Review article

Dehydroepiandrosterone Sulfate and Arterial Hypertension

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Abstract

Dehydroepiandrosterone sulfate (DHEAS) is a steroid molecule whose function and mechanism of action in the human body are still inadequately researched. A potential protective function for the cardiovascular system can be explained by activation of nitric oxide production, impact on endothelial and mitochondrial function, and inhibition of proinflammatory cytokine production (IL-6 and TNF- α). Some research shows the beneficial effects of DHEA/DHEAS on many bodily functions, especially in the cardiovascular and the neurological systems. However, we need to be careful with interpretation of the results because of different criteria used for defining arterial hypertension, the race that was observed, and reproductive status of women, as these factors can change the conclusion. Due to a lack of evidence, DHEAS supplementation is still not recommended. We need multicentric prospective and randomized studies on DHEAS to examine its potential impact on blood pressure regulation and cardiovascular risk.

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Introduction

Dehydroepiandrosterone sulfate (DHEAS) is a steroid hormone created by adding a sulfate group to dehydroepiandrosterone (DHEA) in the zona reticularis of the suprarenal gland (90%) and the gonads (10%). DHEA is also synthesized in the central nervous system, where its concentration is 6–8 times higher than in the serum, which is why it is also called a neurosteroid hormone (1).

Depending on age, DHEAS can serve as a precursor in the production of other hormones (2). Accordingly, in the reproductive age, 40–75% of testosterone is synthesized from DHEAS. On the other hand, more than 90% of circulating estrone is created from DHEAS (3). DHEA

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concentration in the serum is 10 times higher than cortisol and it shows weak androgenic and estrogenic activity. On the other hand, DHEAS is a hormonally inert molecule with the greatest activity in the central nervous system; it is 100 times more concentrated in the serum than cortisol. This concentration makes it the steroid with the highest ratio in the serum (4). In addition, its levels significantly depend on gender and age, with the lowest levels found in childhood and the period before puberty, while in puberty males have DHEAS levels twice as high as females, with the maximum reached in their early 20s. In women, these levels are not dependent on the menstrual cycle. Total DHEAS concentration decreases by 2% annually and after the age of 70, it reaches pre-puberty levels. The half-life of DHEAS in the serum is around 10 hours. In comparison, DHEA has a 20 times shorter half-life than DHEAS (30 minutes) (5).

In recent research, DHEAS has been shown to have a positive impact on learning and memorizing due to allosteric modification of N-methyl-D-aspartate (NMDA) receptors. Likewise, DHEAS can exaggerate neuron excitation through negative allosteric modulation of gamma-aminobutyric acid (GABAA) receptors (6). By activating sigma-1 receptors and producing nerve growth factor (NGF) and brain-derived neurotrophic factor (BDNF), DHEAS serves a neuroprotective function (7–9).

In addition to effects on the central nervous system, DHEAS has other pleiotropic effects, including modulation of mitochondrial and endothelial function, as well as bone metabolism (10). One minute of stimulation of bovine aortic endothelial cells (100 nm for 5 min) with DHEA (abolished responses with nitro-L-arginine methyl ester (L-NAME) or phosphatidylinositol (PI) 3 – kinase inhibitor) increased nitric oxide production, stimulated endothelial cell growth, decreased the growth of smooth muscles in blood vessels and the levels of plasminogen activator inhibitor type 1 (PAI-1), and inhibited leukocyte adhesion (11–13). Likewise, DHEA can inhibit the production of proinflammatory cytokines such as interleukin-6 (IL-6) and tumor necrosis factor α (TNF-α) (11, 14). The release of NO is independent of intracellular calcium mobilization but depends on G protein tyrosine and mitogen-activated protein (MAP) kinases (15). This mechanism of action could be the key to the cardioprotective effect proposed for DHEA.

DHEA and DHEAS levels are often elevated in polycystic ovary syndrome (PCOS), congenital adrenal hyperplasia (CAH), Cushing's syndrome, and in the presence of hormonally active tumors (16).

History of DHEAS research and cardiovascular risk

In 1975, by examining DHEA and DHEAS concentrations by compartmentalization in urine and blood, Feher et al (17) suggested that a significant uptake of DHEA by adipose tissue occurs, causing lower sulfation into DHEAS and its faster metabolism in obese female patients. They also connected low DHEAS concentration with increased insulin resistance in three obese individuals. Later, in 1987, Rotter et al (18) examined the distribution of DHEAS levels in 178 individuals from 26 families and correlated low DHEAS levels with low testosterone levels. Barret-Connor et al (19) examined the connection between low DHEAS levels and 12-year mortality in 242 men aged 50 to 79. DHEAS levels below 3.8 μ mol/L showed a relative risk of 1.5 for death from any cause (without statistical significance), 3.3 ($P < 0.05$) for death from cardiovascular (CV) disease, and 3.2 ($P < 0.05$) for death from ischemic heart disease in males. There was still a lot to learn about DHEAS in the coming years, and Barret-Connor et al (20) expanded their cohort to 1,029 men and 942 women in California, USA, in 1995, linking low DHEAS levels with coronary ischemic disease in postmenopausal women, but without increased CV mortality.

The next significant research was conducted in 1997, when Barna et al (21) found a significant correlation between serum DHEAS concentration and blood pressure (including the dipping profile), from which they concluded that

lower DHEAS levels are associated with higher blood pressure. This research was conducted on 387 white subjects (86 normotensive and 301 hypertensive), suggesting a positive effect of DHEAS supplementation on CV risk.

Two years later, in 1999, Schunkert et al (22) made the opposite conclusion in their study conducted on 646 subjects, associating higher DHEAS levels with higher blood pressure and higher levels of aldosterone. The debate was resolved in 2004 with the discovery by Liu et al (15), who found that DHEAS increases the activity of nitric oxide synthase (eNOS) mediated by tyrosine and MAP kinases in both bovine aortic endothelial cells and human umbilical vein endothelial cells. Further research on DHEAS was rarely conducted until 2010, when the WISE study (Women's Ischemia Syndrome Evaluation), conducted on 270 postmenopausal women, showed that lower DHEAS levels are linked to higher CV mortality in postmenopausal women who underwent coronarography due to myocardial ischemia (23). Furthermore, in 2019, De Paiva Lemos et al (24) found a correlation between DHEAS and lower heart rate variability in old age, but this causality can hardly be confirmed since heart rate variability decreases physiologically with aging, much like DHEAS serum concentration. The other problem with this study was that the sample consisted of only 45 men, divided into three age groups. However, today we assume that lower heart rate variability is linked to a 32–45% higher risk of CV events (25).

Possible reasons why the aforementioned researchers came to different conclusions about DHEAS and its impact on blood pressure may lie in the choice of methods and patients. To date, only three studies have examined the correlation between DHEAS and blood pressure levels. Differences in the methodology used in these studies are shown in Table 1.

Table 1. Methodology of the most prominent studies about DHEAS and arterial hypertension

Authors and year	Correlation between DHEAS and AH	Correlation with nocturnal indices	AH criteria	Race (country)
Barna et al, 1997 (21)	Negative	Positive	> 130/85 mmHg	White (Hungary)
Schunkert et al, 1999 (22)	Positive	/	> 160/95 mmHg	White (Germany)
Jimenez et al, 2019 (26)	Nonexistent	/	> 130/80 mmHg	Latino (Puerto Rico)

AH = arterial hypertension

DHEAS supplementation

Due to the previously mentioned benefits for the CV system and the brain, scientists have been discussing DHEAS supplementation in postmenopausal women for many years. Yet, meta-analyses conducted by Boxer et al. (27) in 2010 and by Wang et al. (28) in 2020 did not show any clear benefits of DHEAS supplementation in postmenopausal women. Longer prospective cohort studies are needed to accurately demonstrate the benefits of this kind of supplementation in women.

Medication and DHEAS

Higher DHEAS serum levels were observed in hypertensive patients treated with beta-blockers and calcium channel blockers (16). On the other hand, lower DHEAS levels were observed in patients treated with ACE inhibitors (29).

Lifestyle changes and DHEAS

Despite the clear evidence of effects of a healthy diet and weight loss on blood pressure, the impact of lifestyle changes on DHEAS levels remains unknown. The exception is smoking, since nicotine can stimulate the production of corticotropin-releasing hormone (CRH) and vasopressin, which stimulate DHEAS synthesis (30). Likewise, smoking can decrease DHEAS clearance, as well as its binding to serum proteins, which also increases its serum concentration (31). Diet rich in pectin can likewise increase DHEAS levels in the serum, but excessive protein intake may reduce DHEA levels (32, 33). An increase of DHEA levels immediately after exercise was found in both genders, but DHEAS levels increased only in women (34). A very small number of studies have examined the impact of exercise on these hormones, with many methodological differences, which complicates their comparison.cardiovascular and renal disease in non-diabetic individuals with arterial hypertension remains a question to be answered.

Conclusion

Although there is clear evidence that DHEAS can stimulate NO production in blood vessels, the conclusions of relatively small and methodologically different studies about its impact on blood pressure are still contradictory. However, some studies have shown increased CV mortality in subjects with low DHEAS levels, but its supplementation is still not recommended. There is a need for larger prospective multicentric studies to be conducted in order to clarify the connection between DHEAS and arterial hypertension.

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