UNIVERSIDADE FEDERAL DO RIO DE JANEIRO - UFRJ

Centro de Ciências da Saúde – CCS

PROGRAMA DE PÓS-GRADUAÇÃO EM PSIQUIATRIA E SAÚDE MENTAL - PROPSAM

Instituto de Psiquiatria – IPUB

Relação entre hormônios sexuais, função sexual e qualidade de vida em mulheres na pós-menopausa e uso da dehidroepiandrosterona no tratamento da depressão, sintomas depressivos e disfunção sexual.

CLAYTON PEIXOTO DE SOUZA

Dissertação de Mestrado submetida como requisito parcial para obtenção do título de Mestre em Saúde Mental pelo Programa de Pós-Graduação em Psiquiatria e Saúde Mental – PROPSAM do Instituto de Psiquiatria – IPUB da Universidade Federal do Rio de Janeiro – UFRJ.

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RESUMO

O climatério é um período em que ocorrem diversas alterações hormonais na vida da mulher. Alterações no humor, na função sexual e na qualidade de vida são comuns neste período e o estudo das relações entre esses quadros e parâmetros hormonais é necessário, assim como é necessário um melhor conhecimento de alternativas de tratamento para essas alterações. **Objetivo**: descrever os efeitos do uso da dehidroepiandrosterona no tratamento da depressão e de sintomas depressivos, bem como o seu efeito sobre aspectos da função sexual, além de apresentar a relação entre hormônios sexuais, função sexual e qualidade de vida. **Método**: os dois artigos de revisão sistemática seguiram a metodologia da declaração PRISMA para relatórios de revisão sistemática e meta-analises. O artigo original relata um estudo de corte transversal, realizado em uma amostra de 36 mulheres na pós-menopausa com idade entre 45 e 65 anos, pacientes de um ambulatório de climatério na cidade de Campo Grande – MS. Todas estas mulheres passaram por avaliação do humor, qualidade de vida e função sexual, além de coleta de sangue para avaliação hormonal. **Resultados**: Uma das revisões sistemáticas demonstrou melhorias significativas em pacientes com depressão e em sintomas depressivos de pacientes com esquizofrenia, anorexia nervosa, HIV e insuficiência adrenal após o tratamento com DHEA. A outra revisão observou que o tratamento com DHEA melhorou vários aspectos da função sexual, como desejo, lubrificação, dor, excitação, orgasmos e frequência sexual. No artigo original foi observada a relação positiva entre aspectos da função sexual e da qualidade de vida, mas opostas ao esperado entre o nível de hormônios sexual e aspectos da função sexual e da qualidade de vida. **Conclusão**: Estudos com DHEA publicado até o momento indicam resultados positivos quanto ao uso do DHEA no tratamento da depressão e sintomas depressivos, especialmente em depressão leve ou resistente a terapia convencional. Também indicam que o tratamento com DHEA é eficaz na melhora de vários aspectos da função sexual, mas esse efeito não foi significativo em todas as populações estudadas. Concluímos também que fatores psicossociais são capazes de influenciar positivamente a função sexual, mesmo diante de condições fisiológicas adversas.

ABSTRACT

The climacteric is a period in which several hormonal alterations take place in a woman's life. Alterations in mood, sexual function and in the quality of life are common in this period and the study of the relation between these frames and hormonal parameter is necessary, as well as it is necessary to have a better knowledge of treatment alternatives for these alterations. **Objective**: to describe the effects of dehydroepiandrosterone use on depression treatment and of depressive symptoms, as well as its effects on aspects of sexual function, besides presenting the relation between sexual hormones, sexual function and quality of life. **Method**: both articles of systematic review followed the PRISMA's declaration methodology for reports of systematic review and meta-analysis. The original article reports a cross-sectional study, conducted on a sample of 36 women on post-menopause between the age of 45 and 65, patients of an outpatient climacteric in the city of Campo Grande – MS. All these women went through a mood, life quality and sexual function assessment, besides blood collection for hormonal assessment. **Results**: One of the systematic reviews demonstrated significant improvements on patients with depression and on depressive symptoms of patients with schizophrenia, anorexia nervosa, HIV and adrenal insufficiency after the treatment with DHEA. The other review observed that the treatment with DHEA improved several aspects of sexual function, such as desire, lubrication, pain, arousal, orgasms, and sexual frequency. On the original article it was observed the positive relation between aspects of sexual function and of life quality, whereas there were opposites of the expected between sexual hormonal levels and aspects of sexual function and of life quality. **Conclusion**: Studies published on DHEA have so far indicated positive results regarding the use of DHEA in depression treatment and depressive symptoms, especially in mild depression or resistance of conventional therapy. It also indicates that DHEA treatment is efficient in improving several aspects of sexual function, but such effect was not significant in all populations studied. We also conclude that psychosocial factors are capable of positively influencing sexual function, even in the face of physiological adverse conditions.

SUMÁRIO

1 INTRODUÇÃO

1.1 A menopausa e suas implicações

O desenvolvimento biológico feminino, diferentemente do que ocorre com os homens possuem eventos que são marcantes e destacam a mudança de fase na vida da mulher. O início e o fim dos ciclos menstruais são importantes eventos que sinalizam estas mudanças de fases. Enquanto a menarca marca a entrada da mulher no período reprodutivo, a menopausa marca o final deste período. A menopausa mais do que um simples acontecimento biológico é um marco com afetações biopsicossociais, em muitos casos, bastante negativas.

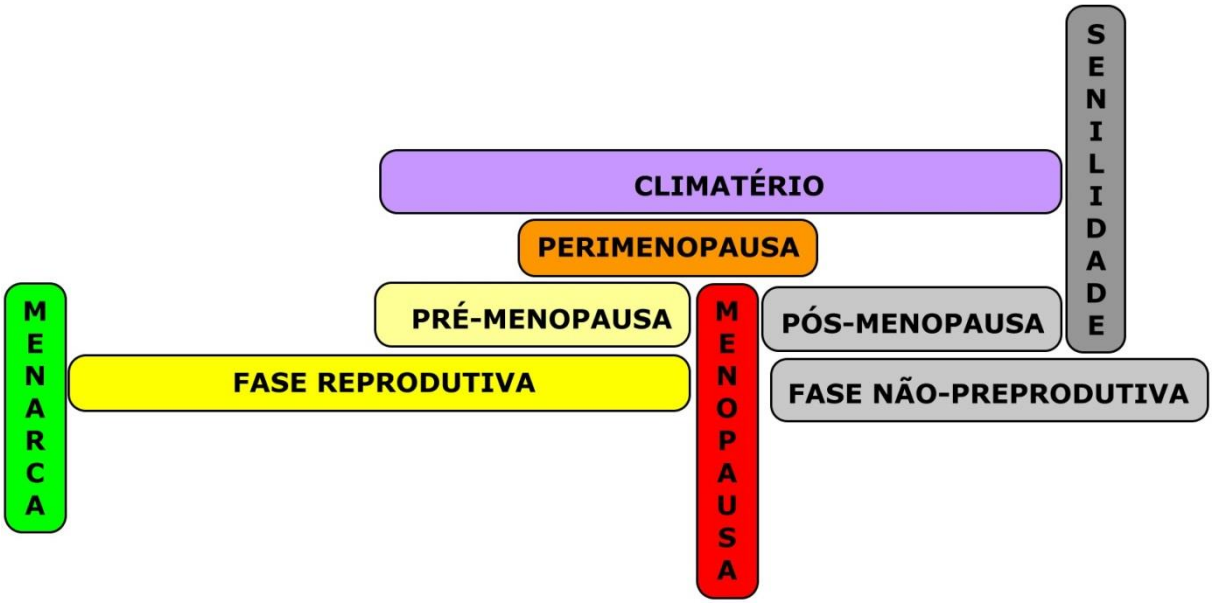
Uma pesquisa etimológica do termo menopausa remete a palavra grega *"emmenopausis",* que é a junção das palavras "*mēn"* (meses ou luas) e "*pausis"* (término). De fato esta palavra aponta para fim do ciclo biológico que é vivenciado todos os meses pelas mulheres em período fértil [1]. Apesar de não ser incomum o termo "menopausa" ser empregado na descrição de uma fase, o correto é entendê-la como um evento que marca a chegada da fase conhecida como pós-menopausa.

Mas se por um lado a menopausa não é uma fase, ela ocorre dentro de uma fase conhecida como climatério. O climatério ocorre justamente no período de transição entre as fases reprodutiva e não reprodutiva da mulher. Durante o climatério ocorrem mudanças hormonais, ocasionadas principalmente pela falência ovariana, que provocarão alterações significativas e que podem afetar tanto o corpo quanto a psique feminina.

O climatério pode ser dividido em três fases: pré-menopausa, perimenopausa, e pós-menopausa [2]. Vale ressaltar que não há consenso nesta subdivisão, pois há autores que dividem a menopausa em duas fases [3], e mesmo os que tratam climatério como sinônimos de perimenopausa [4]. Independente destas divergências conceituais, a pré-menopausa corresponde aos últimos anos da vida reprodutiva feminina, iniciando por volta dos 40 anos (em alguns casos mais cedo) e se

caracteriza pelo início do declínio da produção de hormônios sexuais, especialmente do estradiol e da progesterona [5]. Nesta fase os ciclos menstruais ainda mantem a regularidade [2]. A perimenopausa corresponde ao período que engloba os últimos anos da pré-menopausa até um ano depois da menopausa. A perimenopausa se caracteriza por ciclos menstruais irregulares, que podem ser mais curtos ou mais longos que o normal [2]. Já a pós-menopausa corresponde à fase que se inicia depois da última menstruação e seguirá até os 65 anos, quando começa a fase da vida conhecida como senilidade (Figura 1).

Figura 1 – Fases da vida da mulher



Com algumas exceções, o climatério é um período vivenciado de forma crítica, uma vez que as alterações decorrentes do hipoestrogenismo impactam de forma negativa vários aspectos da vida. Entre as alterações decorrentes do hipoestrogenismo estão: sintomas vasomotores, perda de energia, diminuição da força física, alterações no sono, no trato urinário, no humor, na função sexual e cognição, além de um aumento de risco para o desenvolvimento de doenças cardiovasculares, de osteoporose, de transtornos ansiosos e depressivos [6].

1.2 Transtornos de humor na menopausa

Um aspecto que tem merecido atenção por parte de médicos, psicólogos e pesquisadores diz respeito à prevalência de transtornos de humor no período de transição entre as fases reprodutiva e não reprodutiva feminina. Embora a maioria das mulheres passe por esta fase sem apresentar sintomas depressivos mais relevantes, estima-se que em torno de 9% das mulheres serão acometidas por depressão durante o climatério [7, 8].

É importante destacar que não há evidências suficientes para dizer que esta fase seja a causadora de depressão, mas tudo indica que suas características atuam como facilitadoras do surgimento da depressão e de outros transtornos de humor. Mulheres que tiveram transtorno depressivo ou ansioso prévios a esta fase, têm maior probabilidade de apresentar um novo episódio [9]. Em um estudo com pacientes de um ambulatório de menopausa na cidade do Rio de Janeiro, foi observado uma prevalência de 57% de transtornos ansiosos e do humor, sendo mais comum a ocorrência de transtornos de ansiedade generalizada e de transtorno depressivo maior [10]. Dados semelhantes foram observados em outros estudos [11,12]. Um estudo realizado com 749 mulheres no climatério observou a prevalência de ansiedade de 49,8% naquela população [13]. Tais dados reforçam o entendimento de que, mesmo não sendo a causadora de transtornos de humor existe uma forte correlação entre estas condições patológicas e o climatério.

Esta correlação entre climatério e transtornos de humor pode ter como pano de fundo fatores ambientais típicos deste momento da vida, que associado às alterações corpóreas comuns ao envelhecimento pode agir como desencadeadores de ansiedade e depressão. Entre estes fatores está o medo de envelhecer e de deixar de ser desejada, uma vez que no imaginário feminino a mulher pode ser rejeitada pelo parceiro que tende a buscar parceiras mais jovens [14]. Este medo se justifica pela importância que a sociedade atual dá a juventude em detrimento do envelhecimento. Outro medo muito comum nesta fase é o de ficar só, especialmente por esta fase coincidir, algumas vezes, com a saída (temporária ou definitiva) dos filhos do lar [15]. Outro fator típico deste momento da vida e que pode contribuir para alterações no humor é o sentimento de inutilidade que pode acometer algumas

mulheres, principalmente aquelas que dedicaram maior parte da vida ao exclusivo cuidado dos filhos [7].

1.3 Disfunções sexuais na menopausa

A prevalência de disfunção sexual aumenta com a idade, sendo mais comum em mulheres no climatério do que em idade fértil [16]. Enquanto de 25% a 33% das mulheres com idade entre 35 e 59 anos manifestam disfunções sexuais, entre 60 e 65 anos estes percentuais variam de 51% a 75% [17].

O real impacto da menopausa na função sexual não está totalmente esclarecido. Uma vez que tanto as alterações hormonais como o aspecto global do envelhecimento trazem estas implicações, o mais provável é que exista uma confluência entre estes dois fatores. No entanto, sabe-se que o hipoestrogenismo é responsável direto pela perda da lubrificação natural dos tecidos urogenitais, o que tem como uma das consequências a maior incidência de dor durante ou após as relações sexuais, quadro clínico conhecido como dispareunia [16]. Apesar disso, há de se considerar o impacto que outras alterações típicas desta fase, como a redução do colágeno cutâneo e a mudança na distribuição da gordura corporal. Fatores que além de implicações físicas e estéticas podem afetar negativamente a auto-imagem e a auto-estima da mulher que vivencia um contexto social em que aspectos como infertilidade, cabelos brancos, rugas, flacidez e adiposidade não costumam ser admirados [14,18].

As crenças relacionadas à sexualidade também podem exercer um impacto negativo com a chagada da menopausa. Isso porque a internalização de dogmas que relacionam a prática sexual ao pecado, pode influenciar mesmo que inconsciente a função sexual nesta etapa não reprodutiva, uma vez que o motivo apontado por algumas religiões para a prática do sexo, no caso a reprodução, cessa com a menopausa. Segundo Nobre et al. (2006): “*as crenças sexuais desempenham um papel como fatores de vulnerabilidade para a disfunção sexual”* [19].

A má qualidade da atividade sexual com o parceiro sexual durante a fase reprodutiva, bem como um relacionamento atual distante e conflituoso parece também contribuir, se não para o surgimento de disfunções sexuais ao menos para a falta de interesse em buscar uma resolução de problemas sexuais que por ventura

ocorram durante o climatério. Há casos na literatura onde mulheres que não tiveram relacionamentos sexuais satisfatórios durante a fase reprodutiva, encontra na menopausa uma espécie de “libertação” da imposição da prática sexual a qual foi submetida na fase anterior [20]. Assim, alterações que provocam dor durante a relação sexual, como a perda da lubrificação vaginal, que poderiam facilmente ser tratadas, acabam não recebendo a importância devida, pois não há interesse por parte destas mulheres em continuar sexualmente ativas [20].

1.4 Alterações cognitivas na menopausa

Apesar de o climatério ser um estado de transição marcado especialmente pelo final da vida reprodutiva feminina, os sintomas envolvidos no climatério são em grande parte de natureza neurológica, sendo indicativos da interrupção de sistemas regulados por estrogênios como a termorregulação, sono, ritmo cardíaco e processamento sensorial. Estes elementos afetam direta ou indiretamente vários domínios da função cognitiva [21], além de que existem estudos que apontam para o papel dos estrogênios em várias funções cerebrais, como cognição, memória e aprendizado [22, 23].

Mesmo considerando que um declínio da memória está associado principalmente ao envelhecimento, alguns estudos tem observado relação entre queixas de um declínio da memória com a menopausa, especialmente em mulheres que passam por menopausa cirúrgica [24-26].

A possível correlação entre o hipoestrogenismo e piora na cognição é corroborada por estudos experimentais que apontam para o fato de que os esteroides sexuais apresentam efeitos sobre o cérebro com potencial afetação da cognição, sendo inclusive a estrogenioterapia durante o climatério associada a melhora na concentração e na memória. [27] Contudo, um estudo com 156 mulheres no climatério com queixas neuropsíquicas não observou diferenças significativas entre o padrão cognitivo desta população em comparação a outras amostras de mulheres em idade reprodutiva [28], o que mostra que esta relação precisa ser mais estudada.

1.5 Menopausa e qualidade de vida

Qualidade de vida é uma expressão de difícil conceituação, uma vez que ao longo do tempo o entendimento do que é considerada uma “vida de qualidade” tem mudado. Além de que, por envolver aspectos subjetivos este juízo pode variar de pessoa para pessoa [29].

Apesar disso, a Organização Mundial da Saúde (OMS) empreendeu esforços e definiu a qualidade de vida como *“a percepção do indivíduo sobre a sua posição na vida, no contexto da cultura e dos sistemas de valores nos quais ele vive, e em relação a seus objetivos, expectativas, padrões e preocupações*" [30]. Apesar da generalidade deste conceito, a própria OMS trabalhou na construção de um instrumento para avaliar a qualidade de vida, a “*World Health Organization Quality of Life* (WHOQOL)” [30].

Outra definição descrita por Minayo apud Netto (1994) pode nos ajudar na compreensão deste conceito: *“Vou considerar como qualidade de vida... aquela que ofereça um mínimo de condições para que os indivíduos nela inseridos possam desenvolver o máximo de suas potencialidades...”* [31]. Focando mais especificamente neste último conceito, em que a qualidade de vida é relacionada com a possibilidade de desenvolver o máximo das nossas potencialidades, fica claro que as alterações provenientes da menopausa exercem um forte e negativo impacto na qualidade de vida das mulheres. Apoiando esta afirmação, um estudo qualitativo realizado na cidade de Belo Horizonte –MG investigou a percepção de um grupo de 378 mulheres entre 40 e 65 anos e indicou que, para aquele grupo, a menopausa foi relacionada apenas a perdas. Vale destacar que a amostra deste estudo foi composta por mulheres com pelo menos 11 anos de educação escolar, o que aumento o entendimento do quanto esta fase pode pesar contra a qualidade de vida, mesmo entre mulheres mais esclarecidas [14].

1.6 O potencial terapêutico da dehidroepiandrosterona (DHEA) no tratamento da depressão, disfunções sexuais e na melhora de aspectos da qualidade de vida

A DHEA é um hormônio esteroide produzido principalmente pelas glândulas suprarrenais, gônadas e cérebro [32]. Precursor indireto dos hormônios sexuais testosterona e estrógenos, DHEA e seu sulfato (DHEA-S) são os esteroides mais abundantes em circulação no corpo humano [32, 33]. A produção da DHEA está fortemente relacionada com a idade, alcançando o seu pico de produção entre 25 e 35 anos, quando começa apresentar um declínio que culminará em uma produção de aproximadamente 10% do seu pico por volta dos 70 anos [34].

Atualmente existe um crescente interesse por parte de cientistas e da população geral nos efeitos do DHEA. Enquanto cientistas buscam compreender melhor o seu mecanismo de ação e os efeitos sobre diversos quadros clínicos, a população geral em diversos cantos do mundo demonstra interesse em seu uso como suplemento alimentar, muito pelo fato de a ela ser atribuído diversos “poderes” [35]. Apesar de boa parte do que se atribui a este hormônio ainda carecer de comprovação científica, acredita-se que a DHEA tem capacidade de melhorar o humor, bem-estar, força muscular, cognição, desempenho sexual e aparência, além de uma suposta capacidade de rejuvenescimento [35-38].

Pesquisas utilizando DHEA vêm sendo conduzidas desde o início década de 1990, mas é a partir do ano 1999 que podemos ver um aumento significativo em trabalhos publicados sobre o tema [39]. Este interesse tem se mantido e vários estudos continuam a ser publicados anualmente. A DHEA tem sido estudada em doenças autoimunes, doenças endócrinas, transtornos mentais e disfunção sexual e em muitos destes estudos tem sido observado efeitos significativos, especialmente na remissão de sintomas depressivos e na melhora da função sexual em mulheres na pós-menopausa [39,40].

No período de ocorrência da menopausa os níveis de DHEA encontram-se em declínio. Estudos utilizando DHEA têm sido unânimes em mostrar que o uso deste hormônio aumenta os níveis circulantes de DHEA e DHEA-S [35], apesar deste aumento não ter sido capaz de melhorar todos as variáveis em que foi analisado, de fato houve remissão de sintomas depressivos, melhora na função sexual e na qualidade de vida em vários trabalhos realizados [36-38, 40]. Estes

achados, aliados a efeitos colaterais brandos tem mantido este hormônio como foco de muitos pesquisadores.

1.7 Explanação

Esta dissertação é composta por artigos redigidos entre os anos de 2014 e 2016 e engloba os trabalhos realizados durante o período de estágio probatório e o curso de Mestrado. Os trabalhos consistem em duas revisões sistemáticas e um artigo produzido a partir de dados de uma pesquisa realizada no Centro de Atenção à Mulher da cidade de Campo Grande – MS.

A primeira revisão (Artigo 1), entitulada "The Effects of Dehydroepiandrosterone (DHEA) in the Treatment of Depression and Depressive Symptoms in Other Psychiatric and Medical Illnesses: A Systematic Review" foi publicada no ano de 2014. Com o objetivo de avaliar o efeito do uso da DHEA no tratamento tanto da depressão como de sintomas depressivos de doenças psiquiátricas e não psiquiátricas, como insuficiência adrenal, lúpus eritematoso sistêmico e fibromialgia, este trabalho se pautou pelas orientações do PRISMA Statement for Reporting Systematic Reviews and Meta-Analyses of Studies", procedendo busca eletrônica nas bases de dados bases de dados PubMed, ISI Web of Knowledge e Virtual Health Library. Após seguir a estratégia de busca adotada para este trabalho, 22 artigos foram selecionados para compor esta revisão e permitiram o entendimento de que o tratamento com DHEA é capaz de melhorar sintomas depressivos em pacientes com depressão, bem como os sintomas depressivos de pacientes com esquizofrenia, anorexia nervosa, vírus da imunodeficiência humana (HIV) e insuficiência adrenal. Contudo o tratamento com DHEA não foi efetivo em todas as populações estudadas.

A segunda revisão que integra esta dissertação (Artigo 2), intitulada "The effects of Dehydroepiandrosterone (DHEA) on sexual function: A systematic review" encontra-se submetida ao periódico Climateric da "*International Menopause Society"*. Este segundo trabalho teve como objetivo avaliar o efeito do tratamento com DHEA nos diversos aspectos da função sexual, como desejo, excitação, orgasmo, dor entre outros. O método de revisão sistemática seguiu o "PRISMA

Statement for Reporting Systematic Reviews and Meta-Analyses of Studies" e procedeu busca eletrônica nas bases de dados PubMed, ISI Web of Science e Virtual Health Library (BVS). Após a aplicação metodológica de busca e seleção de artigos foram incluídos 38 trabalhos que observaram melhoria significativa em diversos aspectos da sexualidade como interesse sexual, lubrificação, dor, excitação, orgasmo e frequência sexual. Observou também que seu efeito foi melhor em populações com disfunção sexual, especialmente em mulheres na perimenopausa e na pós-menopausa.

O último artigo (Artigo 3), intitulado "Relação entre Hormônios Sexuais, Função Sexual e Qualidade de Vida" é fruto de uma análise correlacional realizada a partir de um banco de dados construído com informações advindas do projeto de pesquisa: "Alterações sexuais, cognitivas e do humor em mulheres na pós-menopausa com Síndrome de Insuficiência Androgênica", realizado entre os anos de 2013 e 2016 no Centro de Atenção à Mulher em Campo Grande – MS.

Nesta pesquisa, devidamente submetida e aprovada por um Comitê de Ética local, 84 mulheres com idade entre 45 e 65 anos, menopausadas foram avaliadas por meio de um estudo de corte transversal, em que verificamos questões relacionadas a transtornos de depressão e ansiedade, disfunção sexual, qualidade de vida e cognição. Também foi coletado sangue de 36 pacientes e procedido análise hormonal. A avaliação da relação entre hormônios sexuais, função sexual e qualidade de vida deu origem ao último artigo que compõe esta dissertação.

2 DESENVOLVIMENTO

Uma vez que esta dissertação foi construída a partir de um conjunto de artigos (como já dito anteriormente), esta parte do trabalho inicia-se com a apresentação integral dos artigos que a compõe e que podem ser lidos a partir da próxima página.

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The Effects of Dehydroepiandrosterone (DHEA) in the Treatment of Depression and Depressive Symptoms in Other Psychiatric and Medical Illnesses: A Systematic Review

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Abstract: International interest on the benefits of using the steroid hormone Dehydroepiandrosterone (DHEA) on various aspects of human health, including the regulation of mood, is increasing. This study aimed to review the scientific literature on the use of DHEA in the treatment of depression and depressive symptoms in other psychiatric and medical illnesses. PubMed, ISI Web of Knowledge and Virtual Health Library (VHL) databases were independently searched by two researchers using the following terms: depression, treatment, DHEA, and mood. Clinical studies were considered eligible when subjects were treated with DHEA and psychological assessments of depression were conducted. No time limits or language for this research were imposed. One 183 references were identified, and 22 references were selected to compose this review. Significant improvements related to the use of DHEA in patients with depression were observed, in addition to improvements in depressive symptoms in patients with schizophrenia, anorexia nervosa, HIV and adrenal insufficiency. No significant improvements were observed regarding depressive symptoms in patients with fibromyalgia; the results observed in patients with autoimmune diseases and healthy individuals remain contradictory. Although the selected studies demonstrated good methodological applications, most studies consisted of small samples, and only 3 studies were conducted in a young population. Therefore, we concluded that the studies published to date indicate promising results regarding the use of DHEA in the treatment of depression and depressive symptoms, especially in depression that is mild or resistant to conventional therapy.

Keywords: Depressed, depressing, depression, depressive, DHEA, DHEA-S, mood, treatment.

INTRODUCTION

Dehydroepiandrosterone (DHEA) and its sulfate (DHEA-S) are the most abundant circulating steroids in the human body [1-3]. DHEA is primarily produced by the adrenal glands, gonads, and brain and is a (indirect) precursor of the main adrenal hormones. DHEA production is strongly associated with age; it reaches a peak of production between 25 to 35 years, followed by a subsequent decline to approximately 10-20 % of its peak by 70 years of age [3, 4].

DHEA and DHEA-S appear to be important in regulating mood, however, the relationship between DHEA-S levels and depression is complex, and the literature has not indicated a satisfactory way to reconcile these contradictory findings; thus, it is necessary to address the issue with parsimony [3]. In a study that examined the relationship between plasma levels of various hormones and depression, the only hormone that correlated with depressive symptoms was DHEA-S, where it was observed that higher plasma levels of DHEA-S were associated with fewer depressive symptoms [5]. This study is consistent with most studies on the topic which have indicated a negative correlation between DHEA-S and depressed mood [6-9].

However, speculation regarding the therapeutic potential of DHEA is not restricted to its action in improving mood. Research has been conducted to increase knowledge regarding DHEA's actions in patients with eating disorders, autoimmune diseases and cognitive problems [10-13]. The potential to improve well-being, cognition sexual performance and appearance has been attributed to DHEA [4]. These potential benefits coupled with the mild side effects have contributed to a growing interest in this hormone. Although DHEA is marketed freely as food supplementation in some countries, such as USA, its use remains restricted in other countries because there is not sufficient knowledge regarding its effectiveness and particularly the effects of long term use [1, 14-17].

Based on this information and to ascertain the effects of DHEA use on depression, a review of the scientific literature was undertaken to determine whether DHEA is effective in the treatment of depression and depressive symptoms in other psychiatric and medical illnesses.

METHODOLOGY

To identify the effects of DHEA use on depression and depressive symptoms, an electronic search was conducted in

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PubMed, ISI Web of Knowledge and Virtual Health Library (VHL) databases using the following terms: depression (depressive, depressed, depressing), humor, treatment, and/or DHEA. The search was conducted between the months of July and August 2013 and in May 2014. A search strategy was created in PubMed using exactly the following terms and Boolean operators: Depression treatment DHEA OR depressive treatment DHEA OR depressed treatment DHEA OR depressing treatment DHEA OR mood treatment DHEA. The only filter used was Clinical Trial. No limitations of time or language of publication were imposed. Clinical studies and Randomized Clinical Trials (RCT) in which subjects were treated with DHEA and utilized a psychological assessment of depression were eligible. Pre-clinical studies, systematic reviews and clinical studies that had different titles but had their data referenced in previous research that had already been entered in the study were considered ineligible.

The research was conducted by two reviewers who worked independently throughout the selection process, with pre-established criteria including only the databases to be used, search strategy and the terms to be searched. The study selection process involved the following steps: database search; exclusion of repeated references; summary analysis; exclusion of articles deemed ineligible after reading the summaries; full analysis of potentially eligible articles; exclusion of articles deemed ineligible after full reading; and the final selection of studies. At the end of the selection process, the reviewers met to discuss differences regarding the inclusion/exclusion of references. Throughout the selection process of the references, there was divergence in the inclusion/exclusion of three studies. They were referred for the evaluation of a third reviewer. Following the analysis, the third reviewer agreed that the three studies could be excluded because they did not completely fulfill the eligibility criteria.

The data extraction was performed using a protocol specifically designed to meet the objectives of this review. This protocol was previously tested in a sample of 4 items, and the divergences in data extraction were discussed among the authors to reach a consensus. The title, author(s), date of publication, study population, sex, age, type of study, instruments, procedures, daily dose of DHEA used, duration of treatment, number of evaluation, the main results related to mood and hormone levels, adverse effects and possible biases were extracted from the studies.

RESULTS

The initial database search identified 183 references; 48 references were excluded because they had references that appeared in more than one database. Therefore, 135 references were included in the analysis of titles and abstracts. During the analysis of the articles' titles and abstracts, 106 references were excluded because they did not fulfill the eligibility criteria; 29 references were considered potentially eligible and underwent thorough analysis of the full text. During the complete analysis of the references, 7 additional references were excluded. One reference was excluded because the instrument of psychological assessment was not provided, two references were excluded because they reported only information relevant to the review of studies previously included and from which important information had been collected, and 4 references were excluded because they assessed depression using quality of life scales, not specific depression scales. Finally, 22 references were selected to compose this systematic review (Fig. **1**). The search results separated by databases are shown in (Table **1**). A summary of key information of each item included in this review are shown in (Table **2**).

To present clearer results, we separated the results into mental disorders, medical illnesses and healthy populations (Fig. **2**). We selected studies that included eight different types of populations (Fig. **3**).

MENTAL DISORDERS

Depression

Four studies were identified that specifically dealt with the use of DHEA in the treatment of depression. Two studies were conducted only with patients with major depression, and two studies also included patients with dysthymia. The assessment instruments used in the psychological studies were the Hamilton Depression Rating Scale (HAM-D), the Bunny-Hamburg Global Depression (BH), the Beck Depression Inventory (BDI), the Visual Analogue Scale (VAS), the Symptom Checklist (SCL-90), the Cornell Dysthymia Scale (CDS), the Center for Epidemiologic Studies Depression Scale (CES-D) and the Structured Clinical Interview for DSM (SCID). The only instrument used to assess depression that was included in all studies (described in the results) was the HAM-D (Fig. **4**). In all studies, the subjects were free from medication use or their medication use had been stabilized during treatment. Any alteration or addition of drugs in the patients was not allowed.

Of the four studies that evaluated the use of DHEA as a monotherapy for depression, the oldest study was conducted by Wolkowitz *et al.* (1997), which was the first CT to use DHEA as a monotherapy in the treatment of depression. In this pilot study, 6 patients with major depression were treated for 4 weeks with oral doses of DHEA that ranged from 30 to 90 mg/day and were individually adjusted to achieve normal circulating levels of DHEA and DHEA-S at 16:00. The subjects underwent weekly hormonal reviews and psychological assessments at the beginning and end of the study. Wolkowitz (1997) noted that the use of DHEA significantly improved the patients' scores on all psychiatric rating scales used in the study: the HAM-D ($p < 0.03$), the BH ($p < 0.03$), the SCL-90 ($p < 0.001$) and the BDI ($p < 0.01$). The improvements became significant at the end of the second week on the HAM-D and the BH and at the end of the third week on the BDI. The study also identified a significant increase in the circulating levels of DHEA ($p = 0.006$) and DHEA-S ($p = 0.1$) at 16:00. The increase in the circulating levels of DHEA was significantly correlated with decreased scores on the SLC-90 ($p = 0.01$), and the increase in the circulating levels of DHEA-S was significantly correlated with decreased scores on the BDI ($p < 0.008$). The patients' cortisol levels did not decrease significantly, but their DHEA/cortisol and DHEA-S/cortisol ratios increased significantly ($p = 0.02$). The changes in cortisol levels were not significantly correlated with behavioral changes. The increased ratios of DHEA/cortisol were significantly correlated

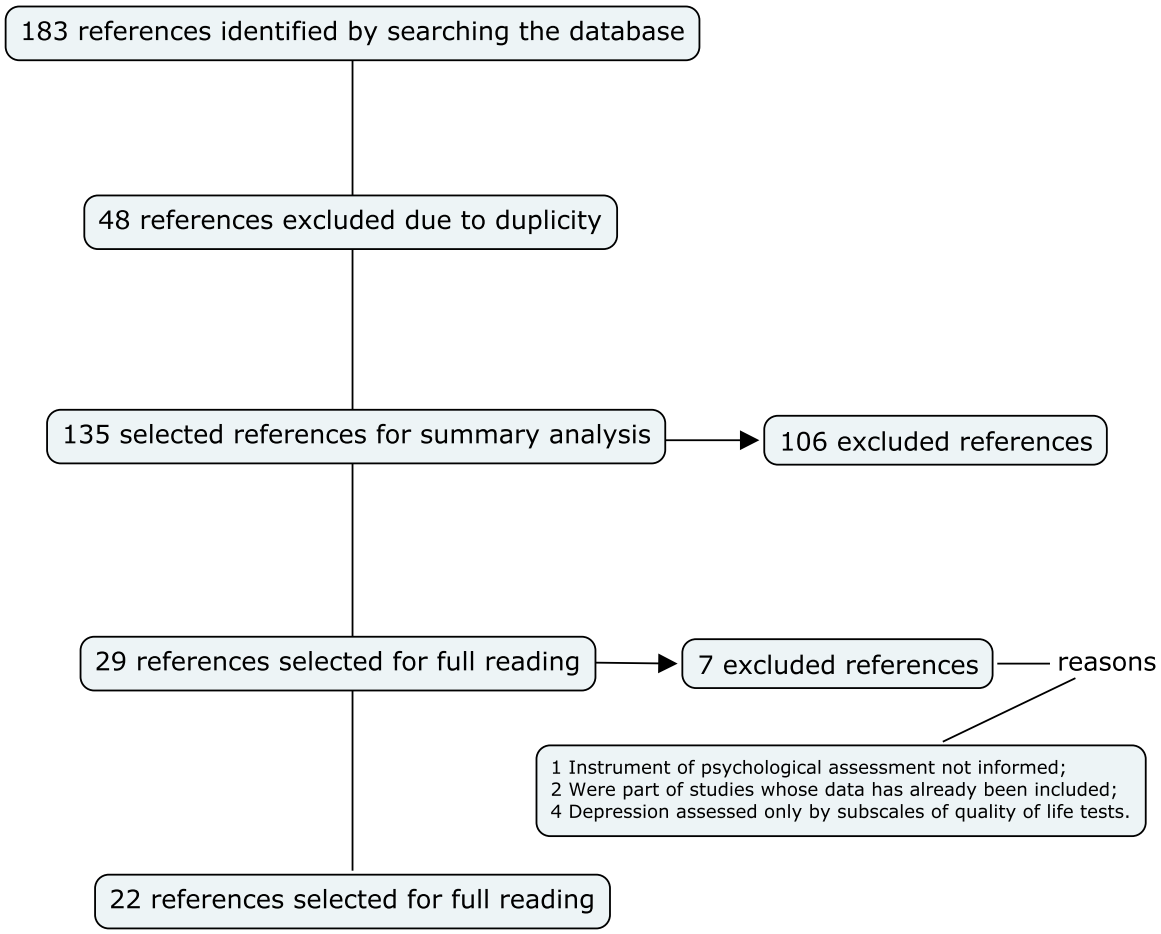


Fig. (1). Flow of information through the different phases of a systematic review.

Table 1. Results of searches for database.

Database	Total References Found	Repeated References	Summary Analysis	Ineligible References	Full Review	Ineligible	Selected
PUBMED	124	0	124	95	29	7	22
ISI	25	15	10	10	0	0	0
VHL	34	33	1	1	0	0	0
TOTAL	**183**	**48**	**135**	**106**	**29**	**7**	**22**

with decreased scores on the HAM- D ($p < 0.04$), and the decreased ratios of DHEA-S/cortisol were correlated with decreased scores on the HAM-D ($p < 0.006$).

At the end of the study, one of the research subjects (a 67-year-old woman with resistant depression) was selected to continue treatment with DHEA for 6 months. During this period, she received 60 mg/day of DHEA for 4 months and then 90 mg/day of DHEA for 2 months. The patient was evaluated monthly during the six months of treatment and also two months after the gradual withdrawal of DHEA. There was an increase in her circulating DHEA and DHEA-S related to the DHEA serum dose, which reached levels typically found in a healthy young adult. Levels of DHEA and DHEA-S reached their peaks in the 5th month of treatment, with the use of 90 mg/day. The patient's levels of DHEA increased 491% over her baseline levels in the 5th month (DHEA 5th Month = 501 ng/dl), and her DHEA-S increased by 1.470% (DHEA-S 5th Month = 206μg/dl). The patient's DHEA and DHEA-S level increases were accompanied by improvements in her HAM-D, BDI and BH scale scores of 48, 57 and 72%, respectively. The improvements were greater at the end of the study (after 2 months of treatment with DHEA 90 mg/day) than at the end of 4 months with 60 mg/day DHEA. The patient's levels of DHEA and DHEA-S and the DHEA/cortisol and DHEA-S/cortisol ratios were inversely correlated with her depression scale scores.

Table 2. Key data from each study.

Author	Year of Publication	N	Gender M/F	Age	Population	Type of Study	Daily DOSE	Treatment Time	Instruments	Results
Wolkowitz *et al.*[8]	1997	6	3/3	Average: NI Range: 51 to 72	Depression	Clinical Trial	30 to 90 mg.	4 weeks	HAM-D, BDI, BH, Depression Rating Scala Global.	The use of DHEA improved scores on depression tests. One patient receiving prolonged treatment improved but 72% on a scale.
Wolkowitz *et al.* [18]	1999	22	12/10	Average:44 (SD = 8) Range: 33 to 54	Depression	Randomized Clinical Trials	30 to 90 mg.	6 weeks	HAM-D	DHEA was associated with a significantly greater reduction in depression compared to placebo.
Bloch *et al.* [9]	1999	15	12/3	Average: 50 (SD = 5.8) Range: 45 to 63	Depression	Randomized Clinical Trials	90 to 450 mg.	6 weeks	HAM-D, BDI, CDS	A robust effect of DHEA on mood was observed compared to placebo. At the end of 6 weeks 60% of patients responded to treatment.
Schimidt *et al.* [19]	2005	46	23/23	Average: 50 (SD = 5.8) Range: 45 to 63	Depression	Randomized Clinical Trials	90 to 450 mg.	6 weeks	HAM-D, BDI, CDS, CES-D	The use of DHEA was associated with significant improvement in HAM-D scores and the CES-D.
Strous *et al.*[20]	2003	27	15/12	Average: 37.4 (SD = 12) Range: 20 to 67	Schizophrenia	Randomized Clinical Trials,	25 to 100 mg.	6 weeks	HAM-D	The results indicated a significant improvement in depressive symptoms in subjects treated with DHEA.
Strous *et al.*[21]	2005	27	15/12	Average: 37.4 (SD = 12) Range: 20 to 67	Schizophrenia	Randomized Clinical Trial	25 to 100 mg.	6 weeks	HAM-D	Minimal effects of DHEA on hormone profiles were observed.
Bloch *et al.* [10]	2012	21	0/21	Average: 26.9 (SD= 8.2) Range: 17 to 47	Anorexia Nervosa	Randomized Clinical Trials	100 mg.	6 months	BDI	Patients treated with DHEA had a significant increase in BMI, which was positively correlated with improvement in mood.
Rabkins *et al.* [22]	2000	45	39/6	Average: 41 (SD = 7.1) Range: 28 to 57	HIV+	Randomized Clinical Trials	100 to 500 mg.	16 weeks	HAMD-D	The use of DHEA shows promising results in the treatment of depression in HIV + patients, but persistence on the placebo response requires further studies to identify the therapeutic efficacy.
Rabkins *et al.* [23]	2006	145	122/23	Average: 44 (SD = 9) Range: (NI)	HIV+	Randomized Clinical Trials	100 to 400 mg.	8 weeks	HAM-D, BDI.	DHEA has been shown to be superior to placebo in reducing depressive symptoms in HIV + patients.
Arlt *et al.* [24]	1999	24	0/24	Average: 42 (SD = NI) Range: 23 to 59	Adrenal Insufficiency	Randomized Clinical Trials	50 mg.	4 months	HAD, Multidimensional Mood Questionnaire, Zerssen Questionnaire.	DHEA significantly enhanced the results of tests of depression compared to baseline and placebo.

(Table 2) contd….

Author	Year of Publication	N	Gender M/F	Age	Population	Type of Study	Daily DOSE	Treatment Time	Instruments	Results
Binder *et al*. [25]	2009	23	0/23	Average 18 (SD = 5.8) Range: 13 to 25	Adrenal Insufficiency	Randomized Clinical Trials	25 mg.	12 months	CES-D	The use of DHEA improved scores for depression tests.
Hunt *et al*. [26]	2000	39	15/24	Average: 40 (SD = NI) Range: 26 to 69	Adrenal Insufficiency	Randomized Clinical Trials	50 mg	3 months	General Health Questionnaire (GHQ-30) of Goldberg	The use of DHEA improved mood compared to baseline and placebo.
Nordmark *et al*. [27]	2005	37	0/37	Average: 47.05 (SD = 12.25) Range: NI	Systemic Lupus Erythemato-sus	Randomized Clinical Trials	20 to 30 mg	12 months	Hopkins Symptom Check List (HSCL); Psychological General Well-Being index (PGWB)	The use of DHEA improved scores of a depression subscale.
Hartkamp *et al.* [11]	2008	60	0/60	Average: 53.5 (SD = NI) Range: 23 to 76	Sjögren Syndrome	Randomized Clinical Trials	200 mg.	12 months	Zung Self-Rating Depression Scale.	The use of DHEA showed no advantage over placebo.
Hartkamp *et al.* [12]	2010	60	0/60	Average 43 (SD = NI) Range: 21 to 71	Systemic Lupus Erythe-matosus	Randomized Clinical Trials	200 mg.	12 months	Zung Self-Rating Depression Scale.	The use of DHEA showed no advantage over placebo.
Finckh *et al.* [28]	2005	52	0/52	Average: 58.9 (SD = 9.2) Range: NI	Fibromialgy	Randomized Clinical Trials	50 mg.	3 weeks	HAD	DHEA did not improve mood in patients with fibromyalgia.
Wolf *et al.* [29]	1997	40	25/15	Average: 69.4 (SD = 1.2) Range: 61 to 76	Healthy Elderly	Randomized Clinical Trials	50 mg	2 weeks	CES-D	The use of DHEA did not improved mood in healthy older adults.
Wolf *et al.* [30]	1998	14	14/0	Average: 71.1 (SD = 1.7) Range: 59 to 81	Healthy Elderly Men	Randomized Clinical Trials	50 mg	2 weeks	Multidimensional Mood Questionnaire (MDBF).	The use of DHEA did not improved mood in healthy elderly men.
Arlt *et al.* [31]	2001	22	22/0	Average: 59.3 (SD = 5.6) Range: 50 to 69.	Healthy Elderly Men	Randomized Clinical Trials	50 mg	4 months	MDBF, HAD.	The use of DHEA showed no advantage over placebo.
van Niekerk *et al.* [32]	2001	41	41/0	Average: 69.4 (SD = 0.9) Range: 62 to 76	Healthy Elderly Men	Randomized Clinical Trials	50 mg	13 weeks	Current mood scale, Profile of Mood States -Short Form (POMS-SF)	The use of DHEA showed no benefit in relation to humor.
Alhaj *et al.* [33].	2006	24	24/0	Average: 23.6 (SD = 5.1), Range: 18 to 34	Healthy Young Men	Randomized Clinical Trials	300 mg	7 days	BDI, VAS.	The use of DHEA improved the mood in subjective evaluation tests.
Kritz-Silverstein *et al.* [34]	2008	225	110/115	Average: 68 (SD = 8) Range: 55 to 85	Healthy Population	Randomized Clinical Trials	50 mg.	12 weeks	BDI	DHEA did not improve mood in healthy elderly subjects.

A loss of effect was observed after two months after the withdrawal of DHEA with a return in the circulating levels of DHEA and DHEA-S to baseline as well as a return of the baseline depression scores on all the scales used.

In a second study, Wolkowitz *et al.* (1999) evaluated 22 patients with major depression in a double-blind placebo-controlled RCT in which the subjects were divided evenly into two groups that received DHEA or a placebo for 6 weeks. During the first two weeks, the patients received DHEA at a rate of 30 mg/day, followed by 60 mg/day of DHEA for the second two weeks and 90 mg/day for the last two weeks. The HAM-D indicated a better antidepressant response in the DHEA-treatment individuals compared with the placebo group (30.5%, SD = 29.1 VS 5.3%, SD = 20.2; p = 0.004). Five of the 11 individuals who received DHEA were considered to be responders, but none of the individuals in the placebo group were considered to be responders. No differences were observed in sex or in the subjects who had pre-existing use of antidepressant medication compared with the subjects who did not use medication.

Bloch *et al.* (1999) conducted a double-blind, crossover, placebo-controlled RCT in 15 patients with major depression

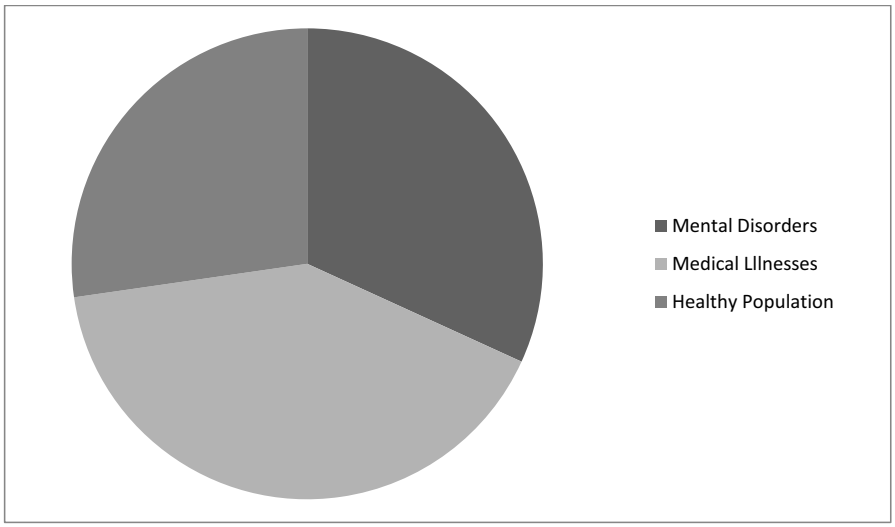


Fig. (2). Number of studies selected by type of population.

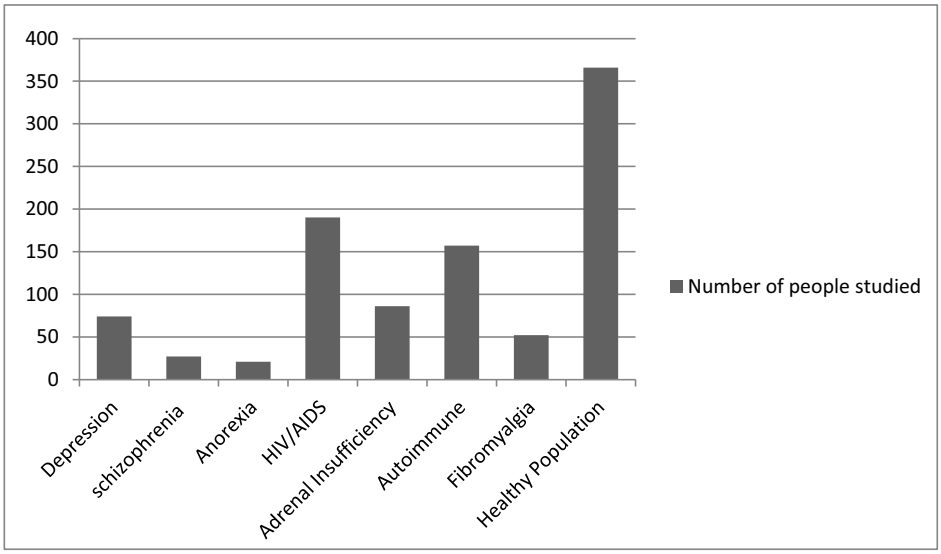
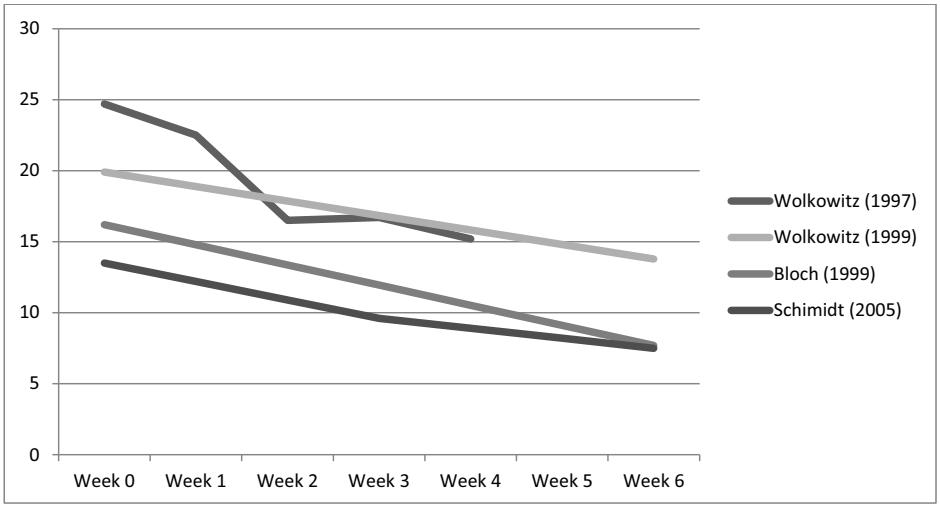


Fig. (3). Number of people studied distributed by population types.



Wolkowitz (1997), ($p < 0.03$); Wolkowitz (1999), ($p < 0.04$); Bloch (1999), ($p < 0.001$); Schmidt (2005), ($p < 0.01$).

Fig. (4). Effect of DHEA on the HAM-D score in samples from patients with depression.

or late onset dysthymia. This study had two 6 week phases, in which one group received a placebo and the other group received DHEA. There was also a crossover phase of the groups. Between the two phases, there was a one-week washout. The DHEA group was treated with a DHEA dose of 150 mg/day in the first 3 weeks of each phase and a dose of 450 mg/day in the final 3 weeks. The patients were assessed at baseline and at the end of weeks 3 and 6 of each phase. A significant effect of treatment with DHEA was observed on the scores of the BDI, the HAM-D and the CDS. No significant changes were observed in the ratings scales related to the treatment time (3 and 6 weeks). A significant reduction in depressive symptoms was observed after the first three weeks of treatment, and similar improvements were observed in the 13 items of the VAS. At the end of the 3rd week of treatment, 7 of the 15 (47%) patients in the DHEA group showed improvement with the use of DHEA compared with only 1 of the 15 (7%) patients in the placebo group. At the end of the 6th week of treatment, 9 of the 15 (60%) patients in the DHEA group had improved and 3 of the 15 (20%) patients in the placebo group had improved. Five individuals were considered non-responders to the DHEA treatment and 10 individuals were considered non-responders to the placebo treatment. The patients who responded to the DHEA treatment were younger compared with the patients who did not respond to treatment. No difference was observed in the basal DHEA and DHEA-S plasma levels between the responders and the non-responders. We observed a tendency of the responders to achieve higher DHEA-S plasma levels during DHEA treatment compared with the non-responders (maximum levels of DHEA-S responders 13.6 ± 7.6 μg/ml VS 7.3 ± 5.1 μg/ml non-responders; $p = 0.08$). Following 3 weeks of 90 mg/day of DHEA, there was a 57 and 275 % increase in the DHEA and DHEA-S plasma levels over baseline, respectively. There was a 180 and 540 % increase in the DHEA and DHEA-S plasma levels over baseline, respectively, after 3 weeks of 450 mg/day of DHEA. No increase was observed in the placebo group. There was also a significant correlation between the changes in the patients' DHEA-S plasma levels and their BDI scores ($p = 0.02$) and a trend towards a correlation with changes in the CDS and HAM-D scores ($p = 0.08$).

Schmidt *et al.* (2005), who collaborated in the study by Bloch (1999), attempted to overcome the shortcomings of the previous study (small sample that primarily consisted of men) by conducting a double-blind, placebo-controlled crossover RCT. The patients suffered from major depression or dysthymia. The study included 46 patients (including data from the 15 subjects studied by Bloch) and followed exactly the same methodological design as Bloch (1999). In this study, there were more subjects with higher levels compared with lower levels (28 VS 18, respectively) of depression. The use of DHEA significantly improved the patients' scores on the HAM-D compared with baseline and the use of a placebo ($p = 0.01$). Similar improvements occurred relative to the BDI and the CDS, but these differences were less robust compared with the placebo. There was a dose-related trend (90 mg/day VS 450 mg/day) ($p = 0.06$), and this is reflected in the lower HAM-D scores following 6 weeks of treatment with DHEA compared with the first 3 weeks ($p = 0.05$). In the crossover study, 23 subjects (12 women and 11 men) treated with DHEA showed a reduction of 50 % or more in their HAM-D scores after 6 weeks compared with the 13 subjects in the placebo group ($p = 0.03$). Only 16 patients (9 women and 7 men) met the criteria for response to DHEA and did not respond to a placebo. When the study was limited to only the stage prior to the intersection, there was a significantly greater number of responders to DHEA (10 of 22) compared with placebo (3 of 24), and these patients showed a reduction of at least 50 % on their HAM-D scores. Upon completion of each stage of the study, 29 subjects were assessed using the SCID. Only 8 subjects who received DHEA met diagnostic criteria for depression compared with 18 subjects who received placebo. Of the 12 patients with major depression, 28 (43%) patients were considered responders, and 11 of the 18 (61%) patients with minor depression were considered responders. The DHEA and DHEA-S plasma levels increased significantly in both men and women compared with the baseline and the placebo. There were no significant differences between the patients' levels of DHEA and DHEA-S at the baseline or in relation to the washout between the phases of the study. The female patients' free testosterone increased by 500 % ($p < 0.01$) after treatment with DHEA compared with the baseline. There was a smaller increase in the free testosterone of the male patients (17 %, $p \leq 0.05$).

Thirteen of the patients who were considered responders agreed to continue in an open study treatment with DHEA at 25 or 50 mg/day. Of these patients, 10 patients were asymptomatic; 7 patients were followed for 12 months, and 3 patients were followed for 6 months. Depression symptoms returned in three of the 10 patients. There were no side effects in the patients who had a prolonged use of DHEA, with the exception of a woman who complained of a moderate but tolerable increase in the oiliness of her skin.

Other Mental Disorders

Strous *et al.* (2003, 2005) published two of the three papers in this group. Both of these articles provided information on a single study with schizophrenic patients admitted to psychiatric hospitals in Israel, where 27 subjects were evaluated with the initial objective of verifying the effect of DHEA on the negative symptoms of schizophrenia. The other study in this group is a recent publication by Bloch *et al.* (2012) that presents the results of a study with a sample of 21 patients with anorexia in which one of the objectives was to evaluate the effects of DHEA on the moods of those studied. Both studies were double-blind, placebo-controlled RCTs, and the studies had similar sample sizes (27 VS 21) and made use of similar DHEA doses. However, the starting dose was lower in the schizophrenic patients (25 mg/day VS 50 mg/day), but the dose progressed to a maximum of 100 mg/day in the final part of both studies. The major methodological difference between the studies involved the treatment time used in each RCT. The Strous (2003, 2005) study ran for 6 weeks, and the Bloch (2012) study ran for 6 months.

The assessment instruments used in the studies were the Positive and Negative Syndrome Scale (PANSS), the Scale for the Assessment of Negative Symptoms (SANS), the HAM-D, the Hamilton Rating Scale for Anxiety (HAM-A), the BDI, the SCID, and the Clinical Global Impression Scale

(CGI-S severity and improved CGI-I). Bloch (2012) made use of only the last three instruments. Of these, only the last two were used in both studies.

The Strous (2003, 2005) study observed a relationship between time and treatment effect in the DHEA group where the patients' HAM-D scores ($p < 0.05$) improved each week. In the placebo group, there were no significant reductions in the patients' HAM-D scores between baseline and the sixth week of treatment. The individuals in the DHEA group showed a significant reduction in their HAM-D scores from the second week compared to baseline ($p < 0.01$), but there was a significant difference between the groups at baseline, which showed that the DHEA group's depression was greater than that of the placebo group's ($p < 0.05$). According to blood tests, eight patients began receiving DHEA before and after the study and showed a significant increase in their DHEA ($p < 0.05$) and DHEA-S ($p < 0.01$) levels, but the DHEA and DHEA-S blood levels of the patients receiving a placebo remained unchanged after the sixth week of treatment. The testosterone levels before treatment showed a significant tendency to correlate with depression as measured by the HAM-D ($p = 0.056$). At the end of the study, except for the changes in the levels of DHEA and DHEA-S, no significant changes were observed in the hormonal measurements for the use of DHEA or a placebo after treatment. The patients' DHEA-S plasma levels increased more than their DHEA plasma levels. Low basal levels of DHEA-S at baseline provided a slightly greater effect on negative symptoms ($p = 0.08$) than DHEA.

Bloch (2012) investigated the effects of DHEA on the mood of patients in a recent RCT in which the main objective was to verify the effect of DHEA treatment on weight and bone metabolism in 21 women with anorexia. The patients underwent psychological evaluation monthly with the BDI and CGI. The results described in his work pointed to improvement in the psychological parameters of both groups. A significant influence of time-related treatment BDI scores ($p = 0.002$) was observed, and these improvements became significant at 3 and 6 months. The patients' CGI-E ($p = 0.01$) score improvements became significant at only the sixth month. There was no significant weight gain at the end of six months in either group, but there were greater initial BMI increases in the DHEA group with a difference peak at 4 months (8.9 % increase), reaching statistical significance ($p = 0.05$). Changes in the patients' moods (CGI-M) were significantly correlated with weight changes in the DHEA group at only months 4 and 6 ($p = 0.001$ and $p = 0.52$, respectively). The patients' DHEA-S levels were significantly higher in the group that received DHEA throughout the study ($p = 0.03$). The DHEA-S and DHEA levels in the testosterone group were higher than their baseline levels and those of the placebo groups after 6 months of treatment ($p = 0.036$). Cortisol levels also decreased after 6 months of treatment in the DHEA group but did not reach statistical significance.

CLINICAL DISEASES

Immunodeficiency Syndrome (AIDS) and Human Immunodeficiency Virus (HIV) Infection

The use of DHEA in AIDS and HIV infection comprised two double-blind, placebo-controlled trials conducted by Rabkin *et al.* (2000, 2006) in HIV+ patients to evaluate the effects of DHEA on mood in these patients. In both studies, HIV+ men and women with depression (major, minor or dysthymia) were included. Both studies used an initial dose of 100 mg/day of DHEA, which was increased to 200 mg/day following one week of treatment. However, in the first study, in the absence of clinical improvement and adverse effects, the dose was increased from 100 mg/day to a maximum of 500 mg/day, while in the second study, the dose limit was 400 mg/day. The study period was 16 weeks in the first study (the 8 week CT was 1st open, followed by the 9th to 12th Open CT only in patients who demonstrated improvement in the first 8 weeks; the 13th to 16th week double-blind phase only involved patients considered responders). The psychological assessment instruments used in both studies included: the SCID, the HAM-D, and the CGI. The Brief Symptom Inventory (BSI) was only used in the first study, and the BDI was only used in the second study. Rabkin (2006) reported that the cutoff of the HAM-D was increased from 7 to 8 because of HIV-related symptoms.

Of the 45 subjects studied by Rabkin (2000), 32 subjects completed at least 8 weeks of treatment. The subjects were an average of 41 years old (SD = 7.1); 51 % of the patients had an AIDS diagnostic average count of 286 cells/mm^3 (SD = 179) CD4 cells. The average number of medications used for HIV was 4.8 (SD = 2.4). Five patients were taking antidepressants with partial response. Four patients were administered testosterone injections and four patients received low doses of trazadone or amitriptyline PRN for insomnia or neuropathic pain. All patients had their medications stabilized for at least eight weeks, and the medications were not changed during the study. In psychiatric terms, 19 (42%) patients met the criteria for minor depression, 13 (28%) patients met the criteria for dysthymia, 6 (13%) patients met the criteria for greater depression and 4 (9%) patients met the criteria for Major Depressive Disorder with partial remission. Three patients had no depressive diagnosis, but were significantly depressed in mood and showed signs of fatigue with 8 points or more on the HAM-D. The baseline mean for the entire group was 12.6 points on the HAM-D. The mean DHEA-S level at baseline was 153 (106) mcg/dl for men and the serum testosterone level was 653 ng/dl (SD = 320). Eight (17%) patients had levels of DHEA-S low for their age. Four (9%) patients had serum testosterone levels considered low. The testosterone level in women was 29 ng/dl (SD = 12) and the average level of DHEA-S was 68 mcg/dl (SD = 69).

Of the 32 participants who completed the study, 23 patients (72%) were classified as responders to DHEA in the 8th week of treatment, with Humor ranked in the CGI as better or much better and with the HAM-D score decreased by at least 50 %. The mean daily dose of DHEA was 322 mg/day (SD = 80) for responders and 383 mg/day (SD = 75) for non-responders. For both groups, the median dose at week 8 was 300 mg/day. Responders improved on all measures of the HAM-D ($p < 0.001$), whereas non-responders only improved on a subsection (vegetative depressive symptoms). When the 7 patients who took antidepressants or testosterone were excluded, the response rate was 68 %, which was not different from the analysis performed on the entire sample. Following two weeks of treatment, 26 % of the 38 patients who were present were classified as "much better".

Basal hormone levels were not associated with the clinical response of the participants. The Humor response on the HAM-D at week 8 was not related to the levels of DHEA or DHEA-S at baseline or at week 8. Of the 21 patients who entered the double-blind phase, 20 responders at week 8 maintained the response at week 12. Eighty percent of patients randomized (8/10) to DHEA and 82 % (9 /11) of the placebo group retained the response. There was a significant increase in the serum levels of DHEA-S in the 30 men who completed 8 weeks of treatment ($p < 0.001$), whereas the average testosterone levels did not change. The two women who completed eight weeks of treatment showed a significant increase in serum DHEA and testosterone. There was no correlation between the baseline levels of DHEA-S and the magnitude of the response in the eighth week. There was no significant change in the CD4 cell count between baseline and 8 weeks in the 29 patients with data available.

In another study that aimed to determine whether DHEA is superior to a placebo in the treatment of depression in HIV+ individuals, Rabkins (2006) studied a larger sample size compared with the first sample (145 VS 45, respectively) for 8 weeks. Of the 145 patients selected, 92 % (133) completed the 8 weeks of treatment. The participants were, on average, 44 years old; 84 % were male and 36 % were female. Two thirds of the patients were diagnosed with AIDS. At baseline, the CD4 cell count was 450 cells/mm (SD = 248). Of the 80 % of patients who took antiretroviral drugs, 42 % had an undetectable viral load. The extent of the basal serum levels of DHEA-S was very extensive for both men (23-457μg/dl) and women (7-212μg/dl). However, the serum DHEA-S levels were correlated with the CD4 cell count ($p = 0.28$). Twenty percent of men in each group maintained a stable regimen of testosterone supplementation. For 70 % of the patients, the duration of the current depressive episode was ≥ 1 year. Sixty percent reported periods that preceded the diagnosis of HIV, of whom 38 % had a probable history of depression. Seventy percent of the patients received some form of treatment for depression at some point prior to study entry. Of the 145 patients, 54 % had dysthymia and 46 % had higher subsyndromal depression.

The response rate was 56 % for the DHEA group and 31 % for the placebo group ($p = 0.003$). The HAM-D score of the DHEA group was numerically, but not significantly lower compared with the placebo group. There was no significant difference in the response rates between men and women (56% VS 54%); women had a higher response rate compared with the placebo (58% for women and 28% for men), but this difference was not significant. Using a ≥ 50 % decrease in the HAM-D as a criterion for treatment response, there was no response in 57 % of the DHEA group and 35 % of the placebo group ($p = 0.009$). The mean changes in the BDI at the 8th week did not differ between the groups; however, in both groups, the subjects classified as responders based on the CGI and the HAM-D showed significantly lower BDI scores compared with non-responders.

Regarding the effects of the treatment on the serum levels of DHEA-S, it was observed that for men, the doses of DHEA were 386 mg/day for responders and 390 mg/day for non-responders ($p = 0.77$). In relation to the serum levels of DHEA-S achieved at week 8, there were no significant differences between responders and non-responders, and the levels were not related to sex. There was no evidence to prove that the basal DHEA-S deficiency increases the likelihood of treatment response. Serum levels of DHEA-S were measured at weeks 4 and 8 as additional criterion of adherence to medication. Sixteen patients were randomly selected to receive DHEA; the serum DHEA-S level in these patients had been identified at week 8 as not having reached at least twice the level compared with the beginning of the treatment or the levels of DHEA-S were decreased at week 8 by more than 50 % compared with week 4. In the patients who had serum levels increased by more than 100 %, the response rate was 70 % compared with 38 % in the 16 patients who did not have the 100 % increase in the levels of DHEA-S increased at week 8 or which decreased by more than 50 % at week 8 compared with week 4. The serum testosterone levels in the men's DHEA group did not change compared with baseline; however, in the women's DHEA group, there was a significant increase in the serum testosterone levels from 44 ng/dl (SD = 20) at baseline to 119 ng/dl (SD = 123) during the 8th week ($p < 0.03$). No significant changes were observed in the testosterone levels for men or women in the placebo group. There were no clinical or significant changes in CD4 cell counts in the DHEA group compared with baseline. No difference in the response rate was observed in men based on steroid treatment.

Adrenal Insufficiency

Three double-blind, placebo-controlled RCT in a population with Adrenal Insufficiency (AI) were selected. Arlt *et al.* (1999) and Binder *et al.* (2009) studied only women with IA, and Hunt *et al.* (2000) studied men and women with Addison's disease. The psychological tools used by Arlt (1999) were: the SCL-90, the Hospital Anxiety and Depression (HAD), the multidimensional Humor Questionnaire, and Questionnaire VAS Zerssen. In addition to the SCL-90, Binder (2009) used the Center for Epidemiological Studies-Depression Scale (CES-D). Hunt (2000) used the General Health Questionnaire (GHQ-30).

To investigate the effects of DHEA on well-being and sexuality in women with AI, Arlt (1999) selected 24 women with AI to receive 50 mg/day DHEA or placebo for 4 months and subsequently crossed between the groups after a one month washout between the phases. The patients were evaluated prior to the beginning and during the washout between phases, as well as after 1 and 4 months of each phase. The women had a mean age of 42 years, and all women had low levels of DHEA and DHEA-S in serum and concentrations of active androgen. During treatment with DHEA, the testosterone concentrations increased to the lower limit of normal ($p = 0.001$). Treatment with DHEA resulted in a significant decrease in the scores on the SCL-90 items for depression ($p = 0.05$). The subsection of the SLC-90 "global severity index" showed a significant improvement for depression following 4 months of DHEA treatment, but not with the placebo ($P = 0.02$). The scores on the three subscales of the Multidimensional Mood Questionnaire also improved significantly following DHEA treatment. Treatment with DHEA significantly improved scores on the HAD depression ($p = 0.01$). The raw data for the list of symptoms related to the Zerssem scores significantly decreased compared with

baseline following four months of DHEA ($p = 0.001$), but the scores were similar at the end for the DHEA and placebo periods. The scores at baseline and the changes following 4 months of DHEA treatment were not significantly different between women with primary or secondary failure, and the order of treatment had no effect on the changes.

To evaluate the use of DHEA in the treatment of adolescents and young women with AI, Binder (2009) conducted a study with 23 patients, average age 18, who received 25 mg/day of DHEA or a placebo for 12 months. Of the 23 participants, 21 (91%) participants completed 6 months of treatment, and 18 (78%) participants completed the entire 12 months of the trial. All 23 patients had hypogonadotropic hypogonadism and underwent sex steroid replacement. At baseline, the DHEA group had higher scores compared with the placebo group on all scales, but the differences were not significant. For all 10 sub-items evaluated by the SCL-90, the DHEA group improved during treatment, whereas the placebo group worsened. Eight of the 10 sub-items showed significant differences, including the global severity index ($p = 0.013$). The CES-D indicated improvement in the depressive group with DHEA treatment between the early symptoms and 12 months. Treatment with DHEA resulted in a normalization of serum DHEA-S, while the placebo had no effect ($p < 0.006$). Serum testosterone levels increased in only two individuals, and only one participant in the DHEA group.

Hunt (2000) evaluated the effects of DHEA on mood and fatigue in Addison's disease. Hunt (2000) randomized 44 patients who received 50 mg/day of DHEA or placebo for three months and later crossed between the groups after one month of washout. The patients were assessed at baseline and at the end of the first phase and the second washout phase. Of the selected participants, 39 (88.7%) participants completed the study, including 24 women and 15 men aged between 18 and 70 years of age. There were significant improvements in mood and fatigue while using DHEA. There were also improvements in all subscales of the QHQ-30, especially in the depression subscale. The use of DHEA significantly improved the levels of DHEA-S compared with placebo in both men and women ($p = 0.0001$). In women, the total serum testosterone increased from subnormal to the lower normal range with the use of DHEA, but not the placebo ($p = 0.003$); in men, no significant change was observed. Following the cessation of treatment, the levels of DHEA-S returned to baseline. The adverse effects reported in this study were limited to acne and hirsutism, all cases were described as mild and there was no withdrawal from the study because of adverse effects.

Autoimmune Diseases

Three double-blind, placebo-controlled RCT in populations with autoimmune diseases were selected. In the oldest trial, Nordmark *et al.* (2005) randomized 41 women with Systemic Lupus Erythematosus who received low doses of DHEA for six months, followed by six months of an open-label study. Of the 41 patients selected for the study, 37 (90%) patients completed the treatment. Nordmark (2005) divided the participants into two age groups, age ≤ 45 and age ≥ 46, to receive daily doses of 30 mg and 20 mg, respectively. The evaluations were performed at baseline and months 3, 6, 9 and 12 during treatment and 3 months after treatment. The patients were psychologically evaluated by the Hopkins Symptom Check List (HSCL-56), the Short Form - 36 (SF-36) and the Psychological General Well-Being (PGWB). Only the group that received DHEA showed an improvement in scores (HSCL-56) during the six-month double-blind study ($p = 0.05$); however, the placebo group also showed a trend towards improvement during the open treatment with DHEA ($p = 0.10$). The use of DHEA did not significantly change the PGWB, and the SF-36 showed improvements only regarding emotional issues, but not regarding physical issues. At baseline, the mean serum levels of DHEA-S were significantly reduced in both groups and inversely correlated with the dose of prednisolone used by the patient. The serum testosterone levels were normal in 37 (95%) of the participants. Treatment with DHEA significantly increased the serum DHEA-S levels to the average normal range ($p < 0.0001$), and the values for two women in the group aged ≤ 45 were slightly above normal. The use of DHEA also significantly increased the levels of testosterone ($p < 0.001$). In this study, no significant side effects were observed.

Hartikamp *et al.* (2008, 2010) adopted the same methodological design in two RCTs. Both studies had samples of 60 participants who were randomly assigned to receive DHEA 200 mg/day or placebo for 12 months; participants were assessed at three, six and twelve months of treatment and six months after treatment completion. The psychological instruments used in both studies included the Multidimensional Fatigue Inventory (MFI), the Zung Self-Assessment Scale for Depression, the VAS and the SF-36. The mean age of the patients in the first study was 53.5 years, whereas the mean age in the second study was 43 years.

Hartkamp (2008) researched the effects of DHEA administration on fatigue, well-being and functioning in women with Sjögren's syndrome. Significant changes in the mental component score ($p = 0.04$) and depressed mood ($p = 0.01$) were observed during the study in both groups, with no significant differences in the use of DHEA compared with the placebo. The changes in general fatigue, depressed mood and mental component were not related to the actual use of the drug, but the belief to be taking a certain medication. The patients who believed they were using DHEA demonstrated improvement in fatigue and depressed mood. The patients with higher serum levels of DHEA-S showed greater improvement on the basis of general fatigue compared with the patients with lower baseline levels ($p = 0.03$). Changes in depressive mood and mental component were not dependent on the basal levels of DHEA-S. Changes in general fatigue, depressed mood and mental component did not depend on the baseline levels of these three variables, with the exception of the decrease in the depressive state on the first assessment, which occurred after 3 months of treatment, where the decrease in the depressive state was higher for the group with a major depressive mood at baseline ($p = 0.04$). At baseline, the average serum DHEA-S levels were 1.9 (SD = 1.1) μmol/L for DHEA and 1, 7 (SD = 1.1) group μmol/L for the placebo group. The average serum testosterone was 0.9 (SD = 0.4) nmol/L for both groups. During treatment with

DHEA, the levels of DHEA-S and supraphysiological testosterone significantly increased (20.0 µmol/L and 4.3 µmol/L, respectively). The values of DHEA-S and testosterone were normal at baseline and remained within normal limits after the discontinuation of treatment with DHEA and during placebo treatment.

In his second study, Hartkamp (2010) investigated the effects of DHEA administration on fatigue and well-being in women with inactive SLE. The characteristics of the study participants were similar for both groups, with the levels of DHEA-S at the beginning of the smaller study in patients receiving glucocorticoids. In the DHEA group, the levels of DHEA-S were 0.06 µmol/L in the patients with Prednisone and 1.9 µmol/L in the patients without prednisone ($p = 0.01$). In the placebo group, the levels were 0.8 VS 2.2 µmol/L for patients with or without Prednisone, respectively ($p = 0.002$). During treatment, the general fatigue improved significantly in both groups, with the best results observed during 12 months of treatment ($p < 0.001$). Depressed mood also showed a significant improvement in both groups, with the lowest scores for the DHEA group at the 3 month assessment and for the placebo group at the 12-month assessment ($p = 0.04$). No significant changes were observed in the well-being, physical and mental functioning in any groups. Changes in general fatigue ($p = 0.04$), as in the previous study, were related to the belief of having used a certain medication; the patients who believed they used DHEA performed better compared with the patients who believed they used placebo. This finding did not occur with mental well-being, depressed mood or physical functioning. During treatment with DHEA, the levels of DHEA-S and supraphysiological testosterone values rose significantly to 22.8 µmol/L (SD = 13.7) and 4.2 nmol/l (SD = 3.1), respectively. The increase in the serum levels of DHEA-S to DHEA was only significant ($p < 0.001$). The changes in the serum levels of DHEA-S were similar in the patients with and without Prednisone in both groups.

Fibromyalgia

Finckh *et al.* (2005) conducted a double-blind, crossover RCT and a placebo-controlled study of 52 women with fibromyalgia with the objective to evaluate the effects of DHEA on the quality of life, pain and cognitive function. Patients received DHEA 50 mg/day or a placebo in two phases of three months duration per phase and a one month washout between phases followed by crossing between groups. The patients were evaluated at the beginning and end of each treatment stage. The following psychological instruments were used: the Hospital Anxiety and Depression (HAD), the Cognitive Difficulties Scale and the VAS.

The participants were, on average, 58.9 years old and had, prior to the research, low DHEA-S levels in serum, on average, 1.4 µmol/L. This study did not identify a significant improvement in depressive symptoms through the HAD in either group. The baseline mean scores of the items that assessed the HAD depression were 8.4 (SD = 4.3) for DHEA and 8.1 (SD = 4) for the placebo group. Following three months of treatment, the mean scores of the DHEA and placebo groups were 8.7 (SD = 4.4) and 8.4 (SD = 4.3), respectively. During treatment with DHEA, the serum concentrations of DHEA-S normal increased, on average, 4.5 µmol/L. The DHEA-S levels were significantly higher at the end of the DHEA treatment ($p = 0.0001$). The authors also evaluated the possibility that the effect of DHEA was better in patients without Hormone Replacement Therapy, without antidepressant medication or with low baseline levels of DHEA-S. No evidence was identified to show that supplementation with DHEA was more efficient in any of these situations. Androgenic effects were more common during the use of DHEA.

Healthy Population

In the studies that met the selection criteria of this review, the largest number of samples evaluated healthy populations. In total, there were 6 RCTs, and Wolf *et al.* (1997, 1998) represent the forerunner of work with this type of population. The other studies were conducted by Arlt *et al* (2001), van Niekerk *et al.* (2001), Alhaj *et al.* (2006) and D. Kritz-Silverstein *et al.* (2008). To investigate the effects of DHEA on cognition, Wolf (1997, 1998) conducted two RCTs with the same methodological design, in which seniors received 50 mg/day of DHEA for two weeks. Despite significant increases in the levels of DHEA-S, no significant benefit in improved mood was observed with the use of DHEA in any study. Wolf (1997) observed that DHEA increased 511 % and 429 % the levels of DHEA-S in women and men, respectively. An increase of 531 % and 26 % in the levels of testosterone in women and men, respectively, was also identified. In the second study, Wolf (1998) examined a sample of men and determined the DHEA-S levels increased above 400 % with the use of DHEA.

The study conducted by Arlt (2001) evaluated the effects of 50 mg/day of DHEA in elderly men for 4 months using the same study design previously adopted in the study of women with IA [24]; assessments were conducted at baseline and after 1 and 4 months in each phase of the crossover study. There was no advantage for the use of DHEA compared with placebo in improving anxiety or depression in the HADS scores. The levels of DHEA-S increased significantly to the expected levels for healthy young adults from the first month of treatment with DHEA, and there was no significant change until the end of treatment. One month after the end of treatment, all hormone levels returned to baseline. There was no significant increase in testosterone levels.

Van Niekerk (2001) conducted a RCT to evaluate the effects of DHEA 50 mg/day for 13 weeks on cognition in a non-clinical sample of 41 healthy elderly men aged 62 to 76 years. In this study, no significant improvements in mood and well-being related to the use of DHEA were observed. However, there was an association between higher levels of DHEA during the night with lower negative mood in the morning ($p = 0.03$), as well as higher levels of cortisol, and the cortisol/DHEA in the morning was associated with greater anxiety ($p = 0.03$) and more general mood disorder ($p = 0.046$).

In his ECR, Kritz-Silverstein (2008) analyzed the effects of DHEA 50 mg/day for 12 months on cognitive function and quality of life in 225 healthy elderly individuals. The participants were evaluated prior to beginning the treatment and at three, six and twelve months after the initiation of

treatment. Men and women showed significant reductions in the BDI scores during treatment ($p < 0.001$ and $p = 0.02$, respectively). In men, the improvement occurred in both groups after the third month and remained stable at the sixth month, but at twelve months, it returned to approximately baseline levels. In women, the reduction also occurred in both groups after the third month, but remained until the end of the study. Treatment with DHEA increased the circulating levels of DHEA and DHEA-S from two to four times in men and women compared with baseline ($p < 0.001$). This increase became significant after three months of treatment and was maintained until the end of the study. Testosterone increased by 60 % and estradiol by 40 % in women who received DHEA, but not in men. These increases were significant after three months of DHEA treatment and remained stable until the end of the study. No change was observed in the placebo group.

To investigate the effects of DHEA on episodic memory in a healthy population, Alhaj (2006) conducted a study that was different from the other studies reported in this topic with regards to three issues: age, dose and duration of treatment. Alhaj (2006) randomized 24 young men with an average age of 23.6 years (SD = 5.1) to receive 150 mg/day of DHEA or placebo twice daily for 7 days. The results of this study also differed from the other studies that examined a healthy population and demonstrated the benefits of using DHEA compared with placebo. Although none of the participants endorsed complaints related to mood at baseline, a significant improvement was observed in the measures of subjective mood and VAS memory. It was observed that the continuous use of DHEA produced a lasting increase in the salivary concentrations of DHEA. A reduction in nocturnal salivary cortisol concentrations was also attributed to the use of DHEA. These results represent the first study to demonstrate the beneficial effects of DHEA use in healthy young men.

No significant adverse effects related to the use of DHEA were observed in the healthy populations. Fatigue, sweating, and decreased quality of life have been reported several times, but were also present during the placebo. The most severe case was reported by Kritz-Silverstein (2008) that described the occurrence of enlarged prostate antigen in 7 of 225 participants; however, 5 cases occurred in the placebo group and only 2 cases occurred in the DHEA group. All cases returned to normal after discontinuation of treatment, with the exception of 1 man diagnosed with cancer; however, it was determined that the cancer was previously established prior to the beginning of the study.

DISCUSSION

The studies in which DHEA was used as a monotherapy for depression showed significant decreases in the ratings of the depression scales used, especially in milder cases, which indicates DHEA is a potential depression treatment choice [8, 9, 18, 19]. The effects of DHEA use were also positive in the remission of depressive symptoms in individuals with other mental disorders, such as schizophrenia and anorexia nervosa, and clinical diseases, such as HIV and Adrenal Insufficiency [10, 20, 22-25]. However, there was no improvement of depressive symptoms in fibromyalgia, and the results observed in autoimmune diseases remain contradictory [11, 12, 27, 28].

Studies in healthy populations did not show significant benefits from the use of DHEA in improving mood in elderly men or women; however, a study of healthy young men showed improvements in mood [29-34]. This difference in results may be linked not only to the age of the samples but also the procedures adopted, emphasizing the dose, because while all studies of healthy elderly individuals used doses of 50 mg/day, the study in healthy young individuals used a dose of 300 mg/day [29-34]. The treatment time used in the studies also differed; it was significantly shorter in the young men, only one week of treatment, which did not enable the assessment of whether the effects observed would remain if the treatment time was extended [33]. Thus, the benefits of DHEA use on mood in healthy young adults should be viewed with caution because in addition to this being the first study that demonstrated benefits, the study sample was small and the results were based on the description of only one subscale of a subjective mood test [33].

One point that requires further clarification is the relationship between the levels of DHEA-S and the improvement in depressive symptoms because only some studies identified this correlation; thus, the relationship is not fully understood [8, 9, 22]. Nonetheless, it is evident that there is no relationship between the baseline levels of DHEA-S and improved antidepressant responses. The potential of DHEA to restore normal levels of DHEA-S in all populations studied is clear.

The DHEA dose used varied between the studies, and this variation was significant across the studies, with a range from 25 to 500 mg/day [20-22, 25]. This variation was associated with the diversity of the population studied and the stage of the studies, but, in general, it appears that DHEA produced positive effects on mood in some populations, even at low doses [20, 21, 25, 26].

The short-term studies indicated a rapid effect of DHEA on the remission of depression within the first weeks of symptom treatment [8, 9, 18, 19]; however, Wolkowitz (1997) noted that although effective in the remission of depressive symptoms, the effect was not maintained after the discontinuation of treatment. Thus, in opting for this therapy, the clinician should consider the need for chronic use or include other alternatives to maintain the treatment effects after the cessation of DHEA, such as psychotherapy or an alternative pharmacotherapy, as needed in each case.

One encouraging point regarding the use of DHEA in the treatment of depression is the low level of drug-related adverse effects. Wolkowitz (1997, 1999) stated that DHEA was well tolerated in their studies, with no withdrawal because of side effects, which were described as mild and infrequent cases of sleep disorders, headaches, muscle pain or paresthesia. Although Bloch (1999) reported the withdrawal of a woman because of side effects (complaints regarding acne and oiliness on hair and skin) in their sample of 15 participants, no changes were observed in weight, blood pressure, pulse, temperature, hematocrit, renal or liver function. Of the 46 participants in the study of Rabikin (2000), only three participants abandoned treatment because of side effects,

which included complaints related to acne, irritability and headache. Other patients also complained of the same symptoms, as well as insomnia and nasal congestion, but only one patient complained more than once of irritability. Even in chronic studies, no higher rates of involvement and no serious adverse effects attributable to the use of DHEA were observed, with the adverse effects primarily restricted to androgenic effects [11, 12, 24, 25, 28, 34]. The symptoms observed in the studies included in this review did not differ from the various reports on the tolerability of DHEA, which also indicated potential, although less frequent, cases of hisurtism and deepening of the voice [15-17]. The mild side effects associated with DHEA reinforce the importance of considering their use in clinical practice.

METHODOLOGICAL LIMITATIONS

Although the selected studies demonstrated good methodological application, only five studies included more than 50 participants [11, 12, 23, 28, 34], and only two participants received more than 100 samples [23, 34]. There is a risk of bias because most studies consisted of very small samples. Another potential bias is related to the age of the subjects studied (predominately older than 40 years of age) because only three studies were conducted with participants under the age of 30. Furthermore, all studies that included younger participants had small samples, which points to the need for additional studies with younger populations.

CONCLUSION

We have identified promising results regarding the use of DHEA in the treatment of depression and depressive symptoms in other psychiatric and medical illnesses, especially in milder types or those resistant to conventional therapy. Most studies selected in this review showed a reduction in depression scores related to the use of DHEA. It also became clear that the use of DHEA exerts a great influence on DHEA-S plasma levels. However, the relationship between increased levels of DHEA-S and the improvement of depression symptoms remains controversial.

ABBREVIATIONS

AI = Adrenal insufficiency

BDI = Back Depression Inventory

BH = Bunny-Hamburg Global Depression

CDS = Cornell Dysthymia Scale

CES-D = Center for Epidemiologic Studies Depression Scale

CGI = Clinical Global Impression Scale

CT = Clinical Trials

DHEA = Dehidroepiandrosterone

DHEA-S = Dehidroepiandrosterone Sulfate

HAD = Hospital Anxiety and Depression

HAM-D = Hamilton Depression Rating Scale

PANSS = Positive and Negative Syndrome Scale

RCT = Randomized Clinical Trials

SANS = Scale for the Assessment of Negative Symptoms

SCID = Structured Clinical Interview for DSM

SCL-90 = Symptom Checklist

VAS = Visual Analogue Scale

CONFLICT OF INTEREST

The authors confirm that this article content has no conflict of interest.

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ARTIGO 02

TITLE PAGE

Title: The Effects of Dehydroepiandrosterone (DHEA) on Sexual Function: A Systematic Review

Running Title: DHEA and Sexual Function

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Abstract

Objective: Faced with the growing interest on DHEA's action and its benefits, as well as the negative impacts sexual dysfunctions have on people's quality of life, this systematic review was proceeded with an objective of evaluating the effect of DHEA use on sexual function aspects.

Method: An electronic search was conducted in the PubMed, ISI Web of Science and Virtual Health Library (VHL)'s databases combining the terms DHEA treatment and DHEA use with terms as sexual dysfunction, sexual frequency and libido. No limits of time and language were imposed. It was considered eligible Clinical Studies the ones where individuals for any reason made use of DHEA and if they had any aspect of sexual function assessed. Pre-clinical studies and systematical reviews were considered ineligible.

Results: The search had identified 183 references and 38 were considered eligible. DHEA improved aspects such as sexual interest, lubrication, pain, arousal, orgasm and sexual frequency. Its effect was better in populations with sexual dysfunction, especially in perimenopausal and postmenopausal women.

Conclusion Considering the studies currently published, DHEA is effective in improving several aspects of sexual function, but this effect did not reach all the populations studied.

Keywords: Sexual dysfunction, Drugs-New, Women, Neuroendocrinology, Men.

INTRODUCTION

Sexuality is one of the most important aspects of human life; its role transcends the reproductive function, being the sexual satisfaction is closely related to the quality of life.[1, 2] Based on an interrelation of psychophysical aspects, men and women possess a sexual response cycle divided into the following three phases: desire, arousal and orgasm. Alterations in any of these phases can be characterized as sexual dysfunction.[2,3]

The aetiology of sexual dysfunction can be organic or psychological, and despite the scientific advances on the topic, its prevalence remains extremely high, nearly 50% in men and women in various countries.[4-6] Given the significant portion of the global population affected by problems related to sexual function, the search for therapeutic assistance is of great importance.[4-6]

Dehydroepiandrosterone (DHEA) and its sulphate (DHEA-S) are sexual hormones abundantly secreted in human beings and other primates.[7-9] These indirect precursors of androgen and oestrogen are produced primarily by the adrenal glands, gonads and brain, allowing DHEA and DHEA-S to be classified as neurosteroids.[10-12] The production of these hormones is strongly linked to age, peaking at the age range of 25 to 35 years and gradually declining thereafter. At approximately 70 years, it is expected that hormone production reaches between 10% and 20% of what was produced during the peak years.

Recent decades have seen much speculation regarding the therapeutic potential of DHEA and its capacity to enhance, among other aspects, mood, cognition, life

quality and sexual function.[13-19] In fact, many studies achieved encouraging results regarding the effect of DHEA on sexual function,[20-39] although other studies have not observed similar results.[40-53]

Based on the preliminary analysis of some works, our hypothesis is that individuals with sexual disfunction can improve aspects of sexual function through the use of DHEA. Thus, faced with the growing interest in DHEA's function and its benefits and considering the negative effects of sexual dysfunction on quality of life, this systematic review proceeded with the objective of evaluating the effect of DHEA use on aspects of sexual function.

METODOLOGY

The selection of articles in this review was the result of an electronic search in the PubMed, ISI Web of Science and Virtual Health Library (VHL) databases. The first search occurred in October 2015, and the final search was in June 2016. As a research strategy in PubMed, the expressions "DHEA treatment" and "DHEA use" were combined with the following key words: sexuality, sexual, sexual dysfunction, sexual frequency, sexual appetite, sexual thought, sexual fantasies, sexual interest, sexual activity, sexual problems, sexual potency, sexual drive, sex drive, sexual desire, and libido. For example, one search used DHEA treatment AND sexuality OR DHEA use AND sexuality. The utilized filter was "Clinical Trial," and limits of time and language were not imposed. Eligible clinical studies included studies in which individuals with or without sexual dysfunction used DHEA for any reason, independently of gender, age, quantity, duration of use and whether they had any aspect of sexual function assessed. Pre-clinical studies and systematic reviews were considered ineligible.

Two reviewers worked independently during the process of selection, utilizing the following research strategy: database research, exclusion of repeated references, abstract reading and selection of potentially eligible articles; a full reading of potentially eligible articles; final selection of articles. There was no divergence between the reviewers regarding the articles composing this review.

For the extraction of data, a protocol was created and tested on 4 articles. The following information was identified and analysed: population, gender, age, study type, posology, manner of administration, time of treatment, assessment tools for sexual function, effects on hormones, effects on sexual function and adverse effects. The risk of bias in this study was evaluated through the Jadad Scale.

RESULTS

Although the database search identified 183 references, only 38 were considered eligible for the current review, which are presented in Figure 1. Of the 38 selected references, 20 reported positive results, 14 reported negative results and 4 reported inconclusive results. A study was considered inconclusive if the study was contradictory or unclear regarding DHEA's effect on sexual function.

General description of studies that found DHEA's effect on sexual function

Population: DHEA treatment has been shown to be effective predominantly in samples with sexual dysfunction.[20-27, 29, 30, 34, 35, 39] However, in some studies, aspects of sexuality improved in patients with endocrine disorders, autoimmune diseases, Chronic Fatigue Syndrome and in healthy subjects.[28, 31-33, 36-38]

Gender: Sixteen studies comprised female samples, and only one study had an exclusively male sample.[39] Three studies used heterogenic samples; however, sexual parameters only showed improvement in women.

Age: Excepting a study in which the average age was 39,[35] the average age for women was over 40, and in thirteen studies, the average age was more than 50.[20-30, 33, 36] The average age for men was over 45 in all studies. In a study in which DHEA improved sexual function in men, the average age was 56.5.[39]

Hormonal parameters: Studies using oral DHEA that assessed levels of DHEA and DHEA-S observed low baseline levels of these hormones, except in some studies conducted on healthy individuals.[28, 33, 35] Studies also showed that DHEA and DHEA-S increased during treatment to values commensurate with young adults, including in men who were more than 70 years old although at a slower pace than in men younger than 70.[36] A study with an acute dose of 300 mg of DHEA observed significant growth in levels of DHEA-S after 50 minutes of administration,[33] and other studies noted a return to baseline levels after suspension of treatment.[31, 36] One study observed that after cessation of treatment, DHEA-S levels decreased less significantly in men and women older than 70 than in men and women younger than 70.[36]

The studies that assessed testosterone (free/total) noted a significant growth in women but not in men.[27, 28, 31, 32, 34-36, 38] In one study of women treated with 50 mg/day of DHEA for 12 months, 10% of the sample exceeded the testosterone levels observed in women during menstruation.[36] Two studies indicated that testosterone levels do not continue after interruption of treatment.[31, 36]

Few studies measured oestradiol and androstenedione although in all cases, these hormones increased in men as well as in women.[27, 28, 31, 32, 35, 36] One study measured androsterone and noted a significant increase in men and women ($p<0.001$, $p<0.05$,

respectively).[27] Another study of women identified an increase in cortisol during DHEA use.[28]

Studies performed with intravaginal DHEA (Prasterone) could not identify changes in hormonal parameters from this manner of administration. All steroids measured, including DHEA, DHEA-S, oestradiol and testosterone, remained unaltered or within the reference range of the studied population's age group after the 12 weeks of treatment.[22, 54]

Sexual parameters: Using sexual scales, studies on oral DHEA observed an improvement in one or more aspects of sexuality, such as sexual thinking, sexual fantasies, sexual arousal, orgasm, sexual desire and vaginal lubrication. Two of those studies indicated an increase in the frequency of sexual intercourse and the quality of relations (including masturbation) during treatment with DHEA.[28, 36] Two studies indicated an improvement in sexual aspects only by self-report or direct questioning,[31, 35] and one study did not specify which sexual aspect increased during treatment.[38] A study of men noted improvement in desire, erection, orgasm, satisfaction with sexual relations and general satisfaction.[39]

The use of Prasterone in women with vulvovaginal atrophy improved several parameters of sexual function.[20-26, 29, 30] Utilizing the Female Sexual Function Index (FSFI), one of the studies observed an increase in scores of desire (29%), sexual arousal (45%), lubrication (106.5%), orgasm (50%), satisfaction (48.5%) and pain (137%) after 12 weeks of treatment compared with the baseline, a larger improvement than was observed with a placebo ($p<0.05$).[23] Another study showed an improvement in all FSFI dimensions after 52 weeks of treatment, highlighting the dimensions of lubrication and pain that improved 115% and 108%, respectively, compared with the baseline.[20] Other studies showed superior effects (up to 43%) on sexual desire, vaginal dryness and

intimacy avoidance, with a significant difference when compared with the placebo ($p \leq 0.0036$)[25, 26, 29, 30] and a reduction of scores on the gravity of dyspareunia greater than 45% when compared with baseline ($p=0.013$ compared with the placebo).[22] One hundred men were assessed regarding their perception of their partners' vaginal dryness after 12 weeks of treatment. In this study, the men, responding to a specific questionnaire, reported an improvement of 81% compared with the placebo ($p=0.0347$) and 59% compared with the baseline.

Other parameters: When compared to the placebo, Prasterone reduced the percentage of parabasal cells by 45.8% ($p<0.0001$), increased superficial cells in 4.7% ($p<0.0001$) and vaginal dryness in 42% ($p=0.013$) of subjects.[22] Gynaecologic evaluation identified an improvement in vaginal secretions, epithelial integrity, thickness of the epithelial surface and vaginal coloration; similar results were not observed in the placebo group.[22]

Correlations between hormonal and sexual parameters: In women, correlations were observed between the levels of bioavailable testosterone and sexual cognition ($r = 0.47$), arousal ($r = 0.61$) and orgasm ($r=0.49$); and DHEA-S was correlated with satisfaction ($r=0.47$) [27]. In men, correlations were identified between total serum levels of testosterone and arousal ($r = 0.45$), sexual drive ($r = 0.50$) and orgasm ($r = 0.55$); nevertheless, there was not a significant improvement in sexual parameters in men in the present study.[27] In a study in which women were randomized to receive DHEA or testosterone, there was improvement in sexual function in both groups compared with the baseline, showing that DHEA itself is just as effective as testosterone in improving sexual parameters.[28]

Posology: Among studies of oral DHEA, eight studies used doses of between 50 and 100 mg/day, two studies used doses of between 10 and 15 mg/day and one study used an acute dose of 300 mg. The majority of studies that reported some sort of effect on

sexuality lasted longer than 12 weeks with a low dosage (up to 50 mg/day).[28, 31, 32, 36-38] However, there was an effect on sexuality in studies up to 12 weeks but with a dosage higher than 50 mg/day.[27, 33] Intravaginal DHEA was used with doses between 3.25 and 13 mg in a period of 12 to 52 weeks. Its effect was better with a 6.5 mg dose, and results significantly greater than placebos were observed in assessments conducted during the fourth week of treatment.[26, 29, 30]

A summary of articles included in this review that observed DHEA's effect on sexual functions is presented in Table 1. The percentage of increase in scores of assessment tools used in some of the studies with oral DHEA is presented in Figure 2. A study that only lasted for a day[33] and two studies that only stated that there was an improvement in some aspect of sexual function but did not indicate how much improvement was not included in Figure 2.[31, 36] The percentage of increase on scores of assessment tools used in studies with intravaginal DHEA can be observed in Figure 3. The risk of bias in the studies that observed DHEA effect on sexual function can be seen on the Table 2.

General description of studies that did not identify a DHEA effect on sexual function

Population: DHEA did not improve sexual function, particularly in healthy individuals.[42, 46, 47, 50-53] In addition, DHEA did not improve any other aspect of sexual function in two studies with subjects in conditions that affected their quality of life and in three studies with subjects with endocrine problems.[43-45, 48, 49] Only two studies no improvement with treatment with samples comprising subjects with sexual dysfunction.[40, 41]

Gender: The majority of these studies had men in their samples, eight in total, being that four of them were focused solely on men. Six studies had samples exclusively comprising females.

Age: Among men, the average age was greater than 48 years old, except in a study in which the average age was 40.[48] In women, the average age was primarily greater than 46 years old; however, in 3 studies, the medium age ≤ 40 years,[46, 48, 53] and in one of these studies, the average age was 27 years.[46]

Hormonal Parameters: Levels of DHEA, DHEA-S, oestradiol and androstenedione increased in men and women in all studies that rated these hormones. Testosterone increased in women in all of the studies; however, in men, testosterone increased in only two studies.[40, 50] Cortisol did not change in a study with patients with Addison's disease but decreased in a study of postmenopausal women.[49]

Posology: Only oral DHEA was used in these studies. The most common dose was 50 mg/day, used in ten of the fourteen studies. Two studies used a 100 mg/day dose.[50, 11] One study used a 25 mg/day dose, and another study used an acute dose of 300 mg/day.[46] Eight studies lasted up until 12 weeks, and six lasted 16 weeks or more.

A summary of the articles included in this review that did not report any DHEA effect on sexual function is presented in Table 3.

General description of studies with inconclusive results

Population, gender, age, posology: The studies that presented inconclusive results presented no clear standard. Their samples presented varied characteristics, different ages and both genders. In addition, the dosages used were not consistent among the studies.[55-58]

Hormonal Parameters: Levels of DHEA, DHEA-S and androstenedione increased in both men and women. Testosterone increased in all women assessed. In a study with a low dose (20 to 30 mg/day), the level of testosterone increased but did not reach normality.[56] In a study with a high dose (200 to 500 mg/day), serum testosterone increased in two women on <20 ng/dl to 98 and 134 ng/dl after 8 weeks.[57] In men, testosterone showed a decrease in two studies, yet an increase in most male carriers of Addison's disease, although less expressive than in women.[55] Oestradiol was only assessed in one man, and there was an increase.[58]

Sexual Parameters: In one of the studies, although DHEA use did not lead to improvement in sexuality aspects when compared to the baseline, 3 of 13 men and 1 of 7 women reported an increase in sex interest following treatment.[55] A study that had a phase controlled by a placebo and another by an open label observed an improvement in sexual relationships only in the open phase ($p=0.06$).[56] HIV+ individuals witnessed an improvement in libido; however, this improvement was always associated with a mood enhancement, and was not specifically associated with the effect of DHEA on sexual function.[57] In a case report of two patients, an elderly subject complained of loss of libido whilst a younger patient with depression reported an improvement of depression and libido.[58] A summary of the articles included in this review with inconclusive results is presented in Table 4.

Side Effects

In general, the studies included in this review identified only smooth and transitional androgenic effects, including studies in which no adverse effects were reported by the subjects.[28, 39, 44, 50] Side effects were more common: acne, skin and hair oiliness, and an increase in body hair growth. A study that analysed alterations in

prostate volume during treatment with DHEA did not show any alteration.[39] Another study of elderly men analysed specific antigen increase of the prostate in the DHEA group; however, the increase was scarcely greater than in the placebo group.[42] During DHEA use, a patient reported paraesthesia and numbness of the upper extremity,[53] and another patient showed psychiatric alteration (self-harm attempt).[40]

DISCUSSION

Oral DHEA showed significant effects on the psychological and physiological aspects of sexuality in 11 studies, improving factors such as sexual desire, quality, frequency, arousal, orgasm and lubrication. Its effect was clearly better in women; however, a study of men with erectile dysfunction also showed DHEA to be effective.[39] In 4 other studies, DHEA appeared to cause some type of improvement although its results were not sufficiently consistent to be classified as positive results.[55-58]

Improvement occurred more commonly in the population with sexual dysfunction and was less effective in a healthy population. However, there were studies on subjects with sexual dysfunction who did not demonstrate any improvement[40, 41] as well as studies on healthy individuals in which there was an improvement.[36] In fact, elements such as gender and reproductive stage of life appear to be more related to positive results than specific clinical profiles.

The majority of studies with positive results were conducted using women who were perimenopausal or postmenopausal. Although there was a study in which DHEA demonstrated effectiveness in improving erectile dysfunction, other studies on men reported no improvement. This result may be because of the apparent incapacity of DHEA to increase testosterone levels in men with the same efficiency that occurs in women. As a general rule, the use of DHEA increased levels of DHEA-S in men and

women;[27, 40, 42, 44, 48, 52] however, in only a few cases did levels of testosterone increase in men, and the increase did not appear capable of improving male sexual function.[40, 47, 50] The study that showed improvement in erectile function in men did not assess levels of testosterone, which limits our ability to aver that the increase in testosterone levels is in fact responsible for improving sexual function among individuals who received oral DHEA.[39] However, when the fundamental role of testosterone in libido and other aspects of sexual function in men and women was specifically considered,[59] it was then considered that although testosterone is not the only variable responsible for the increase or decrease in sexual function, testosterone is certainly what was indicated by the results of this review.

Among the studies that showed DHEA's effect on sexual function and the studies that did not show this effect, the most commonly used dose was between 50 and 100 mg/day in oral form. However, DHEA also demonstrated its effectiveness in studies with doses starting at 10 mg/day.[28-32] Two similar studies with acute doses of 300 mg of DHEA obtained different results: in one study there was no effect of DHEA on sexual arousal whilst in the other study, there was of an effect.[33, 46] These results strengthen the idea of the reproductive phase in women as a possible determining response to the use of DHEA: whereas there was an effect in postmenopausal women, there was no effect in premenopausal women.

While most studies with positive effect lasted longer than 12 weeks of duration, studies without effects generally lasted less than 12 weeks. However the importance of time factor remains unclear, once the DHEA displayed effects in a short period of time,[33] and there were cases in which the effect of DHEA on sexual function took longer to appear.[56]

All works using intravaginal DHEA were conducted on postmenopausal women with vulvovaginal atrophy symptoms, and the medication was deemed effective in several manners in all studies included in this review with doses starting from 3.25 mg/day. Furthermore, Phase III, long-term, multicentric studies also confirmed the reliability of this form of application after 52 weeks with a dose of 6.5 mg.[20, 25] However, despite the methodological quality observed and promising results that indicate an effective medication for treatment of dyspareunia, a common dysfunction in postmenopausal women, it is advisable that other studies be conducted in the future with the same form of administration. This recommendation is a specific result of the conflicts of interest involved, since all of these studies were financed by the medication's manufacturer, and the company's president is the author or co-author of the studies.[20-26, 29, 30]

The low incidence of serious side effects observed in the current studies (in oral and intravaginal forms) is encouraging. Even long-term studies did not observe significant adverse effects.[20, 25] Adverse effects such as psychiatric alterations and paraesthesia were reported in one patient among the thousands of patients who have used the medication; thus, the chances of these symptoms arising specifically from the use of DHEA are quite small.[40, 53] Another review that assessed the use of DHEA for the treatment of depression reached a conclusion consistent with this review regarding the side effects of DHEA, which corroborates the safety of this medication.[14]

LIMITATIONS

Although most studies with positive DHEA effects on sexual function have had an appropriate methodological application and most were accomplished with samples larger than 100 participants, eight studies had samples of fewer than 50 participants. Of

these studies, half had fewer than 30 participants, which may be a bias of this review. However, the primary limitation observed was the diversity of assessment tools for sexuality used in the studies. Some assessment tools even had no proven validation, which to some degree compromises the quality of the assessment's results. Furthermore, there were cases in which the scoring was not described in an objective format, avoiding declarations that DHEA did or did not have an effect on sexual function and thus limiting the capacity to describe the results. This limitation is partially because the assessment of sexuality was not the primary goal of the several studies included in this review.

CONCLUSION

In the current work, promising results were identified regarding the use of DHEA on sexual function, improving aspects such as sexual interest, quality, frequency, arousal, orgasm, lubrication, and dyspareunia. However, DHEA's effect appears to be more effective in perimenopausal or postmenopausal women than in other populations.

The use of oral DHEA to increase the circulating level of DHEA and DHEA-S in men and women increased testosterone levels in nearly all women but in only a few cases in men. Therefore, more studies that specifically focus on the relation between increased testosterone and improvement in sexual function in individuals who use oral DHEA are required to increase understanding of this effect, particularly in men.

Considering the low prevalence of serious side effects in the studies included in this review, even in long-term studies, the use of DHEA has been demonstrated to be one more important alternative in the medical arsenal on the treatment of problems related to sexual function, particularly problems that occur with ageing.

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Figure 1 - Flow of information through the different phases of a systematic review.

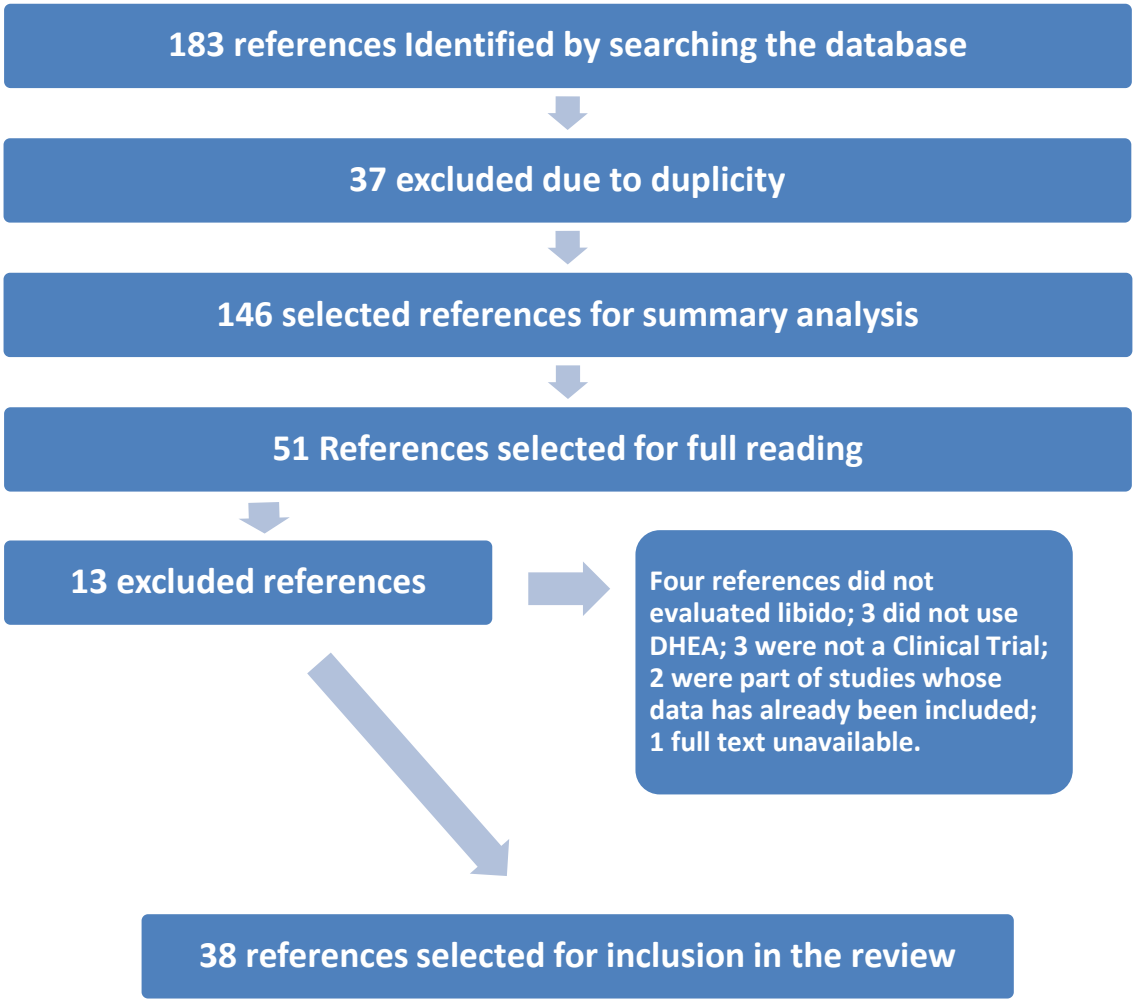
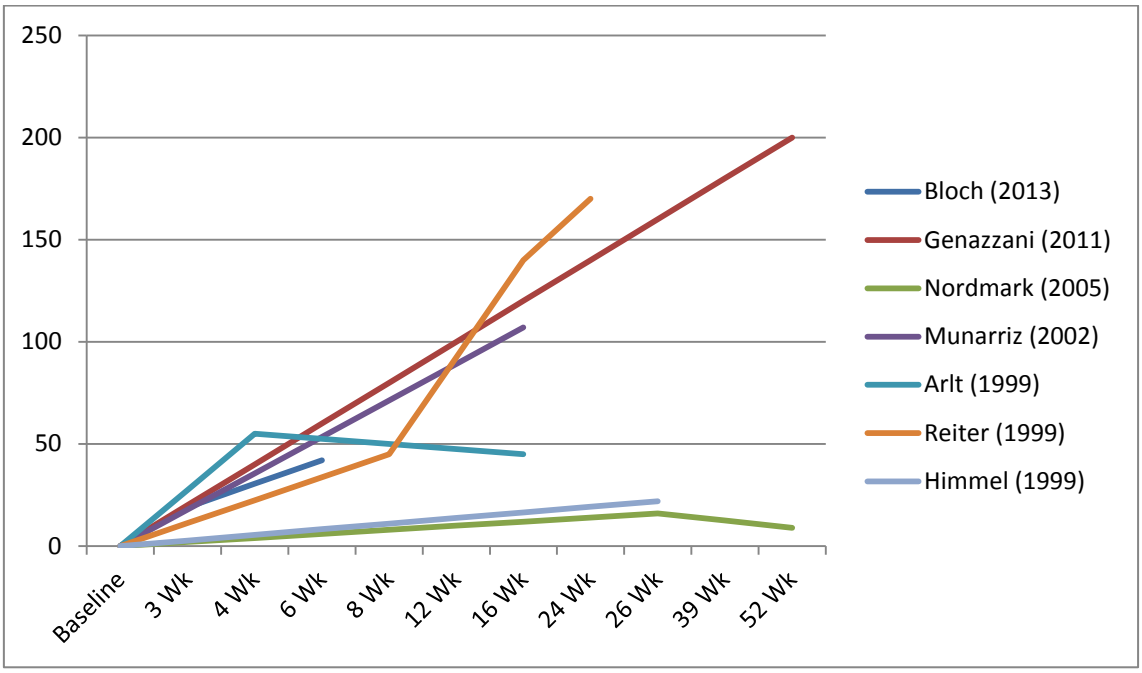
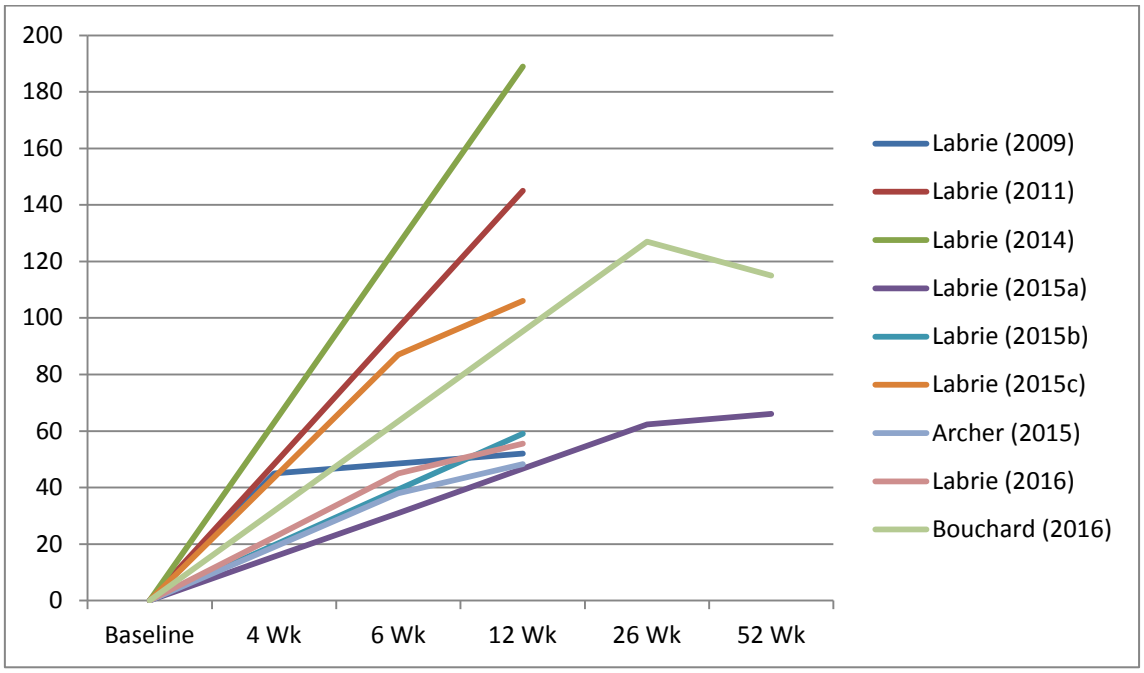


Figure 2 – Percentage increase in the score of the assessment tools used in studies where oral DHEA was effective



Bloch (2013): Female Sexual Function Inventory (FSFI) – sexual arousal, scores reported for weeks 0, 3 and 6, (p = 0,001); Genazzani (2011): McCoy Female Sexuality Questionnaire (McCoy) – sexual intercourse, scores reported for weeks 0 and 52 (p<0,01); Nordmark (2005): McCoy Female Sexuality Questionnaire (McCoy) – score total, scores reported for weeks 0, 26 and 52 (p<0,05); Munarriz (2002): Female Sexual Function Inventory (FSFI) – sexual arousal, scores reported for weeks 0 and 16, (p = uninformed); Arlt (1999): Visual-Analogue Scale (VAS) – sexual interest, scores reported for weeks 0, 12 and 16, (p=0,05); Reiter (1999): International Index of Erectile Function (IIEF) – erectile function, scores reported for weeks 0, 8,16 and 24, (p<0,001); Himmel (1999): Modified Health Assessment Questionnaire-II (MHAQII) – sexual problems, scores reported for weeks 0 and 26, (p = 0,06).

Figure 3 – Percentage increase in the score of the assessment tools used in studies where intravaginal DHEA was effective



Labrie (2009): Menopause-Specific Quality of Life (MENQOL) – sexual domain, scores reported for weeks 0, 4 and 12 (<0,0001); Labrie (2011): Vaginal examination – dispareunia, scores reported for weeks 0 and 12 (p<0,0001); Labrie (2014): Abbreviated Sexual Function (ASF) – arousal/lubrication, scores reported for weeks 0 and 12 (p<0,05); Labrie (2015a): Vaginal atrophy symptoms questionnaire – dispareunia, scores reported for weeks 0, 12, 26 and 52 (p<0,0001); Labrie (2015b): Specific questionnaire - perception of vaginal dryness of partner, scores reported for weeks 0 and 12 (p<0,0001); Labrie (2015c): Female Sexual Function Index (FSFI) – Lubrication, scores reported for weeks 0, 6 and 12 (p<0,0005); Archer (2015): Vaginal Atrophy Symptoms Questionnaire (VASQ) – dispareunia, scores reported for weeks 0, 6 and 12 (p=0,013); Labrie (2016): Vaginal Atrophy Symptoms Questionnaire (VASQ) – Pain, , scores reported for weeks 0, 6 and 12 (p<0,001); Bouchard (2016): Female Sexual Function Index (FSFI) – Lubrication, scores reported for weeks 0, 6 and 12 (p<0,0001).

Table 1 – Summary of studies that have found effects of DHEA on sexual function

Author (year)	Population	Gender M/F	Age M/F	Dayle dose	Time in weeks	Avaluations Instruments	Results
Reiter et al. (1999)	Erectile Dysfunction	40/0	56.5	50 mg	24	IIEF	Improved erectile function, orgasmic function, sexual desire, intercourse satisfaction and overall satisfaction.
Arlt et al. (1999)	Adrenal Insufficiency	0/24	42	50 mg	16	VAS	Increased sexual interest degree, as well as sexual thoughts frequency and sexual fantasies.
Himmel & Seligman (1999)	Chronic Fatigue Syndrome	0/23	44.6	25 to 100 mg	26	MHAQII	Sexual problems improved 22%.
Baulieu et al. (2000)	Healthy elderly	140/140	60 to 79 years	50 mg	52	GWB, and Scale of Dupuy.	There was an improvement in most libido parameters in women over 70 years old. In women under 70 years old and in men there was no improvement.
Guay (2001)	Perimenopausal women with decreased libido.	0/12	39	50 to 100 mg	>8	Self-report	Improved sexual aspects as desire, lubrication, arousal and orgasm.
Munarriz et al. (2002)	Androgen insufficiency	0/113	43.5	50 mg	16	SDS and FSFI	Improved sexual aspects as desire, arousal, lubrication, orgasm, satisfaction and pain.
Hackbert and Heiman (2002)	Postmenopausal healthy women	0/16	59.8	300 mg	Single dose	DISF, OFQ and FES.	Increased the sexual arousal.
Nordmark et al. (2005)	Systemic Lupus Erythematosus	0/37	47.6	10 to 15 mg	52	McCoy	Improved sexual problems, vaginal dryness and dyspareunia.
Brooke et al. (2006)	Hypopituitarism	18/26	48.7/ 47.8	50 mg	52	Sexual Self-efficacy Scale	Only in women, increased the sexual thoughts frequency.
Labrie et al. (2009)	Postmenopausal women with vulvovaginal atrophy symptoms	0/216	58	*3,25 to 13 mg.	12	ASF, MENQOL, and SC.	Improved the libido and sexual function.
Labrie et al. (2011)	Postmenopausal women with vulvovaginal atrophy symptoms	0/114	58	*3,25 to 13 mg.	12	Self-report	It was highly effective in reducing pain during sexual intercourse.
Genazzani et al. (2011)	Postmenopausal healthy women	0/48	54.5	10 mg	52	McCoy	Improved McCoy s total score and increased sexual intercourse frequency.
Bloch et al, (2013)	Hypoactive Sexual Desire Disorder	21/27	45.9/ 55.8	100 mg	6 to 12	DISF, FSFI.	Improved some sexual function parameters in women, but not in men.
Labrie et al. (2014)	Postmenopausal women with vulvovaginal atrophy	0/216	58	*3,25 to 13 mg.	12	ASF, MENQOL,	Improved sexual function in women with dyspareunia regardless of the pain level at the beginning of treatment.

	symptoms					and SC.	
Labrie et al. (2015a)	Postmenopausal women with vulvovaginal atrophy symptoms	0/435	57.9	*6.5 mg	52	VASQ	Improved pain during sexual activity.
Labrie et al. (2015b)	Postmenopausal women with vulvovaginal atrophy symptoms.	0/100	40 to 80 years	*6.5 mg	12	Questionnai-re directed to partner	Male sexual partner indicated an improvement in their perception in relation in vaginal dryness feeling of their partner after treatment.
Labrie et al. (2015c)	Postmenopausal women with vulvovaginal atrophy symptoms	0/554	59.5	*6.5 mg	12	FSFI	Improve all sexual function parameters.
Archer et al (2015)	Postmenopausal women with vulvovaginal atrophy symptoms	0/255	58.5	*3.25 to 6.5 mg.	12	VASQ	Improved pain during sexual activity.
Labrie et al. (2016)	Postmenopausal women with vulvovaginal atrophy symptoms	0/463	59.5	*6.5 mg	12	VASQ	Improved pain during sexual activity.
Bouchard et al. (2016)	Postmenopausal women with vulvovaginal atrophy symptoms	0/154	40 to 75 years	*6.5 mg	52	FSFI	Improved all sexual function parameters.

ASF = Abbreviated Sexual Function; DISF = Derogatis Interview Sexual Functioning Inventory; FES = Film Evaluation Scale; FSFI = Female Sexual Function Index; GWB = General Well Being; IIEF = International Index of Erectile Function; McCoy = McCoy's Sex Scale Questionnaire; MENQOL = Menopause-Specific Quality of Life; SC= Sexual Concern questionnaire; MHAQII = Modified Health Assessment Questionnaire-II;OFQ = Orgasmic Functioning Questionnaire; SC = Sexual Concern questionnaire; SDS = Sexual Distress Scale; VAS = Visual Analog Scale; VASQ = Vaginal Atrophy Symptoms Questionnaire; * = intravaginal cream (Prasterone).

Table 2 – Description from the risk of bias of the studies thatfound DHEA effect on sexual function

Reference	1 a)	1 b)	2 a)	2 b)	3
Bouchard et al. 2016*	No	No	No	No	No
Labrie et al. 2016	Yes	Yes	Yes	No	No
Labrie et al. 2015a	Yes	Yes	Yes	No	No
Labrie et al. 2015b	Yes	Yes	Yes	No	No
Labrie et al. 2015c *	No	No	No	No	Yes
Archer et al. 2015	Yes	Yes	Yes	No	No
Labrie et al. 2014	Yes	No	Yes	No	Yes
Bloch et al. 2013	Yes	Yes	Yes	No	Yes
Genazzani et al. 2011	Yes	Yes	No	No	Yes
Labrie et al. 2011	Yes	No	Yes	No	No
Labrie et al. 2009	Yes	No	Yes	No	No
Brooke et al. 2006	Yes	Yes	Yes	No	Yes
Nordmak et al. 2005	Yes	Yes	Yes	No	Yes
Hackbert et al. 2002 #	Yes	No	Yes	No	Yes
Munarriz et al. 2002	No	No	No	No	No
Guay et al. 2001 **	No	No	No	No	No
Baulieu et al. 2000	Yes	Yes	Yes	No	No
Arlt et al. 1999	Yes	No	Yes	No	No
Reiter et al. 1999	Yes	Yes	Yes	No	Yes
Himmel et al. 1999 ##	No	No	No	No	No

Risk of bias analysed through the Jadad Scale: 1 a) = The study was outlined as randomized? 1 b) = The method of randomization was outlines on the document and it was appropriated? 2 a) = The

study was outlined as double-blind? 2 b) = And the method of masking was outlined and it was appropriated? 3) = Was there a description on losses and waivers? * Study of phase III open-label with 52 weeks period. # Study of one day of period, There was no loss in the sample. ** Clinic report of a series of cases. ## Unclear methodology description.

Table 3 – Summary of studies that did not found effects of DHEA on sexual function

Author (year)	Population	Gender M/F	Age M/F	Dayle dose	Time in weeks	Avaluations Instruments	Results
Morales et al. (1994)	Healthy elderly	13/17	53.7/ 54.5	50 mg	12	Self-report	Did not improve libido.
Wallace et al. (1999)	Healthy men	40/0	48.1	10 mg	12	VAS	Did not improve libido.
Flynn et al. (1999)	Healthy elderly men	39/0	60 to 84 years	100 mg	12	BMSFIU	Did not improve libido.
Barnhart et al. (1999)	Perimenopausal healthy women	0/60	48.8	50 mg	12	HAM-D	Did not improve libido.
Hunt et al. (2000)	Addison's Disease	15/24	40	50 mg	12	Questionário derivado do GRI	Did not improve any aspect of sexual function.
Arlt et al. (2001)	Healthy elderly	22/0	53.9	50 mg	16	VAS	Did not improve any aspect of sexual function.
Menton & Heiman (2002)	Healthy women premenopausal	0/12	27.7	300 mg	Single dose	SRS	Did not improve sexual arousal.
Lovas et al. (2003)	Adrenal insufficiency	0/39	46	25 mg	36	McCoy	Did not improve any aspect of sexual function.
van Thiel et al. (2005)	Secondary Adrenal Insufficiency	15/16	52.6/ 61.5	50 mg	16	EQSF	Did not improve any aspect of sexual function.
Finckh et al. (2005)	Fibromyalgia	0/52	58.9	50 mg	12	McCoy	Did not improve any aspect of sexual function.
Kritz-Silverstein et al. (2008)	Men and women healthy	110/115	68.9	50 mg	52	IIEF and FSFI	Did not improve any aspect of sexual function.
Panjari et al. (2009)	Healthy women with loss of sexual interest	0/85	55.1	50 mg	26	SSS and SSEs	Did not improve libido.
Morales et al. (2009)	Sexual dysfunction and hyperandrogenism	79/0	60.9	50 mg	16	IIEF and AMS	Did not improve any aspect of sexual function.
Zimmerman et al. (2015)	Young healthy women	0/99	18 to 35 years	50 mg	24	McCoy	Did not improve libido.

AMS = Aging Male Symptoms Scale; ASF = Abbreviated Sexual Function; BMSFIU = Brief Male Sexual Function Inventory for Urology; EQSF = Eleven Questions on Sexual Function; FSFI = Female Sexual Function Index; GRI = Golombok Rust Inventory of Sexual Satisfaction; HAM-D = Hamilton Depression Rating Scale; IIEF = International Index of Erectile Function; McCoy = McCoy's Sex Scale Questionnaire; SRS = Self-Report Rating Scale of Heiman & Rowland; SSEs = Satisfactory Sexual Events; SSS = Sabbastberg

Sexual Self-Rating Scale; VAS = Visual Analog Scale.

Table 4 - Summary of studies with inconclusive results

Author (year)	Population	Gender M/F	Age M/F	Dayle dose	Time in weeks	Avaluations Instruments	Results
Rabkin et al. (2000)	HIV+	39/6	41	200 to 500 mg	8 to 16	The Clinical Global Impressions Scale and Visual Analog Scale	Improved libido of patients with low libido at baseline.
Johannsson et al. (2002)	Hypopituitarism	0/38	51	20 to 30 mg	26	Self-report and questionnaire directed to partner.	Did not improve sexual interest during double-blind phase, however most women reported improvement in sexual interest during open label phase.
Nadjafi-Triebsch (2003)	Fatigue and depressed mood	2/0	48 and ± 80	25 to 50 mg	52	Self-report	One patient reported improvement in libido, but the other reported to have worsened the libido.
Libè et al. (2004)	Addison's or Central Hypoadrenalism	13/7	45/ 45.8	50 mg	16	Psychological Adjustment Illness Scale.	Although the results have not been better than placebo, some patients reported increase in sexual interest after treatment.

ARTIGO 03

Título: Relação entre hormônios sexuais, qualidade de vida e função sexual na pós-menopausa.

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RESUMO

Objetivo: avaliar a relação entre hormônios sexuais, função sexual e qualidade de vida em mulheres na pós-menopausa. **Metodologia**: Estudo de corte transversal com amostra por conveniência composta por trinta e seis mulheres com idade entre 45 e 65 anos, na pós-menopausa. Todas as pacientes responderam questionários de avaliação da função sexual (IFSF), qualidade de vida (SF-36) e fizeram exame hormonal. **Resultados**: Foram observadas relação entre orgasmo e LH (*r*=.37; *p*=.02) e SHBG (*r*=.39; *p*=.01). SHBG apresentou relação com menor dor durante a atividade sexual (*r*=.44; *p*<.01), satisfação sexual (*r*=.33; *p*=.04) e com o escore total da escala IFSF (*r*=.39; *p*=.02). DHEA apresentou relação com desejo sexual (*r*= -.45; *p*=<.01) e a Prolactina com lubrificação (*r*=.33; *p*=.04). Na análise de relação da função sexual e qualidade de vida, desejo sexual apresentou relação Vitalidade (*r=.46; p=,004*), Aspectos Sociais (*r=.51; p=.001*), Estado de Saúde Geral (*r=.35; p=.03*) e Saúde Mental (*r=.38; p=.02*). A excitação, o orgasmo e a satisfação com a vida sexual e escore total da IFSF apresentaram relação com o domínio Dor da SF-36 (*r=.40; p=.01*), (*r=.42; p=.01*), (*r=.43; p=.009*), (*r=.37; p=.02*), respectivamente. A satisfação com a vida sexual apresentou relação com Vitalidade da SF-36 (*r=.33; p=04*). **Conclusão**: Fatores psicossociais relacionados à função sexual podem exercer influência positiva sobre a função sexual de mulheres com perfil hormonal desfavorável.

Palavras-chaves: hormônios sexuais; qualidade de vida, função sexual, disfunção sexual.

INTRODUÇÃO

A menopausa é um acontecimento na vida da mulher que marca o final do ciclo reprodutivo e o inicio da fase não-reprodutiva conhecida como pós-menopausa. A pós-menopausa é um período vivenciado de modo crítico pela maioria das mulheres devido às alterações decorrentes da falência ovariana. Estima-se que os sintomas comuns a este período atinjam aproximadamente 80% das mulheres com diferentes níveis de intensidade [1]. Entre os sintomas que se manifestam neste período estão: fogachos, diminuição da força física e da energia, alterações no sono, no humor, no trato urinário, na cognição e na função sexual [2].

Embora o impacto real da menopausa na função sexual não esteja totalmente claro, sabe-se que o hipoestrogenismo é responsável direto pela perda da lubrificação vaginal e o consequente aumento na incidência de dispareunia [3], assim como a drástica redução nos níveis de testosterona é responsável pela redução da libido [4]. Estes dois fatores podem ser responsável pela redução da frequência de relações sexuais relatada em alguns estudos [5-7]. Um estudo brasileiro com mulheres na pós-menopausa entre 45 e 60 anos relacionou a satisfação sexual com menor intensidade de sintomas climatéricos [5], tendo o mesmo achado sido observado em estudo com população chilena [6].

Sendo a sexualidade um dos pilares da qualidade de vida [5], as disfunções sexuais, que aumentam significativamente com o envelhecimento, tendem a contribuir de modo importante para a perda da qualidade de vida desta população. A qualidade de vida entre mulheres na pós-menopausa é uma temática de crescente interesse, devido especialmente ao aumento da parcela da população feminina que entra todos os anos na pós-menopausa.

Apesar da existência de muitos trabalhos que avaliam questões relacionadas à qualidade de vida da mulher na pós-menopausa [8-10], assim como outros que avaliam a sexualidade ou as alterações hormonais que ocorrem neste período [11, 12], estudos que investiguem a relação entre estes três elementos, normalmente afetados na pós-menopausa não são habitualmente encontrados na literatura. Diante disso, este trabalho

tem como objetivo avaliar a relação entre hormônios sexuais, função sexual e qualidade de vida em mulheres na pós-menopausa.

METODOLOGIA

Realizamos um estudo de corte transversal, utilizando uma amostra por conveniência composta por trinta e seis pacientes do Ambulatório de Climatério do Centro de Atendimento à Mulher de Campo Grande – MS. Todas as pacientes eram mulheres com idade entre 45 e 65 anos, com diagnóstico ginecológico de pós-menopausa (menopausa ocorrida há mais de 12 meses) e em acompanhamento em um ambulatório ginecológico especializado para queixas ligadas à menopausa. Não foram incluídas nesta pesquisa pacientes com diabetes ou outras condições metabólicas capazes de alterar significativamente o padrão hormonal dos sujeitos.

O estudo está de acordo com a normatização ética vigente e foi aprovado por Comitê de Ética em Pesquisa, tendo todos os participantes assinado termo de consentimento livre e esclarecido. Os participantes que preencheram os critérios de inclusão e aceitaram participar deste estudo realizaram as avaliações em duas etapas: sendo a primeira etapa avaliação do humor, qualidade de vida e sexualidade e a segunda etapa a coleta de sangue para avaliação hormonal.

A qualidade de vida foi avaliada por meio do Short Form – 36, versão brasileira (SF-36). O SF-36 é um instrumento composto por 36 itens que avaliam oito domínios relacionados à qualidade de vida. Os domínios avaliados pela escala são: Capacidade Funcional, Aspectos Físicos, Dor, Saúde Geral, Vitalidade, Aspectos Sociais, Aspectos Emocionais e Saúde Mental. Cada domínio apresenta escores que podem variar entre 0 e 100 sendo que zero indica pior condição naquele domínio e 100 melhor condição [13].

A função sexual foi avaliada por meio do Índice de Funcionamento Sexual Feminino, versão brasileira (IFSF). O IFSF é um instrumento composto por 19 itens que avalia 6 aspectos da função sexual: desejo, excitação, lubrificação, orgasmo, satisfação e dor. Excetuando-se a dimensão desejo que possui escores que podem variar entre 1,2 e 6, todos as demais dimensões podem apresentar escores entre 0 e 6. Embora possam ser avaliados individualmente, a soma de todas as subescalas formam o escore total deste instrumento que pode apresentar pontuações entre 1,2 e 36. Escores mais baixos em qualquer uma das dimensões, bem como no escore total indicam disfunção sexual [14].

Avaliação hormonal foi realizada para os seguintes hormônios: Hormônio Luteinizante (LH), Hormônio Folículo Estimulante (FSH), Estradiol, Progesterona, Testosterona Total (T-Total), Testosterona Livre (T-Free), Globulina Ligadora de Hormônios Sexuais (SHBG), Cortisol, Prolactina, Androstenediona, Dehidroepiandrosterona (DHEA) e Sulfato de Dehidroepiandrosterona (DHEA-S). A coleta de sangue para a avaliação hormonal ocorreu entre 7:00 e 9:00 hs da manhã. Todas as pacientes estavam em jejum de 12 horas. O material utilizado para a avaliação hormonal foi o soro e o método de análise hormonal utilizado foi o de quilominescência para todos os hormônios, exceto para o DHEA, cujo método utilizado foi o de radioimunoensaio.

Análise de dados: São apresentados dados descritivos da amostra em número bruto e percentagem para variáveis qualitativas ou média e desvio padrão para variáveis contínuas. As análises de relações foram executadas com teste de correlação de Pearson bicaudal. Não houve "missing values". O estudo adota valor de p inferior a 0,05 para estabelecimento de significância estatística.

RESULTADOS

A amostra foi composta predominantemente por mulheres casadas (63%, N=23), que se declararam do lar ou estudante (44%, N=16), católicas (47,2% N=17), com idade média de 55,3 anos (DP=4,6), tendo estudado em média 7,3 anos (DP=4,4) e tido a média de 2,6 filhos (DP=1,7). Mais detalhes sobre as características gerais da amostra podem ser visto na (Tabela 1). O perfil hormonal pode ser visto na (Tabela 2) e os escores relacionados a função sexual e a qualidade de vida são descritos na (Tabela 3).

As seguintes relações entre hormônios sexuais e aspectos da função sexual descritos pela IFSF foram encontradas: relação moderada positiva entre orgasmo e LH (r=.37; p=.02) e entre orgasmo e SHBG (r=.39; p=.01). SHBG também apresentou correlação moderada com as dimensão Dor da IFSF (r=.44; p<.01), Satisfação (r=.33; p=.04) e com o escore total da escala IFSF (r=.39; p=.02). DHEA apresentou correlação moderada negativa com Desejo (r= -.45; p=<.01) e a Prolactina apresentou correlação moderada positiva com lubrificação (r=.33; p=.04). Todas essas correlações foram consideradas estatisticamente significativas e podem ser observadas na (Tabela 4).

Para a relação entre os hormônios sexuais e os parâmetros de qualidade de vida, avaliado por meio da SF-36, foi encontrada relação positiva moderada entre progesterona e limitações por aspectos físicos (*r*=.35; *p*=.03); entre SHBG e aspectos sociais (*r*=.35; *p*=.03), entre cortisol e dor (*r*=.46; *p*=.004). Uma relação moderada negativa foi encontrada entre DHEA e aspectos sociais (*r*= - .40; *p*=.01). Essas correlações também foram consideradas estatisticamente significativas e podem ser observadas na (Tabela 5).

Na análise de relação entre função sexual e qualidade de vida observou-se que o desejo sexual apresentou correlação positiva moderada com as dimensões da SF-36 Vitalidade (*r=.46; p=,004*) e Aspectos Sociais (*r=.51; p=.001*). Desejo também se correlacionou de forma positiva com Estado de Saúde Geral (*r=.35; p=.03*) e Saúde Mental (*r=.38; p=.02*) da SF-36. A excitação, o orgasmo e a satisfação com a vida sexual apresentaram relação moderada positiva com o domínio Dor da SF-36 (*r=.40; p=.01*), (*r=.42; p=.01*), (*r=.43; p=.009*), respectivamente. O escore total da IFSF também apresentou relação positiva com o domínio Dor da SF-36 (*r=.37; p=.02*). A satisfação com a vida sexual apresentou relação positiva fraca com o domínio Vitalidade da SF-36 (*r=.33; p=04*). Estas correlação são apresentadas na (Tabela 6).

DISCUSSÃO

As relações encontradas entre hormônios e função sexual, bem como entre hormônios sexuais e qualidade de vida chamam a atenção por serem opostos ao esperado do ponto de vista fisiopatológico. O LH é um hormônio hipofisário envolvido no processo de ovulação. Em decorrência da falência ovariana, um aumento em seus níveis de produção é esperado, mas não existe na literatura evidências de uma relação entre maiores níveis de LH e a qualidade do orgasmo em mulheres, conforme observado neste estudo (*r*=.37; *p*=.02).

O SHBG é uma glicoproteína que tem como função transportar hormônios sexuais como a testosterona e os estrógenos. Maiores níveis de SHBG indicam menor quantidade de testosterona biodisponível [15]. Levando em consideração a importância da testosterona para a função sexual, maiores níveis de SHBG deve ter um efeito negativo sobre a função sexual. Entretanto, neste estudo maiores níveis de SHBG estiveram positivamente relacionados com três aspectos da função sexual avaliados por

meio da IFSF: orgasmo (*r*=.39; *p*=.01), satisfação (*r*=.33; *p*=.04) e dor (*r*=.44; *p*<.01). O que indica que, nesta amostra quanto maiores os níveis de SHBG melhor foi qualidade do orgasmo, melhor nível de satisfação com a função sexual e menos dor genital durante ou após a relação sexual. SHBG também apresentou uma correlação moderada positiva com o escore total da IFSF (*r*=.39; *p*=.02). Este resultado indica que maiores níveis de SHBG estão relacionados a um melhor funcionamento global da função sexual.

A prolactina apresentou relação, embora menos robusta, estatisticamente significativa com a lubrificação vaginal (*r*=.33; *p*=.04). O que também é um resultado inesperado, pois existe uma correlação negativa entre a prolactina e a testosterona [15]. Consequentemente a lubrificação vaginal, uma das variáveis relacionadas ao nível de excitação sexual e que sofre influência da testosterona não deveria apresentar uma relação positiva com a prolactina.

O único hormônio que apresentou relação negativa (com significância estatística) com um aspecto da função sexual foi a DHEA, que se relacionou moderadamente com o nível de desejo sexual (*r*=-.45; *p*=<.01). Sendo a DHEA um precursor indireto da testosterona [16-18], o esperado seria encontrar um relacionamento positivo entre este hormônio e o desejo sexual, contudo nesta amostra maiores níveis de DHEA estiveram relacionados ao menor desejo sexual. Tal resultado contraria estudos que usaram DHEA em mulheres na pós-menopausa e observaram melhora em diversos aspectos da função sexual e aumento nos níveis de DHEA no sangue [19-21].

Dos quatro hormônios que apresentaram relação estatisticamente significativa com domínios da qualidade de vida avaliada por meio da SF-36, três apresentaram resultados opostos ao esperado. Cortisol apresentou correlação positiva moderada com a dimensão Dor da SF-36 (*r*=.46; *p*=.004). O SHBG e DHEA apresentaram correlação com a dimensão Aspectos Sociais da SF-36 (*r*=.35; *p*=.03), (*r*= - .40; *p*=.01), respectivamente. Níveis mais altos de cortisol são esperados em pessoas com dor [22]. Diante da ação do SHBG sobre os andrógenos, seria esperado que maiores níveis de SHBG indicasse maior prejuízo nos aspectos sociais. Isso porque estudos mostram que a deficiência de andrógenos pode ocasionar redução da libido, do bem-estar, alterações no humor, fadiga e falta de motivação [23, 24]. Alguns estudos relacionaram maiores níveis de DHEA a melhora humor e qualidade de vida de algumas populações [25]. Único hormônio a apresentar uma correlação esperada foi a progesterona, que se

relacionou de forma positiva moderada com Aspectos Físicos (*r*=.35; *p*=.03). Embora a dimensão Aspectos Físicos não avalie especificamente a dor, certamente a dor pode influenciar os escores deste domínio. Para além do seu papel conhecido na reprodução, estudos mostram o potencial da progesterona na redução da dor [26]. É possível que a ação da progesterona sobre a dor justifique a relação encontrada neste estudo.

A análise da relação entre função sexual e qualidade de vida apresentou diversas correlações sobre as variáveis dos instrumentos que avaliaram estes dois elementos. Desejo sexual, avaliado pelo IFSF foi o aspecto da função sexual que mais se relacionou com a qualidade de vida. Desejo sexual se correlacionou com as seguintes dimensões da SF-36: Aspectos Sociais (*r=.51; p=.001*), Vitalidade (*r=.46; p=,004*), Saúde Mental (*r=.38; p=.02*), Saúde Geral (*r=.35; p=.03*). A dimensão Aspectos Sociais avalia o quanto problemas físicos e emocionais interferem nas atividades sociais; Vitalidade avalia o quanto a pessoa sente seu nível de energia a maior parte do tempo; Saúde Mental avalia aspectos relacionados à depressão, ansiedade e bem-estar psicológico; Saúde Geral avalia a percepção do indivíduo sobre a sua própria saúde. A satisfação com a vida sexual esteve relacionada com o dimensão Vitalidade da SF-36 (*r=.33; p=04*) e a dimensão Dor da SF-36 apresentou correlação moderada positiva com vários aspectos da função sexual: excitação (*r=.40; p=.01*), orgasmo (*r=.42; p=.01*), satisfação (*r=.43; p=.009*), escore total (*r=.37; p=.02*). Tendo em vista que a função sexual não é um fenômeno estritamente fisiológico [27], e que o bom funcionamento sexual é um dos pilares da qualidade de vida [5], estas correlações seriam comuns se ocorressem em uma amostra com um perfil hormonal mais favorável. No entanto, estes resultados levantam a hipótese da possível existência de fatores psicossociais capazes de influenciar positivamente a função sexual, mesmo em mulheres que apresentam um perfil hormonal desfavorável. Todavia, estes dados precisam ser tratados com parcimônia, uma vez que diversos fatores que não foram avaliados neste estudo podem ter influenciado positivamente tal correlação.

CONCLUSÃO

Este estudo aponta para a possibilidade de fatores psicossociais influenciarem a função sexual mesmo em mulheres com um perfil hormonal desfavorável para um bom funcionamento sexual. No entanto estes resultados ainda são insuficiências para

confirmar esta hipótese, de forma que outros trabalhos visando abranger mais variáveis que possam ter contribuído para esta relação devem ser realizados. Apesar disso, os resultados observados neste estudo podem contribuir para a construção de bases para futuros estudos, além de reforçar o entendimento da importância dos fatores psicossociais para a função sexual e para a qualidade de vida.

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Tabela 1- Características gerais da amostra

	N (%) or mean (SD)
Idade	55,39 (4,68) Min= 45; Max=65
Renda Familiar (BRL)	1.770,92 (849,62) Min=300,00; Max=4.000,00
Anos de estudo	7,33 (4,49) Min=0; Max=17
Ocupação	
Estudante / Do lar	16 (44,4%)
Desempregado	2 (5,6%)
Trabalhando	11 (30,6%)
Licença médica	4 (11,1%)
Aposentada	3 (8,3%)
Estado Civil	
Solteira	3 (8,3%)
Casada / relação estável	23 (63,9%)
Divorciada / Separada	5 (13,9%)
Viúvo	5 (13,9%)
Gestações	
Número de gestações	3,11 (2,36) Min=0; max=14
Número de partos	2,56 (1,66) Min=0; max=9
Número de abortos naturais	0,47 (1,13) Min=0; max=5
Número de abortos provocados	0.11 (0,3) Min=0; max=2
Filhos	
Tem filhos	34 (94,4%)
Número de filhos	2,67 (1,74) Min=0; Max=9
Saúde geral e hábitos de vida	
Hipertensão	6 (16,7%)
Cardiopatia	2 (5,6%)
Tabagismo	3 (8,3%)
Etilismo	0
Prática de atividade física	14 (38,9%)

Tabela 2 – Perfil hormonal da amostra

Hormônio	Unidade de medida	Mínimo	Máximo	Média	Desvio padrão
LH	mIU/mL	11,80	76,90	40,47	16,26
FSH	mIU/mL	22,7	171,1	81,88	33,11
Estradiol	pg/mL	11,8	175,2	21,72	27,50
Progesterona	ng/mL	,21	,51	,24	,07
T-Total	ng/dL	10,0	104,8	26,34	19,84
T-Livre	nmol/L	,003	,056	,01	,01
SHBG	nmol/L	14,3	131,0	49,73	26,84
Cortisol	µg/dL	,7	26,4	14,11	5,00
DHEA	ng/mL	,4	6,6	2,09	1,29
Prolactina	ng/mL	2,8	74,2	10,33	11,96
Androstenediona	ng/mL	,30	2,54	,73	,44
DHEA-S	µg/dL	15,0	120,0	43,67	28,31

Tabela 3 – Dados de qualidade de vida e função sexual.

	Mínimo	Máximo	Média	Desvio padrão
Short Form - 36				
Capacidade Funcional	10	100	65,28	27,77
Limitações por aspectos físicos	0	100	48,61	43,07
Dor	0	100	50,64	24,90
Estado Geral de Saúde	22	92	63,17	17,13
Vitalidade	5	90	51,53	22,35
Aspectos Sociais	13	100	73,26	23,37
Limitações por aspectos emocionais	0	100	62,04	45,88
Saúde mental	8	100	55,44	24,77
Índice de Funcionamento Sexual Feminino				
Desejo	1,2	5,4	2,32	1,02
Excitação	,0	5,1	1,69	1,54
Lubrificação	,0	6,0	1,89	1,91
Orgasmo	,0	5,6	1,81	1,79
Satisfação	,4	6,0	2,99	1,97
Dor	,0	6,0	2,60	2,39
Escore total	1,6	31,7	13,31	9,15

Tabela 4 – Relações entre hormônios e função sexual avaliada por meio do Índice de Funcionamento Sexual Feminino (IFSF)

		LH	FSH	Estra-diol	Proges-terona	T-Total	T-Livre	SHBG	Cortisol	DHEA	Prolac-ctina	Andros-tenediona	DHEA-S
Desejo	***r***	,016	-,172	,112	,247	-,028	-,137	,052	-,141	**-,453****	-,041	-,270	-,327
	Sig.	,924	,316	,514	,147	,873	,427	,762	,411	**,006**	,812	,112	,051
Excitação	***r***	,314	,217	,228	-,176	,073	-,189	,377*	,165	-,098	,308	-,124	-,136
	Sig.	,062	,204	,181	,304	,670	,269	,023	,335	,569	,068	,472	,429
Lubrificação	***r***	,262	,228	,211	-,259	,039	-,168	,315	-,112	-,165	**,331***	-,195	-,135
	Sig.	,123	,182	,218	,127	,821	,329	,062	,514	,335	**,049**	,255	,431
Orgasmo	***r***	**,377***	,207	,271	-,153	,147	-,131	**,393***	,185	-,112	,251	-,078	-,148
	Sig.	**,024**	,225	,110	,372	,393	,447	**,018**	,281	,515	,140	,650	,388
Satisfação	***r***	,281	,159	,107	-,078	,220	-,010	**,331***	,228	-,034	,110	-,039	-,197
	Sig.	,097	,354	,535	,653	,197	,954	**,049**	,180	,842	,524	,821	,248
Dor	***r***	,197	,132	,290	-,251	-,006	-,249	**,445****	,118	-,039	,300	-,229	-,154
	Sig.	,249	,443	,086	,140	,972	,143	**,006**	,491	,823	,075	,179	,370
Escore total	***r***	,294	,173	,246	-,168	,091	-,174	**,398***	,104	-,141	,266	-,175	-,199
	Sig.	,082	,313	,149	,328	,596	,309	**,016**	,546	,413	,116	,308	,245

Tabela 5 – Relações entre hormônios e qualidade de vida avaliada por meio do Short Form – 36 (SF-36).

		LH	FSH	Estra-diol	Proges-terona	T-Total	T-Livre	SHBG	Cortisol	DHEA	Prolac-ctina	Andros-tenediona	DHEA-S
Capacidade Funcional	***r***	-,106	-,149	,117	,236	-,063	-,061	-,101	-,060	-,006	-,247	,033	,056
	Sig.	,539	,387	,497	,166	,716	,724	,559	,730	,975	,147	,846	,747
Limitações por aspectos físicos	***r***	,067	,044	,187	**,352***	-,149	-,144	,090	,154	-,143	-,192	-,062	,120
	Sig.	,696	,798	,275	**,035**	,387	,402	,603	,368	,406	,261	,721	,485
Dor	***r***	,216	,084	,131	-,032	,143	,005	,182	**,467****	-,009	-,128	,147	,089
	Sig.	,206	,625	,446	,853	,406	,978	,288	**,004**	,959	,458	,392	,606
Estado Geral de Saúe	***r***	-,012	-,103	,204	,158	,151	,123	-,078	-,285	-,022	-,034	,176	,014
	Sig.	,943	,551	,233	,358	,378	,475	,652	,092	,897	,842	,303	,935
Vitalidade	***r***	-,004	-,137	,195	,275	,117	-,055	,306	-,075	-,196	-,036	-,032	-,095
	Sig.	,983	,424	,253	,104	,496	,751	,070	,665	,251	,834	,853	,582
Aspectos Sociais	***r***	,013	,005	,170	,279	,101	-,129	**,353***	,126	**-,405***	,156	-,004	-,136
	Sig.	,939	,978	,323	,100	,559	,454	**,035**	,464	**,014**	,363	,984	,428
Limitações por aspectos emocionais	***r***	,021	,024	,109	,297	,099	,030	,172	,220	-,142	,085	,079	-,022
	Sig.	,905	,891	,527	,079	,565	,861	,316	,197	,408	,620	,646	,900
Saúde mental	***r***	,120	,090	,084	-,086	-,018	-,155	,208	,185	-,185	-,082	-,054	-,109
	Sig.	,487	,601	,628	,618	,916	,368	,223	,281	,280	,635	,753	,527

*Correlação significativa no nível de 0,05 (2 extremidades), ** Correlação significativa no nível de 0,01 (2 extremidades).

Tabela 6 – Relações entre função sexual e qualidade de vida avaliada por meio do Índice de Funcionamento Sexual Feminino (IFSF) e do Short Form 36 (SF-36)

		Capacidade Funcional	Limitações por aspectos físicos	Dor	Estado de saúde geral	Vitalidade	Aspectos Sociais	Limitações por aspectos Emocionais	Saúde Mental
Desejo	***r***	,126	,224	,186	**,350***	**,467****	**,511****	,157	**,387***
	Sig.	,462	,188	,277	**,037**	**,004**	**,001**	,369	**,020**
Excitação	***r***	,051	,027	**,402***	-,043	,279	,057	,150	,189
	Sig.	,768	,877	**,015**	,805	,099	,740	,381	,269
Lubrificação	***r***	,012	-,069	,213	-,063	,220	-,042	,086	,002
	Sig.	,946	,691	,213	,714	,197	,808	,617	,992
Orgasmo	***r***	,049	,012	**,420***	-,081	,260	,013	,231	,272
	Sig.	,775	,947	**,011**	,637	,125	,941	,176	,109
Satisfação	***r***	,028	,003	**,432****	-,039	**,332***	,001	,291	,323
	Sig.	,871	,985	**,009**	,821	**,048**	,995	,085	,054
Dor	***r***	-,052	-,044	,263	-,025	,138	,060	-,113	,049
	Sig.	,761	,797	,122	,883	,421	,728	,512	,777
Escore total	***r***	,027	,007	**,375***	-,012	,303	,076	,138	,210
	Sig.	,876	,970	**,024**	,945	,073	,658	,422	,219

*Correlação significativa no nível de 0,05 (2 extremidades), ** Correlação significativa no nível de 0,01 (2 extremidades).

2. 1 Discussão

A depressão e o funcionamento sexual feminino são tópicos de grande importância na clínica do climatério, pois são comuns e afetam a qualidade de vida desta população [41]. Os artigos de revisão sistemática que compuseram esta dissertação, embora não tenham focado apenas em mulheres no climatério, certamente trazem contribuições para esta área.

Os resultados descritos no artigo 1 “The Effects of Dehydroepiandrosterone (DHEA) in the Treatment of Depression and Depressive Symptoms in Other Psychiatric and Medical Illnesses: A Systematic Review” mostra o potencial da DHEA na remissão dos sintomas depressivos, tanto indivíduos com depressão quanto em indivíduos com sintomas depressivos decorrentes de outros transtornos mentais ou doenças clínicas. Quatro estudos incluídos nesta revisão, realizados com pacientes com diagnóstico de depressão apresentaram redução significativa nos escores da escala de Hamilton de Depressão, sendo que em um estudo que fez avaliação dos sintomas depressivos na semana 0 e na semana 1, foi possível a verificação de um menor escore apenas uma semana após o início do tratamento [42-45]

Diante de uma estimativa de 9% de incidência de depressão em mulheres no período do climatério, estudos com DHEA, bem como com outros medicamente capazes de tratar a depressão ou sintomas depressivos são de grande importância para a área [7, 8]. Como o artigo 1 mostra, os estudos com DHEA evidenciam que este hormônio apresenta baixa incidência de efeitos colaterais, sendo que os mesmos costumam ser leves e transitórios, o que deve ser destacado como um fator muito positivo, uma vez que efeitos colaterais mais intensos favorecem o abandono do tratamento. Assim, os elementos apresentados colocam a DHEA como uma alternativa a mais a ser estudada para compor o arsenal medicamentoso para o tratamento da depressão em um público específico.

O artigo 2: “The effects of Dehydroepiandrosterone (DHEA) on sexual function: A systematic review” descreve resultados que salientam a eficácia da DHEA sobre diversos aspectos da função sexual em mulheres no climatério, bem como a melhora da dispareunia, disfunção sexual muito comum nesta

população. Segundo Dennerstein et al. (2001, apud LORENZI & SOLITO, 2006):

> A diminuição da libido e da frequência das relações sexuais no climatério pós-menopáusico estariam associadas principalmente à maior prevalência de dispareunia e fogachos nesse período. Entre as causas do decréscimo da atividade sexual no climatério, estão a maior ocorrência de dispareunia decorrente de atrofia urogenital e a diminuição do desejo sexual. [4]

Esta capacidade demonstrada em alguns trabalhos, de melhorar aspectos da função sexual, bem como tratar a dispareunia, reforça a importância de estudos com este hormônio para mulheres climatéricas. Esta importância fica ainda mais clara quando levamos em consideração o aumento da longevidade e a prevalência de disfunções sexuais durante o climatério [4].

Um ponto bem estabelecido na literatura é a relação entre os níveis circulantes de DHEA e a idade, sendo que com o envelhecimento há uma redução deste hormônio no corpo humano [33-35]. Como precursor indireto de hormônios sexuais como a testosterona e os estrógenos, uma redução nos níveis circulantes de DHEA pode influenciar negativamente a libido e outros aspectos da função sexual [46-48]. Embora ainda não esteja totalmente claro o mecanismo de ação que possibilita a melhora de aspectos da função sexual por meio do uso da DHEA, estudos que avaliaram o perfil hormonal e parâmetros sexuais observaram um aumento nos níveis circulantes de testosterona com o uso do DHEA [49, 50]. Este poder de aumentar os níveis de testosterona esteve presente mais comumente em mulheres no climatério.

Apesar dos estudos com DHEA oral mostrarem a capacidade deste hormônio de reestabelecer os níveis circulantes de DHEA aos níveis encontrados em jovens adultos [49,50], um estudo que avaliou os parâmetros hormonais de mulheres tratadas de disfunção sexual por meio da DHEA intravaginal não observou alterações nos parâmetros hormonais, indicando um efeito exclusivamente tópico para a forma intravaginal [51].

A DHEA intravaginal foi capaz de melhorar os escores de todos os parâmetros da IFSF. Isso, em parte pode estar relacionado à capacidade demonstrada de melhorar a secura vaginal, principal causadora da dispareunia e da consequente evitação de relações sexuais por parte da mulher. Segundo Cabral et al. (2012):

> Durante o climatério, o hipoestrogenismo torna o epitélio do trato genital mais delgado e frágil. Na vulva, ocorre decréscimo na secreção das glândulas sudoríparas, sebáceas e atrofia das glândulas de Bartholin, o que propicia a secura e o estreitamento da vagina, com redução de sua rugosidade e elasticidade. A menor capacidade de lubrificação frente à estimulação sexual pode causar a dispareunia, caracterizada por dor na relação sexual, fato que prejudicará o funcionamento sexual da mulher. [52]

Considerando os benefícios apresentados, bem como a ausência de relato de efeitos colaterais graves nos estudos que compuseram o artigo 2, entendemos que a DHEA apresenta-se como uma boa alternativa no tratamento de problemas relacionados a função sexual, particularmente aqueles que decorrem do envelhecimento.

Diferentemente dos artigos de revisão (artigos 01 e 02) que não focaram em mulheres no climatério, mas sim em dois problemas comuns ao climatério, o artigo 3 é o relato de pesquisa conduzida com 36 mulheres na pós-menopausa e que encontrou correlações opostas ao esperado entre hormônios sexuais e função sexual, bem como entre hormônios sexuais e qualidade de vida.

Neste trabalho, os hormônios SHBG, LH, e prolactina apresentaram correlação positiva moderada com uma melhor função sexual avaliada por meio do Índice De Funcionamento Sexual Feminino (IFSF), enquanto a DHEA apresentou correlação negativa moderada com o desejo sexual, também avaliado por meio da IFSF. Todas as correlações foram estatisticamente significativas ($p<0,05$).

O SHBG é uma glicoproteína, que funciona como meio de transporte para alguns hormônios sexuais, entre eles a testosterona [53]. Níveis altos de SHBG representa uma menor quantidade de testosterona livre biodisponível [53]. O LH, cuja atividade está relacionada ao processo de ovulação que ocorre no período fértil, tende aumentar à medida que a mulher se aproxima da menopausa, sendo que maiores níveis deste hormônio são esperados na pós-menopausa [54]. A prolactina, que tem como principal função estimular a produção de leite e é um hormônio que está relacionado à redução da testosterona. Assim, correlações entre maiores níveis destes hormônios e a função sexual não é esperado, muito pelo contrário.

O único hormônio que apresentou correlação negativa com a função sexual foi a DHEA, justamente aquele que, pautado por nossos estudos com este hormônio, acreditávamos que apresentaria uma correlação positiva com a função sexual.

No entanto, as correlações entre função sexual e qualidade de vida, mostraram relação positiva entre melhor função sexual e melhor qualidade de vida ($p<0,05$). Estas relações não nos permita atribuir uma melhor função sexual a uma melhor qualidade de vida, nem o contrário. Entretanto, a relação encontrada entre estas duas variáveis levantam a hipótese da existência de fatores psicossociais capazes de influenciar positivamente a função sexual mesmo em condições hormonais desfavoráveis para um bom funcionamento. De fato, fatores não hormonais como: insatisfação com o parceiro, status social e questões culturais relacionadas ao envelhecimento da mulher são importantes e afetam a sexualidade feminina [55].

3 CONCLUSÃO

Embora seja vendido livremente em muitos lugares do mundo como suplemento alimentar, a DHEA não está regulamentada para uso em muitos países, entre eles o Brasil.

Diante das evidências apresentadas em nossos trabalhos com este hormônio, indicando o seu potencial no tratamento de depressão e sintomas depressivos de outros transtornos mentais e em algumas doenças clínicas, bem como na melhora de aspectos da função sexual e no tratamento de algumas disfunções sexuais e seus efeitos colaterais brandos, acreditamos que deve ser incentivado estudos com este hormônio no Brasil, visando a sua regulamentação e consequente benefício da população brasileira, principalmente mulheres no período do climatério e homens mais velhos.

Considerando nosso estudo de correlação entre hormônios sexuais, função sexual e qualidade de vida, entendemos que precisamos avançar muito na compreensão dos elementos que envolvem um bom funcionamento sexual de mulheres no climatério, especialmente os fatores psicossociais, de forma que mais estudos visando avançar estes conhecimentos se fazem necessários.

Apesar das limitações do conteúdo desta dissertação, o material nela exposto traz algumas contribuições para a melhor compreensão dos efeitos do uso da dehidroepiandrosterona sobre o humor e a função sexual. Quanto às relações existentes entre hormônios sexuais, função sexual e qualidade de vida em mulheres na pós-menopausa, este trabalho contribui indicando a possível existência de fatores psicossociais envolvidos na função sexual que podem ser benéficos mesmo em situações em que os parâmetros de hormônios sexuais não estejam em níveis favoráveis para um bom funcionamento sexual feminino.

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