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REVIEW

- 79 Artificial intelligence ecosystem for computational psychiatry: Ideas to practice
Liu XQ, Ji XY, Weng X, Zhang YF

MINIREVIEWS

- 92 Lipocalin-2 as a biomarker for diabetic nephropathy
Dahiya K, Prashant P, Dhankhar R, Dhankhar K, Kumar S, Vashist S
- 102 Dehydroepiandrosterone sulfate supplementation in health and diseases
Jethwani P, Rastogi A, Shukla R

SYSTEMATIC REVIEWS

- 112 Current approach for Boerhaaves syndrome: A systematic review of case reports
Yamana I, Fujikawa T, Kawamura Y, Hasegawa S

META-ANALYSIS

- 125 Role of baricitinib in COVID-19 patients: A systematic review and meta-analysis
Thakur M, Babu A, Khatik GL, Datusalia AK, Khatri R, Kumar A

ABOUT COVER

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Dehydroepiandrosterone sulfate supplementation in health and diseases

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Abstract

Dehydroepiandrosterone sulfate (DHEAS) is a hormone produced by the zona reticularis of the adrenal gland and the ovaries. Initially considered as an inert compound merely serving as an intermediate in the conversion of cholesterol to androgens, interest in DHEA began to grow in the 1960s when it was found that DHEAS is the most abundant steroid hormone in human plasma and that its levels decline with age. In many countries, DHEA is considered a nutritional supplement. It has been used for a multitude of conditions which include sexual dysfunction, infertility, genitourinary syndrome of menopause, musculoskeletal disorders, cardiovascular diseases, ageing, neurological diseases, autoimmune conditions, adrenal insufficiency, and anorexia nervosa. We describe an overview of the historical evolution of DHEA, its physiology, and the disease states where it has been evaluated as a supplement.

Key Words: Dehydroepiandrosterone; Adrenal; Health supplements; Hypothyroidism; Autoimmunity; Depression; Cardiovascular disease

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Core Tip: In this review we discuss the current evidence for the nutraceutical utility of dehydroepiandrosterone sulfate (DHEAS). Initially regarded as a panacea for a multitude of human diseases, studies conducted with DHEA supplementation have yielded largely inconclusive results, with the possible exception as an alternative agent in adrenal insufficiency patients with low energy and low libido (in affected females), and genitourinary syndrome of menopause (vaginal preparation). However, with its easy availability as a relatively inexpensive over-the-counter supplement in many countries, DHEA, like vitamin D, has continued to evoke curiosity in the scientific community. Hence, the subject of DHEA supplementation requires a pragmatic approach, backed by robust evidence, with careful weighing of potential benefits (or lack thereof) and possible adverse effects.

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INTRODUCTION

Dehydroepiandrosterone (DHEA) was first isolated and characterized by Adolf Butenandt in 1934, and he was subsequently awarded the Nobel Prize in 1939 for his “work on sex hormones”. The sulfated form of DHEA, dehydroepiandrosterone sulfate (DHEAS), was then isolated in 1944 by Munson, Gallagher, and Koch in 1944[1]. The hormone was named dehydroepiandrostenedione by Lieberman in 1949[1].

In the 1980s, despite a lack of human studies and information on its function, efficacy, and safety, DHEA began to be marketed as a non-prescription drug in the United States (US) for multiple indications such as anti-ageing, anti-cancer, and anti-obesity. It gained limelight as a “super hormone” and an “anti-ageing” wonder drug which led to multiple studies around its use in various conditions.

Soon thereafter in 1985, the US FDA predictably banned over-the-counter sales of DHEA considering the lack of health benefits and long-term safety data. However, in 1994, DHEA was re-introduced in the market with the dietary supplement health and education act, which allowed certain substances to be marketed as dietary supplements not requiring FDA approval. Marketing as a cure-all elixir and the lack of regulation led to skyrocketing production of DHEA and it became easily available as an over-the-counter supplement. However, research around the hormone has made rapid strides ever since with implications for the diagnosis and treatment of a host of human diseases (Table 1).

SEARCH STRATEGY

The following databases were used to identify the relevant studies: PubMed/Medline, Scopus, and Cochrane. We also applied Reference Citation Analysis (RCA) to further enhance our search results. All the databases were searched from their inception till December 10, 2022. We did a search again and the search was extended up till February 7, 2023 to look for any additional articles. Keywords used were mainly related to the topics of interest, including “DHEA,” “adrenal insufficiency,” “menopause,” “autoimmunity,” “immunity,” “cognition,” “infertility,” “sexual function,” “genitourinary,” “anorexia,” “bone,” “muscle,” “musculoskeletal,” “systemic lupus erythematosus” or “SLE,” “schizophrenia,” “depression,” “cardiovascular disease,” “rheumatoid arthritis,” and “hypothyroidism”.

There was no restriction for study design and language (where English language translation was available). All articles related to DHEA supplementation were reviewed and relevant articles were considered for inclusion in this scoping review.

NORMAL PHYSIOLOGY

About 75%-90% of DHEA is produced by the zona reticularis of the adrenal gland while the rest is produced in the ovaries and the brain. Its sulfated form, DHEAS, is exclusively synthesized by the adrenals. DHEA has a shorter half-life and is secreted in a pulsatile manner, mirroring the circadian rhythm of corticotrophin. In contrast, DHEAS has a longer half-life and relatively more stable levels across the day, providing a continuous reservoir of DHEA.

DHEA and DHEAS start increasing in boys and girls around the age of six to eight years, and this increase in adrenal androgens is known as adrenarche and the concomitant clinical appearance of pubic hair is known as pubarche. The levels rise steadily and peak in the second to third decade of life.

Table 1 Proposed therapeutic indications of dehydroepiandrosterone

Indication	Current evidence
Sexual dysfunction	Equivocal[6]
Infertility	Equivocal[13]
Genitourinary symptoms (alternative agent)	Positive[7,9]
Peri-menopausal and menopausal women	Equivocal[5]
Adrenal insufficiency (alternative agent)	Positive[17]
Anorexia nervosa	Equivocal[19]
Autoimmune diseases	Equivocal[24,27]
Musculoskeletal	Equivocal[43]
Neuropsychiatric diseases	Equivocal[48]
Anti-ageing agent	Negative[35,36]
Cardiovascular disorders	Equivocal[54,55]

Thereafter there is a progressive decline by around 2%-5% each year with advancing age, such that levels decrease by 80%-90% in the eighth to ninth decade of life[2].

The exact mechanism of action of DHEA remains uncertain with some evidence suggesting that it has pleiotropic effects. As DHEA has minor steroidogenic activity, it acts predominantly by conversion to androgens and estrogens in peripheral target tissues (Figure 1). It also functions as a neurosteroid and acts *via* receptors for N methyl-D aspartate receptors (NMDA) and gamma amino butyric acid alpha (GABA α), peroxisome proliferator-activated receptor α (PPAR α), or receptors for pregnane X, androstanol, and estrogen receptor β [3].

DHEA IN DISEASE STATES

DHEA and sexual dysfunction

Serum levels of DHEA and DHEAS start declining from the third decade, leading to decreased androgen levels. In a randomized, double-blind, placebo-controlled trial by Panjari *et al*[4], 93 post-menopausal women with low libido were included and the effect of DHEA on sexual function was assessed. They observed that there was no significant improvement in sexual function with regard to the primary outcome measures which included the change in total satisfying sexual events and the Sabbatsberg Sexual Self-Rating Scale total score. There was no significant change in secondary outcome measures as well, which included measures of well-being and quality of life.

In a systematic review and meta-analysis of 28 studies of DHEA therapy in 1273 post-menopausal women, DHEA therapy did not improve sexual function, quality of life, or menopausal symptoms and was associated with androgenic side effects[5]. It is to be noted that these studies had a duration less than 3 mo. Also, oral DHEA was used in all of these, and there are no studies on local DHEA (*see below*). Currently, the endocrine society guidelines recommend against the use of DHEA for sexual dysfunction and other related indications because of a lack of long-term safety efficacy data[6].

Genitourinary syndrome of menopause

Genitourinary syndrome of menopause (GSM), a term first introduced in 2014, is a relatively common entity with a prevalence ranging from 27% to 82%. It encompasses symptoms ranging from vulvovaginal dryness and dyspareunia to urinary urgency and dysuria, and leads to significant impairment in quality of life and sexual function. In a randomized prospective double-blind placebo-controlled trial by Labrie *et al*[7], the efficacy of 0.5% intravaginal DHEA in women with GSM was assessed. They observed that vaginal DHEA (Prasterone) significantly relieved dyspareunia with improvement in vaginal secretions and epithelial integrity. Prasterone was first approved by the FDA in 2016 for the treatment of dyspareunia due to GSM[8]. Recent guidelines suggest vaginal DHEA as an alternative agent in individuals with GSM symptoms after the initial use of non-hormonal agents[9].

DHEA and infertility

DHEA has been found to improve ovarian steroidogenesis and also leads to an increase in IGF-1 which is speculated to have a favorable effect on oocyte quality and follicular development[10,11]. In a randomized prospective study by Wiser *et al*[12], they enrolled 33 women with poor ovarian reserve (17 in the DHEA group and 16 in the control group) and observed the effects of DHEA supplementation on

enhancing T-cell and NK cell cytotoxicity[20]. In accordance, DHEAS levels have also been found to be decreased in multiple autoimmune diseases including systemic lupus erythematosus, rheumatoid arthritis, autoimmune hypothyroidism, fibromyalgia, and polymyalgia rheumatica[21-23].

In a randomized double-blind placebo-controlled study by Nordmark *et al*[24], they included 41 women with SLE on steroids and assessed the efficacy of DHEA supplementation. They observed significant improvement in some domains of health-related quality of outcome measures which included an improvement in mental health. There was also an improvement in sexual well-being while there was no improvement in other domains such as physical function, general health, or vitality.

Similarly, DHEA levels have also been found to be low in Sjogren's syndrome, which has been hypothesized as a potential cause of fatigue in these individuals. In a multicenter randomized controlled trial by Virkki *et al*[25], they included 107 individuals with primary Sjogren's syndrome and assessed the efficacy of DHEA administration on several measures of fatigue. They observed that DHEA supplementation at a dose of 50 mg significantly improved measures of fatigue but a similar improvement was observed with placebo as well. Their results were similar to an earlier study by Hartkamp *et al*[26], and hence the authors suggested cognitive behavioral interventions in these individuals. In autoimmune hypothyroidism, Shukla *et al*[27] investigated the relationship between DHEAS levels and arthralgias in individuals with primary hypothyroidism. They assessed 73 individuals with subclinical hypothyroidism and observed that DHEAS levels < 43.6 mcg/dL significantly predicted early rheumatoid changes in individuals with primary hypothyroidism. They postulated the inhibition of 11- β HSD1, a possible bystander effect due to hypothalamic-pituitary-axis suppression and its immunosuppressive effects as some of the mechanisms to explain the effects. Thus, there is some evidence to suggest a potential role of DHEA in multiple immunological diseases, and clinical interventions targeting this area merit further investigation.

Cognition

Ageing is associated with declining DHEA levels and deterioration in cognition. Several studies have explored the relationship of DHEA supplementation with cognitive outcomes. DHEA is synthesized in the brain and is the most abundant neurosteroid in humans. DHEA and DHEAS have multiple actions including neuroprotection, acting *via* AMPA and NMDA receptors, neuronal differentiation and apoptosis *via* tyrosine kinase receptors, inhibition of 11- β HSD1 activity, and anti-oxidant and anti-inflammatory actions[28,29]. In a study by Wolf *et al*[30], the authors studied the effect of DHEA supplementation on cognition in healthy elderly men and women. This was a double-blind placebo-controlled study and they observed that DHEA supplementation at a dose of 50 mg had no effect on cognitive abilities in these individuals. In a double-blind placebo-controlled study by Alhaj *et al*[31], they studied the effects of DHEA administration on episodic memory in 24 healthy young men and observed that DHEA was associated with both subjective and objective improvements in memory when given at a dose of 150 mg over a period of 7 d. In a Cochrane review by Grimley Evans *et al*[32] that included five trials, they observed that DHEA supplementation was not associated with any beneficial effects on cognitive outcomes in healthy individuals over 50 years of age. Subsequently, in a double-blind placebo-controlled cross-over study by Merritt *et al*[33], 50 mg of oral DHEA supplementation did not improve short-term memory in post-menopausal women. Hence, although DHEA does seem to play a role in cognitive function, there is little evidence to support its role as therapy for the same. Therefore, large-scale clinical studies are needed to assess whether DHEA could be used as a diagnostic and therapeutic tool for clinical implications.

Anti-ageing agent

Concomitant to its potential multiple actions on well-being, sexual function, and cognition, early interest in DHEA came about with it being promoted as the "fountain of youth hormone." In the DHEAge study by Baulieu and colleagues, they observed the effects of DHEA supplementation at 50 mg daily for a year in 280 older men and women (age 60-79, 140 each). While there was some improvement in some parameters such as sexual function in women over 70 years of age, BMD at the femoral neck, and skin indices, there was no difference in libido, BMD, or sexual function in men[34]. Moreover, there was no difference in body composition or muscle strength in women. Thereafter, in a double-blind randomized placebo-controlled study by Nair *et al*[35], they investigated the effects of DHEA administration in 87 elderly men with low levels of DHEAS and bioavailable testosterone and 57 elderly women with low DHEAS levels. There was no improvement in body composition, quality of life, physical performance, or insulin supplementation with DHEA supplementation. Similarly, there have been studies that have found no effects of DHEA supplementation on sexual function or well-being parameters[36,37]. Taken together, studies have argued against the use of DHEA as a cure-all elixir and the lack of long-term safety data does not justify the use of DHEA in healthy elderly individuals.

DHEA and the musculoskeletal system

As age-related decline in androgens and estrogens is said to contribute to the loss of muscle mass and bone mineral density in older adults, DHEA has been suggested as a potential agent for minimizing these losses. Moreover, the peak and nadir of BMD mirror the rise and fall in levels of DHEA,

respectively, and this has led to multiple studies of DHEA supplementation for bone health.

In bone, DHEA has been postulated to have a dual, pro-anabolic, and anti-catabolic effect. The anabolic effect of DHEA comes from its ability to increase the activity of osteoblasts secondary to raised IGF-1 levels *via* the GH/IGF-1 pathway. The anti-catabolic action involves its ability to inhibit the overall function of osteoclasts *via* direct and indirect actions on the estrogen receptor. DHEA also results in increased osteoprotegerin levels, which contributed to reduced resorption by osteoclasts.

In a recent pooled analysis of four double-blind randomized control trials by Jankowski *et al*[38], they examined the efficacy of DHEA in 295 women and 290 men aged 55 years or older given DHEA or placebo daily for 12 mo. They observed that men had a significant increase in DHEAS, estradiol, and IGF-1 while women in addition had a significant increase in testosterone levels as well. There was no effect of DHEA on BMD in men, while there was a small increase in lumbar spine ($1.0\% \pm 3.4\%$) and trochanter ($0.5\% \pm 3.8\%$) with maintained hip BMD in women. This modest increase in BMD is less than that found with other anti-osteoporotic agents including bisphosphonates, denosumab, and teriparatide. However, these trials did not primarily involve women with osteoporosis which may explain these findings.

DHEA is also said to contribute to muscle growth and strength through an anabolic effect augmenting protein synthesis. The mechanisms suggested involve the ability of the skeletal muscle to metabolize DHEA to active androgens and increased bioavailability of insulin-like growth factor-1 (IGF-1). IGF-1 is said to be involved in the proliferation of myogenic cells leading to muscle growth and repair[39,40].

Scattered studies have found some positive effects of DHEA on muscle strength, muscle mass, and mobility, as well as physical function[41,42]. However, in a systematic review by Baker *et al*[43], they included eight randomized control trials and observed that the effects of DHEA on muscle strength and physical performance were inconclusive.

DHEA supplementation in schizophrenia

DHEA has also been found to play a role in the pathophysiology of schizophrenia. It has been suggested to modulate neuronal differentiation and synaptogenesis. Additionally, it also interacts with multiple hormone receptor systems including gamma-aminobutyric acid, glutamate, and dopamine[44]. In a systematic review and meta-analysis by Misiak *et al*[45] which included 19 studies, DHEAS levels were found to be significantly elevated in individuals with schizophrenia.

DHEA supplementation in depression

DHEA being a neurosteroid has also been evaluated in depression on account of its multiple actions. Its direct actions involve its ability to regulate neuronal excitability by interactions with neurotransmitter receptors known to modulate mood. Other indirect actions involve its ability to regulate cortisol levels and its potential to increase IGF-1 levels.

In one of the initial studies by Wolkowitz *et al*[46], they included 22 individuals with major depression and observed that DHEA was associated with a significant improvement in depressive score compared to placebo. Thereafter in 2005, Schmidt *et al*[47] evaluated the efficacy of DHEA in 46 individuals (23 men and 23 women) aged 45 to 65 years with depression in a randomized double-blind placebo-controlled study. They observed that 6 wk of DHEA supplementation was associated with a significant improvement in measures of depression. In a recent meta-analysis by Peixoto *et al*[48] which included 14 studies, DHEA was associated with a beneficial effect on depressive symptoms compared to placebo. However, the quality of evidence was low due to high clinical heterogeneity in clinical studies. Hence, although DHEA has been found to have some beneficial effect on depressive symptoms, the results should be interpreted with caution and further well-designed larger clinical trials will help in assessing these findings.

DHEA and cardiovascular disease

DHEAS levels have also been found to be decreased in cardiovascular disease in a few studies, suggesting a possible therapeutic role in atherosclerosis and coronary artery disease[49,50]. The mechanisms suggested to explain these effects include inhibition of platelet aggregation, smooth muscle cell proliferation and plasminogen activator inhibitor-1 generation, increased nitric oxide generation, and vasodilation[51,52]. In the Women's Ischemia Syndrome Evaluation study, lower DHEAS levels were associated with higher cardiovascular mortality and all-cause mortality and this was independent of other major cardiovascular risk factors. However, when adjusted for the presence or severity of obstructive coronary artery disease, the risk became non-significant[49]. DHEAS levels have also been found to be associated with arrhythmias. In the Rotterdam study which involved 1180 individuals without atrial fibrillation at baseline, after a mean follow-up of 12.3 years, DHEAS levels were found to be inversely associated with the risk of atrial fibrillation[53]. However, several studies have also failed to show an association between DHEA levels and cardiovascular disease[54,55]. In a case-control study by Golden *et al*[54], they assessed the correlation between DHEAS levels and atherosclerosis in 364 post-menopausal women and observed that DHEAS levels were not associated with the risk of atherosclerosis which was assessed by carotid artery intimal medial thickness. In a recent study by Zhao *et al*

[56], they observed that while increased testosterone levels were associated with an increased risk of cardiovascular diseases, DHEAS levels were not associated with these outcomes. In fact, some studies have found DHEA supplementation to be associated with increased cardiovascular risk. DHEA supplementation has been found to be associated with a pro-atherogenic state *via* upregulation of lipoprotein processing genes leading to macrophage foam cell formation[57]. Similarly, DHEA supplementation has also been found to be associated with deranged lipid profiles[58,59]. In a double-blind randomized cross-over study by Srinivasan *et al*[58], they assessed the effect of 50 mg DHEA supplementation for 3 mo on lipid parameters, they observed significantly decreased levels of high-density lipoprotein (HDL) in women supplemented with DHEA. Hence, the association of lower DHEAS levels with increased cardiovascular risk remains uncertain. On the contrary, evidence suggests a cautionary approach in using DHEA supplementation in view of a possible association with adverse cardiovascular profile.

ADVERSE EFFECTS

The major concerns with DHEA revolve around its ability to convert to androgen and estrogen metabolites. Reported androgenic side effects involve mild acne, facial hair growth, and seborrhea[60]. DHEA has also been associated with a pro-atherogenic state with decreased HDL levels[57,58]. It has also been seen that DHEA leads to proliferation of breast cancer cells *via* stimulation of estrogen receptors[61]. Hence, there have been concerns with the use of DHEA in hormone dependent cancers including breast cancer, endometrial cancer, and prostate cancer[62,63]. Currently, there is limited evidence with a paucity of long-term safety data and caution needs to be exercised.

CONCLUSION

Initially marketed as a magic bullet for a myriad of human diseases, its clinical utility remains limited with conflicting results across multiple studies. Nevertheless, it remains an important physiological precursor in the synthesis of androgens and estrogens. While there is considerable evidence to suggest the role of DHEA in adrenal insufficiency and GSM, its role in menopausal females, elderly individuals, and other conditions such as sexual dysfunction, infertility, autoimmunity, and neurological and cardiovascular diseases remains to be fully elucidated. The studies done till date are limited by variations in diagnostic thresholds, DHEA dosing and timing of treatment, relatively small sample size, and shorter duration. Further large-scale, multicentric, robust randomized control trials to assess the effects of DHEA supplementation going forward will help gain a foothold in this untapped research area.

FOOTNOTES

Author contributions: Shukla R conceptualized the topic and formulated the search strategy; Jethwani P performed the search, curated the data, and wrote the preliminary draft; Rastogi A critically reviewed the manuscript and added figures and tables; all three authors approved the manuscript.

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