aluna Monique Oliveira Rodrigues, Periodontia FOUFRJ – Incidentaloma Adrenal: Um novo fator preditivo de periodontite?

- Membro avaliador de trabalhos acadêmicos em três eventos: Jornada On-line da Faculdade de Odontologia da UFRJ, 2020; 3º Encontro de Odontologia de Excelência - EOEX 2020; e Avaliador de mesa clínica sobre infecção cruzada por coronavírus na FOUFRJ 2020

I. Outros:

- Implementação (Presidente) e gerenciamento do serviço de Notificação e Monitoramento de COVID-19 da FOUFRJ.
- Plantonista 48h/semana no Notificação e Monitoramento de COVID-19 da FOUFRJ.
- Revisão e postagem dos vídeos educativos produzidos pelos grupos de alunos de Clínica Integrada da FOUFRJ.
- Aquisição de recurso para o Programa de Pós-graduação em Odontologia, área de concentração Periodontia: Edital FAPERJ Nº05/2020.
- Atividade de pesquisa interinstitucional envolvendo FOUFRJ, HUCFF|Nutrologia, GUCFF|Hepatologia, e Laboratório de Imunofarmacologia da Fiocruz.
- Atividade de pesquisa interinstitucional FOUFRJ–FOP/UPE, tendo resultado na publicação de um artigo nesse período, na aplicação de um Projeto no Edital Universal CNPq no ano de 2021 (não contemplado).
- Carga horária superior a 1.000 horas de disciplinas integralizadas durante o curso.

ANEXOS

THE JOURNAL OF PROSTHETIC DENTISTRY

SYSTEMATIC REVIEW

Toxicity potential of denture adhesives: A scoping review

Rayanna Thayse Florêncio Costa, DDS, MS,[a] Davi da Silva Barbirato, DDS, MS, PhD,[b] Joel Ferreira Santiago Junior, DDS, MS, PhD,[c] Maria Cynésia Medeiros de Barros, DDS, MS, PhD,[d] Eduardo Piza Pellizzer, DDS, MS, PhD,[e] and Sandra Lúcia Dantas Moraes, DDS, MS, PhD[f]

ABSTRACT

Statement of problem. Denture adhesives are widely used products, but limited evidence regarding their toxicity is available.

Purpose. The purpose of this scoping review was to map the existing literature on the toxic potential of denture adhesives.

Material and methods. This scoping review was structured based on the 5-step methodology proposed by Arksey and O'Malley and The Joanna Briggs Institute Manual for Evidence Synthesis and followed the Preferred Reporting Items for Systematic reviews and Meta-Analyses extension for Scoping Reviews. The methods were registered on the Open Science Framework (<osf.io/nqryt>). The following research question was formulated: Are there any toxic effects related to the use of denture adhesives? The electronic literature search was performed independently by 2 authors in the following databases: PubMed/MEDLINE, Scopus, Web of Science, and the Cochrane Library. The inclusion criteria were in vitro and clinical studies; studies that evaluated the cytotoxic properties of denture adhesives as local or systemic implications; and studies published in English.

Results. The search conducted in October 2020 provided 1099 articles. In total, 33 studies were included, 14 in vitro and 19 clinical studies. Commercially available denture adhesives have a dose-dependent cytotoxic effect on fibroblasts and keratinocytes, with poor cell recovery noted in older human fibroblasts. Patients presented different levels of neurologic or hematological alterations associated with the excessive use of denture adhesives.

Conclusions. Most commercially available denture adhesives have a dose-dependent cytotoxic effect, and the use of well-adapted removable dental prostheses, proper patient follow-ups, and correct instructions for their use when indicated should be a priority. (J Prosthet Dent 2021;■:■-■)

Edentulism is a public health problem[1] that influences the composition of the oral microbial flora, quality of speech and mastication, socialization, quality of life, nutrition, and systemic conditions related to metabolism and intestinal dysbiosis.[2-5] Removable dental prostheses are the most commonly used rehabilitation treatment, and access to this type of treatment is high because of their low cost. Removable prostheses are often chosen based on patient preferences or contraindications to dental implant placement.[6]

Limitations of removable dental prostheses include their ability to remain in an ideal functional position because of unsatisfactory retention and stability.[7-9] Denture adhesives (DAs) represent a conservative way to improve prosthetic retention, stability, and masticatory performance.[10-13] Their use has also been reported to increase patient satisfaction in the postinstallation phase[14,15] and benefits patients with xerostomia,[16,17] lack of muscle control,[18] severe bone resorption, and maxillofacial deformities.[8]

DAs for removable dental prostheses can be classified as soluble (creams, pastes, and powders) and insoluble

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Lateral periodontal cyst: A rare clinicopathological presentation mimicking a residual cyst

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Abstract

This article describes an unusual clinical-radiographic presentation of a lateral periodontal cyst, as a differential diagnosis of a residual cyst, following the 'CARE guidelines for case reports'. The radiolucent lesion was identified on the imaging exam of a 53-year-old male patient. Based on radiographic findings and aspiration puncture, the probable diagnosis was a residual cyst; however, histological analysis revealed a thin, non-inflamed fibrous capsule covered by some epithelial layers in most of the lesion. The definitive diagnosis was a lateral periodontal cyst with unusual clinical and radiographic features. The cyst was surgically enucleated and local bone neoformation was observed, with no signs of recurrence after 12 months. The results of this study suggest that a radiolucent lesion, suggestive of a residual cyst or keratocyst in the maxilla, may correspond to a lateral periodontal cyst. In this context, the histopathological analysis of the cyst is essential for the definitive diagnosis.

Key words: *Cysts, odontogenic cysts, periapical cysts, periodontal cysts.*

Introduction

The lateral periodontal cyst (LPC) is an uncommon entity, representing 0,4% to 0,7% of all oral and maxillofacial cysts and 0,6% to 2% of the odontogenic cysts (1-6). It is considered a non-inflammatory developmental cyst associated with the proliferation of odontogenic remnants, possibly from the dental lamina, reduced enamel epithelium or epithelial rests of Malassez (2,6-9). It is characterized by a unilocular radiolucency between the roots of vital erupted teeth, mostly premolars, canines