Review

DOI: 10.5582/bst.2021.01320

Effect of dehydroepiandrosterone on atherosclerosis in postmenopausal women

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SUMMARY In China, cardiovascular disease (CVD) has surpassed malignant tumours to become the disease with the highest mortality rate, and atherosclerosis (AS) is an important pathological cause of CVD. Dehydroepiandrosterone (DHEA) is the most abundant steroid hormone in circulating human blood and is a precursor of estrogen and androgen. DHEA is converted into a series of sex hormones in local peripheral tissues where its acts physiologically. DHEA also acts therapeutically, thereby avoiding the adverse systemic reactions to sex hormones. DHEA inhibits AS, thus inhibiting the development of CVD, and it improves the prognosis for CVD. The incidence of CVD in postmenopausal women is substantially higher than that in premenopausal women, and that incidence is believed to be related to a decrease in ovarian function. The current review analyzes the mechanisms of postmenopausal women's susceptibility to AS. They tend to have dyslipidemia, and their vascular smooth muscle cells (VSMCs) proliferate and migrate more. In addition, oxidative stress and the inflammatory response of endothelial cells (ECs) are more serious in postmenopausal women. This review also discusses how DHEA combats AS by countering these mechanisms, which include regulating the blood lipid status, protecting ECs (including coping with oxidative stress and inflammatory reactions of the vascular endothelium, inhibiting apoptosis of ECs, and inducing NO production) and inhibiting the proliferation and migration of VSMCs. As a result, DHEA has great value in preventing AS and inhibiting its progression in postmenopausal women.

Keywords dehydroepiandrosterone, atherosclerosis, postmenopause, vascular smooth muscle cells, endothelial cells, blood lipid

1. Introduction

Cardiovascular disease (CVD) is a common disease that jeopardizes the health of postmenopausal women (*1*) and atherosclerosis (AS) is the most critical pathological cause of CVD (*2*). Premenopausal women rarely suffer from CVD. However, the incidence of CVD in postmenopausal women is 2-6 times higher than that in premenopausal women of the same age group (*3*), due to its close relationship to a postmenopausal estrogen deficiency (*4*) (Figure 1). A study (*5*) involving 879 women suggested that menopause was significantly associated with the risk of developing carotid plaques. Females with an earlier onset of menopause (< 45 years) had a significantly higher atherosclerotic plaque volume than those with an intermediate (45-52 years) or later onset of menopause (> 52 years), irrespective of other cardiovascular risk factors (*6*). The mean carotid intima-media thickness (CIMT) of the common carotid artery in postmenopausal women was significantly thicker than that in premenopausal women, with a mean difference of 0.068 mm (*7*). A recent prospective cohort study (*8*) also found that an elevated or persistently high level of Aβ1- 40, an aging peptide, is related to the rate of progression of subclinical AS in postmenopausal women and negatively correlated with levels of DHEA-S. An increasing number of women are prescribed hormone replacement therapy (HRT) after menopause or ovarian resection to prevent and treat CVD, osteoporosis, Alzheimer's disease, and other related long-term postmenopausal complications (*9-12*).

Dehydroepiandrosterone (DHEA) is the precursor of estrogen and androgen and is thought to prevent the development of AS (*13*). Dehydroepiandrosterone

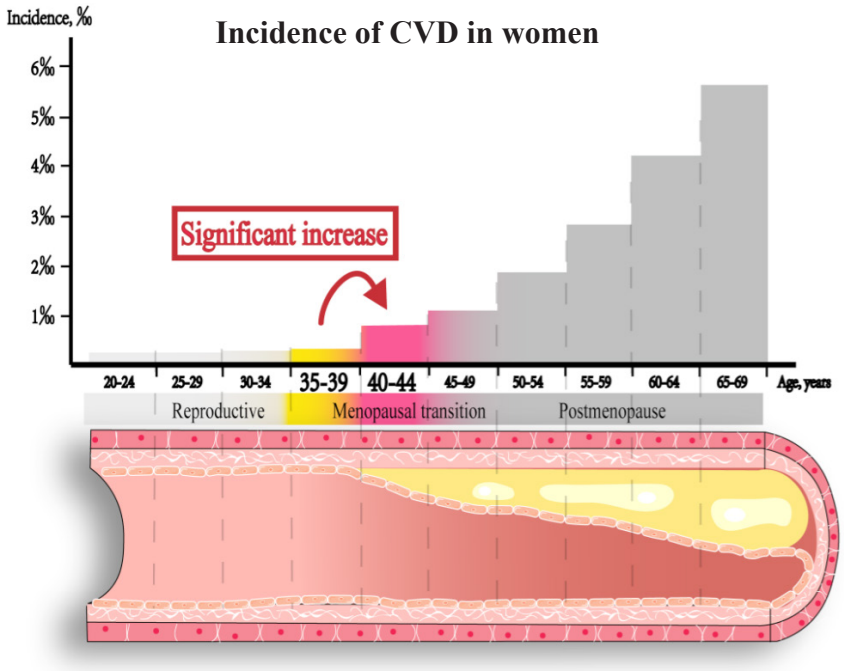

Figure 1. Incidence of CVD and vascular status in women. The incidence of CVD in women was stable at around 0.25‰, and it increased significantly after the age of 40. The intima-media thickness of blood vessels in women also increased, with more lipid deposition.

sulfate (DHEA-S) is the metabolite of DHEA, and the level of DHEA-S is significantly inversely correlated with the incidence of CVD (*14-17*). For postmenopausal women with coronary risk factors, a lower DHEA-S level means a higher mortality due to CVD (*18*). The new immunosenescence paradigm proposed in recent years offers an explanation. Senescence leads to the loss of DHEA, which causes semi-activated macrophages to be immunosuppressed and unable to differentiate, while releasing pro-inflammatory cytokines in an unregulated manner. These dysfunctional cells accumulate in vascular tissue and lead to the development of AS (*19*). That said, DHEA also has positive effects on the brain, bones, emotions, and sexual function of postmenopausal women, so its clinical use warrants consideration.

2. Metabolism and pathway of DHEA

As early as 1934, DHEA was successfully separated from urine. In 1944, Munson discovered the sulfated form of DHEA (*20*). DHEA, also known as 3β-hydroxyandrost-5-en-17-one, is the most abundant steroid circulating in human blood and is synthesized from cholesterol.

2.1. Generation of DHEA

The production of DHEA in the adrenal cortex and ovaries is regulated by adrenocorticotropic hormone and gonadotropin, respectively. DHEA is mainly produced in the adrenal cortex, only 10% of DHEA is produced in the gonads, and the brain also produces a small amount of DHEA (*21*). Approximately 6-8 mg of DHEA are produced per day in humans (*22*). In the blood, DHEA is mainly bound to albumin, a small amount will also bind to sex hormone-binding globulin (SHBG), and the remaining amount is free.

The level of DHEA changes during aging. The fetal adrenal gland produces a large amount of DHEA, but the level decreases rapidly after birth. The level of DHEA increases rapidly in the first two years of puberty, reaching a peak at 20-30 years of age, and then decreases at a rate of 2 to 5% annually. In individuals ages 70-80 years, the level of DHEA in the blood is only 10 to 20% of the peak level (*23*). The downstream hormones of the HPA axis have inhibitory feedback action on the upstream hormones, but DHEA does not participate in negative feedback regulation of the HPA axis. Thus, when the serum DHEA level is low, the body is unable to increase output through an endogenous feedback mechanism. Therefore, the body is unable to compensate for the deficiency in DHEA levels alone.

2.2. Conversion of DHEA

In the adrenal gland, endogenous DHEA is translated into DHEA-S by sulfation at the C3β position. In addition, oral DHEA is converted into DHEA-S *via* the first pass effect of the liver and intestine. As mentioned above, DHEA-S is a circulating reservoir of DHEA. Circulating DHEA is transferred to related peripheral tissues (*e.g.*, the ovaries, prostate, bone, adipose tissue, and brain) and then converted into testosterone, androstenedione, estrone, dihydrotestosterone (DHT), and estradiol (E2).

DHEA has biological action locally and indirectly.

It is known to be a multi-directional "hormone buffer" and to supplement hormones in the body, which explains why it has been used to treat menopause-related diseases. At the same time, since only a small amount of DHEA is in free circulation and DHEA is only converted into estrogen in the peripheral tissues, systemic estrogen-like adverse effects, such as cholelithiasis (*24*) and venous thromboembolic and ischemic stroke events (*25*), can be avoided (*26*). In addition, when the level of DHEA in humans reaches 7 μg/L, the saturation of invertase occurs during the conversion of DHEA into active sex hormones, helping avoid a state of excess sex hormone levels in women.

2.3. Pathway of DHEA

DHEA and its oxidative metabolites have been found to activate some nuclear receptors, like the constitutive androgen receptor (AR), estrogen receptor (ER) alpha and beta, pregnane X receptor, peroxisome proliferator activated receptor (PPAR), and G protein-coupled ER (GPER1) (*27,28*). Since DHEA can be converted into androgen/estrogen, researchers have not clearly determined whether AR/ER are directly activated by DHEA or indirectly by the converted androgen/estrogen. However, the low affinity of ER for DHEA makes the latter a poor agonist of ER (*27*). In addition, the effects of DHEA on the proliferation and apoptosis of endothelial cells (ECs) and vascular smooth muscle cells (VSMCs) are not associated with ER and AR (*29,30*). DHEA and its analogues are not converted to estrogen or androgen but nonetheless have beneficial action on CVD, suggesting that DHEA interacts with its own specific receptor.

3. Pathogenesis of AS

Many theories on the mechanism of AS have been proposed from different perspectives. In recent years, most scholars have supported the "endothelial injury response" theory (*31*), which posits that endothelial dysfunction is an initial step in the pathogenesis of AS. The major risk factor for this disease is damage to the arterial intima, and the formation of atherosclerotic lesions results from the inflammatory-fibrotic proliferative response of arteries to intimal injury (Figure 2). AS is commonly regarded as a chronic inflammatory disease of the arterial wall caused by an imbalance in lipid metabolism and changes in inflammatory responses, whereby the body is unable to prevent the recruitment of inflammatory cells alone. However, a recent hypothesis suggests that AS is not just an inflammatory reaction of the blood vessel wall. Neither inflammatory cells nor necrotic cells are removed, and thus effector cell proliferation and tissue regeneration are eventually induced (*32,33*).

Blood vessels begin to change in the early stages of

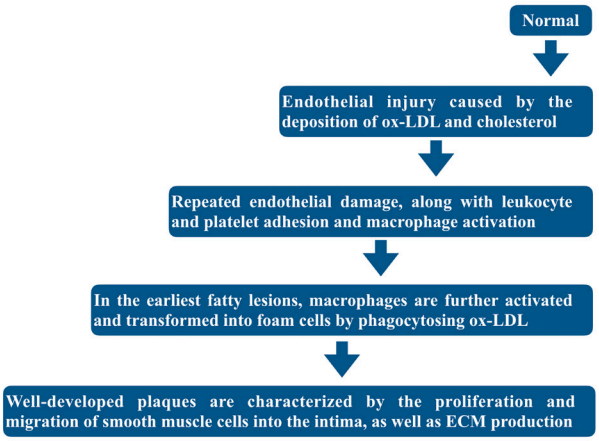

Figure 2. Pathogenesis of AS.

menopause. Endogenous estrogen and ERs decrease in postmenopausal women (*34,35*), resulting in the loss of inhibition of AS by estrogen, thus making them more vulnerable to AS. The mechanism may be an increase in the serum cholesterol level and high-density lipoprotein (HDL) particle size as well as interference with VSMC proliferation as a result of the decrease in endogenous estrogen and ERs (*36*).

4. The effects of DHEA on AS in postmenopausal women

4.1. DHEA alleviates dyslipidemia in postmenopausal women

Several early cross-sectional and prospective studies have revealed that the lipoprotein profile tends to worsen in postmenopausal women: plasma triglyceride (TG), total cholesterol (TC) low-density lipoprotein cholesterol (LDL-C), and lipoprotein levels increase and HDL cholesterol (HDL-C) levels decrease (*37,38*). In addition, studies (*39,40*) have indicated that age has more adverse effects on TC, LDL-C, TG, and non-HDL-C in postmenopausal women than BMI or smoking. This adverse change seems inevitable for postmenopausal women. However, dyslipidemia, which is mainly elevated LDL-C, is the most important factor for AS. Therefore, if AS in postmenopausal women is to be treated, then alleviating dyslipidemia is a very important aspect.

Substantial differences in the results of studies that have examined the effect of DHEA on blood lipid levels have been noted. Elevated plasma DHEA levels are reported to be correlated with HDL-C levels (*41*) but inversely correlated with LDL-C (*42*) and TC (*43,44*) levels. The correlation between plasma DHEA and TG levels was the most consistent. In a study by Jankowski *et al.*, treatment with DHEA resulted in a 17% reduction in serum TG levels (*48*). Lasco A *et al.* (*42*) reported that the serum TG levels of 20 postmenopausal women

decreased by about 20% after receiving DHEA (25 mg/d) for 12 months. A similar finding was noted in another study (*45*). However, one study (*46*) found that administration of DHEA does not change blood lipid parameters, which is consistent with the results of a previous study by the current authors (*47*). Use of lipid-lowering drugs may be a potential source of the inconsistency in the response of TG levels to DHEA (*48*). Therefore, whether DHEA can change blood lipid parameters or not needs to be studied more rigorously.

In addition to affecting blood lipid levels, DHEA can also directly inhibit lipid deposition (*49*). Fujioka *et al.* (*50*) found that DHEA can reduce the proliferation of adipocytes, which may be mediated by AR *via* an intracrine mechanism. DHEA also can promote lipid mobilization in adipose tissue by increasing the expression and activity of adipose triglyceride lipase (ATGL) and hormone-sensitive lipase (HSL) (*51*).

At present, there are conflicting results on improvement of blood lipid levels by DHEA. However, blood lipids are an important factor in the development and progression of AS, so the effect of DHEA on blood lipids needs to be studied further. Moreover, most of these studies involve normal people, and research needs to pay more attention to postmenopausal women.

4.2. DHEA corrects endothelial dysfunction in postmenopausal women

The loss of estradiol during postmenopausal may lead to a decline in endothelial function. For example, a decline in estradiol may alter the redox balance, thereby increasing oxidative stress and impairing endothelial function (*52*).

Endothelial dysfunction is involved in the pathogenesis of AS and CVD (*53*). One of the strategies for treating AS is to correct endothelial dysfunction (*54*). DHEA does not improve endothelial function through AR- or ER-mediated mechanisms (*55,56*). The effects of DHEA on ECs are shown in Figure 3.

4.2.1. DHEA inhibits EC oxidation

A study (*57*) has suggested that menopause is a risk factor for oxidative stress (OS). In postmenopausal women, not only progressive loss of estrogen and its protective effects (*58*), but also a further reduction in tocopherol and retinol levels as well as total antioxidant activity lead to OS (*59*). In a study by Taleb-Belkadi *et al.*, high levels of TBARS and carbonyl production and low levels of enzymatic defense found in

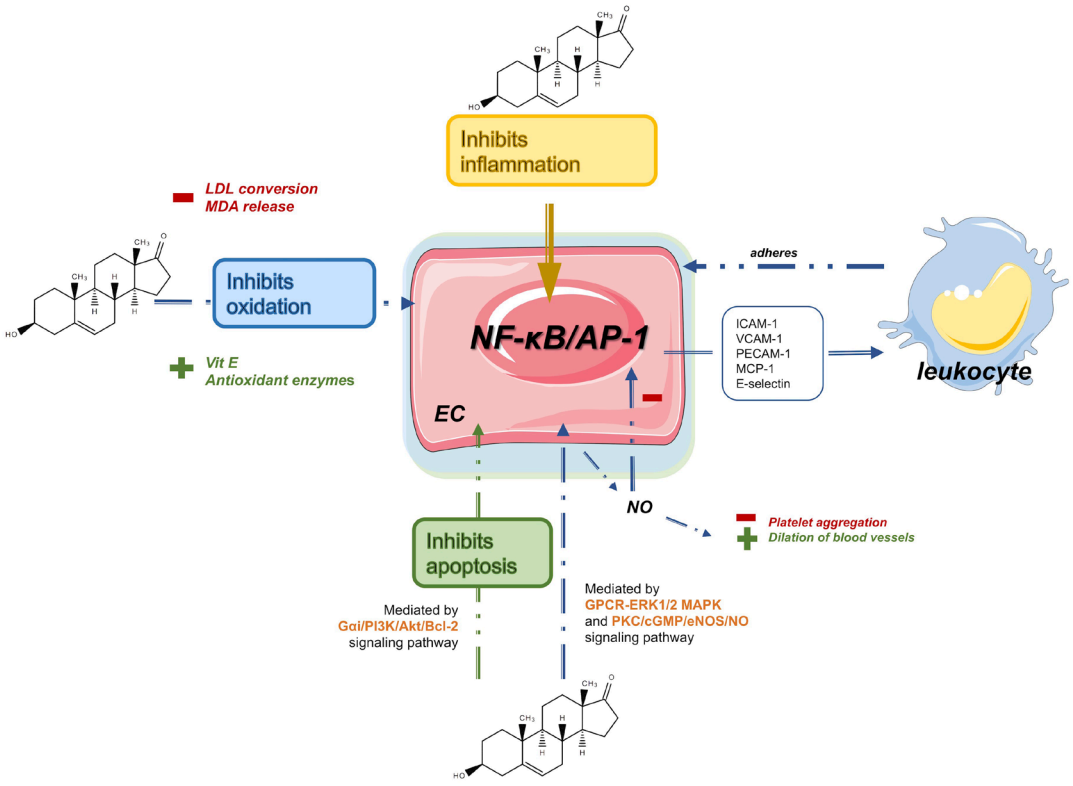

Figure 3. The effects of DHEA on ECs. First, DHEA inhibits EC oxidation by preventing the conversion of LDL to ox-LDL and the release of MDA, as well as by protecting endogenous vitamin E and the level and activity of antioxidant enzymes. Moreover, DHEA inhibits the production of MCP-1, ROS, ICAM-1, VCAM-1, PECAM-1, and E-selectin by ECs to prevent leukocytes from adhering to ECs, which involves NF-kB and AP-1. In addition, DHEA promotes NO production through the activation of eNOS *via* a GPCR-ERK1/2 MAPK cascade and the PKC/cGMP/eNOS/NO signalling pathway. NO subsequently inhibits platelet aggregation and the invasion and adhesion of leukocytes and it promotes the dilation of blood vessels. Moreover, DHEA protects ECs from apoptosis by activating the DHEAR/Gαi/PI3K/Akt/Bcl-2 signalling pathway.

postmenopausal women indicated that the women were exposed to OS. OS, and especially the oxidation of LDL in the arterial wall, can lead to worse AS through the stages of the menopausal transition in healthy women (*60*). In addition, the production of the superoxide anion O^{2-} and an increase in the levels of peroxynitrite are also characteristics of atherosclerotic lesions (*61,62*).

According to a previous study (*63*), the synthesis of reactive oxygen species (ROS) promotes AS by increasing superoxide production and suppressing EC function. The production of large amounts of ROS overwhelms the antioxidant defenses in cells, causing neutrophil activation, protein modification, lipid peroxidation, and DNA damage, which are key factors that promote the development of AS and CVD (*64,65*) (Figure 3).

DHEA effectively inhibits the oxidation of low-density lipoprotein (LDL) to oxidized low-density lipoprotein (ox-LDL) (*47,66*), it inhibits ox-LDL-induced ROS production (*67*), it reduces superoxide production, it ameliorates endothelial dysfunction, and it prevents the development of AS.

In some experiments, DHEA increased the antioxidant capacity of LDL by protecting endogenous vitamin E (*68*) and by significantly reducing the chemotactic activity of monocytes (*69*), directly removing the free radicals produced by the lipoprotein oxidation process (*70*), and counteracting the cellular damage caused by LDL and ox-LDL, all of which enable DHEA to function as an antioxidant (*66,68*). In addition, DHEA restores the levels and activities of glutathione peroxidase, SOD, and catalase (*71,72*). Moreover, DHEA significantly inhibits the secretion of malondialdehyde (MDA) in ECs (*47*). As a cytotoxic end product of lipid peroxidation, MDA causes cross-linking polymerization of macromolecules such as proteins and nucleic acids and it affects the respiratory function of the mitochondria *in vitro*. At the same time, DHEA also increases the antioxidant capacity of certain subcellular structures (*73*).

In summary, DHEA has antioxidant action by inhibiting the production of ox-LDL and MDA, removing free radicals, reducing monocyte adhesion, and protecting antioxidant enzymes.

4.2.2. DHEA inhibits EC inflammation

The level of inflammation is higher in postmenopausal women, which is evident in higher levels of TNF-α, IL-1 α, and CRP (*74,75*). Novella *et al.* suggested that this may be due to the change in estrogen-mediated regulation of female inflammatory biomarkers (*76*) which were identified as independent risk factors for CVD in postmenopausal women (*77*). DHEA can reduce inflammation, and especially in ECs, and ECs are closely related to AS.

DHEA alleviates inflammation of ECs independent of the ERα or ERβ pathway. *In vitro*, DHEA significantly inhibits monocyte chemoattractant protein-1 (MCP-1) secretion, ROS production, and expression of intracellular adhesion molecule-1 (ICAM-1), vascular cell adhesion molecule 1 (VCAM-1), platelet and EC adhesion molecule 1 (PECAM-1), and E-selectin (*78*). Moreover, DHEA also reduces the expression of adhesion molecule receptors in the U937 monocyte-like cell line, which suppresses the adhesion of monocytes to injured ECs (*47*). In one study (*79*), DHEA significantly reduced the LPS-induced transcription of nuclear factor kappa B (NF-κB). Moreover, DHEA impairs monocyte adhesion by suppressing the activity of NF-κB, thereby inhibiting the development of AS (*47*). A recent study (*80*) also indicated that DHEA restrains neutrophil recruitment and adhesion to ECs by reversing inflammation-induced down-regulation of developmental endothelial locus 1 (a secreted homeostasis factor) expression.

4.2.3. DHEA protects ECs by inducing NO production

The ability of vascular ECs to resist AS and antithrombotic factors largely relies on the production and release of active substances such as NO. NO blocks the expression of pro-inflammatory molecules as well as adhesion molecules in ECs. NO also inhibits the infiltration and adhesion of leukocytes (*81*).

Healthy endothelium, which normally produces NO, avoids the development and complications of AS (*82*). Nevertheless, the production of estrogen is reduced in postmenopausal women, and thus the activity of NO synthase decreases (*83,84*), which leads to a decrease in NO synthesis in ECs. A study found that a lack of NO and damaged endothelial progenitor cells resulted in vasodilation dysfunction in postmenopausal women, who are more prone to CVD, and especially AS.

DHEA activates eNOS through genomic and non-genomic mechanisms, and DHEA directly regulates human vascular walls by controlling the synthesis and stability of the eNOS protein in ECs (*85*). DHEA also effectively increases serum NO levels by activating PKC/cGMP/eNOS/NO pathways to prevent platelet aggregation, improve EC function, and alleviate early pathological changes associated with AS (*44,47,86*).

4.2.4. DHEA promotes EC proliferation and inhibits EC apoptosis

During aging, EC apoptosis increases, which affects the development of AS (*87,88*). The production of TNF-α induced by LPS and testosterone promotes apoptosis of ECs, whereas DHEA has the opposite effect on ECs. DHEA increases EC proliferation *in vitro* (*44*) and protects ECs from apoptosis (*89*). This anti-apoptotic effect of DHEA does not rely on ER or conversion into E2, but it is associated with the GTP-binding protein (Gαi) and the downstream phosphatidylinositol 3-kinase

(PI3K)/Akt signalling cascade (*90*).

4.3. DHEA inhibits the proliferation and migration of VSMCs

Lee *et al.* (*91*) noted marked proliferation of aortic VSMCs in ovariectomized mice. During aging, the level of sirtuin 1, a novel modulator of neointima formation caused by arterial injury, decreased (*92*). The reduction in this protein indirectly promotes the proliferation and migration of VSMCs (*93*). VSMC proliferation and migration of surrounding extracellular matrix (ECM) are the main reasons for thickening of the intimal wall, which will lead to AS (*94*).

DHEA is involved in relaxing VSMCs and inhibiting the proliferation and migration of VSMCs (*30,95*). DHEA does not have a significant effect on the phenotypic transition of VSMCs but rather reduces OS and inflammation in VSMCs by directly interrupting the ROS-dependent ERK1/2 signalling and p38 mitogen-activated protein kinase (MAPK)/NF-κB signalling pathways, thereby inhibiting the proliferation of VSMCs (*95*). Regardless of whether VSMCs undergo a phenotypic shift, DHEA can have a beneficial effect on these cells. DHEA-specific receptors are present in human VSMCs, and DHEA regulates the proliferation and apoptosis of VSMCs *via* a mechanism independent of ER and AR (*30,44*).

All of the aforementioned effects of DHEA on AS are shown in Figures 4 and 5 and Table 1.

5. Use of DHEA in the treatment of AS

As early as 1996, one study (*102*) proposed that DHEA is the source of youth, but the clinical use of DHEA is still hotly debated.

Several of the aforementioned studies have indicated that DHEA has anti-atherosclerotic action in animal models. DHEA improves cardiovascular risk-related parameters (*42*) and can be used as a drug for primary prevention of CVD (*103*). However, some studies have indicated that DHEA has no effect on CVD risk (*104-106*) and no effect on endothelial function (*92,107-109*). A meta-analysis (*110*) by Wu *et al.* noted no correlation between the level of DHEA-S and AS. However, other meta-analyses (*15,111*) noted that the lower the level of DHEA, the worse the prognosis for patients with CVD.

Qin *et al.* (*38*) suggested that DHEA had no effect on the blood lipid profile, and especially that of healthy postmenopausal women (*112*). This finding is consistent with the results of a previous study by the current authors (*47*). Nevertheless, there may be health benefits for women with adrenal insufficiency (*113,114*).

There are many factors responsible for the differing results of those studies. At present, many studies are based on rats and other rodents as models, but they are not the best model because they have almost no endogenous DHEA (*115*). In addition, the dosage of DHEA in those experiments is usually too high and it differs (*112,113*). Moreover, DHEA is rapidly metabolized, leading to somewhat differing results of many studies (*43*). A recent meta-analysis (*116*) suggested that publication bias and small flawed studies may also explain the discrepancy.

Therefore, whether postmenopausal women should

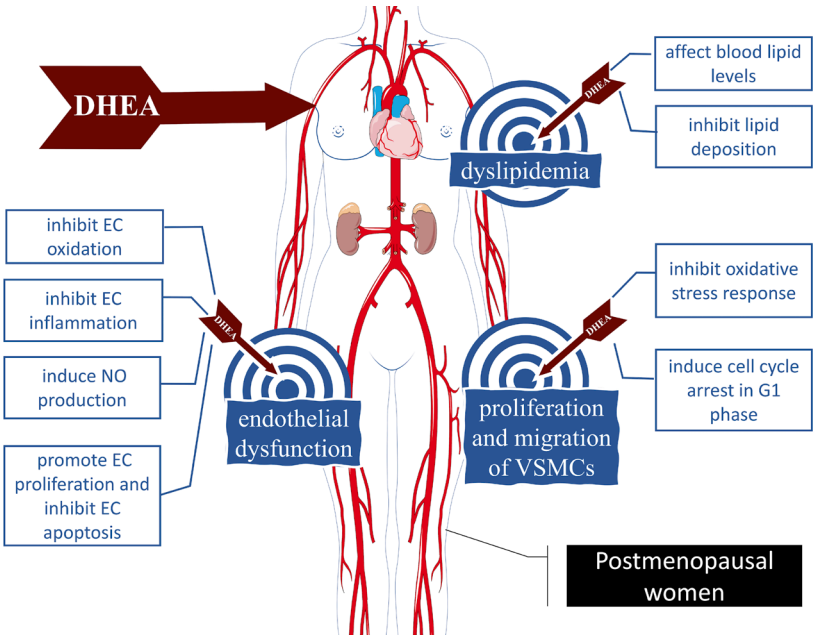

Figure 4. DHEA has specific action against aspects of AS in postmenopausal women. Postmenopausal women have dyslipidemia, abnormal proliferation and migration of VSMCs, and endothelial dysfunction. DHEA can play a role in alleviating these adverse aspects. First, it can improve dyslipidemia by affecting blood lipid levels and inhibiting lipid deposition. Second, DHEA can inhibit the oxidative stress response and induce cell cycle arrest in the G1 phase. In addition, DHEA can inhibit the oxidation and inflammation of ECs, induce NO protection, promote the proliferation of ECs, and inhibit the apoptosis of ECs.

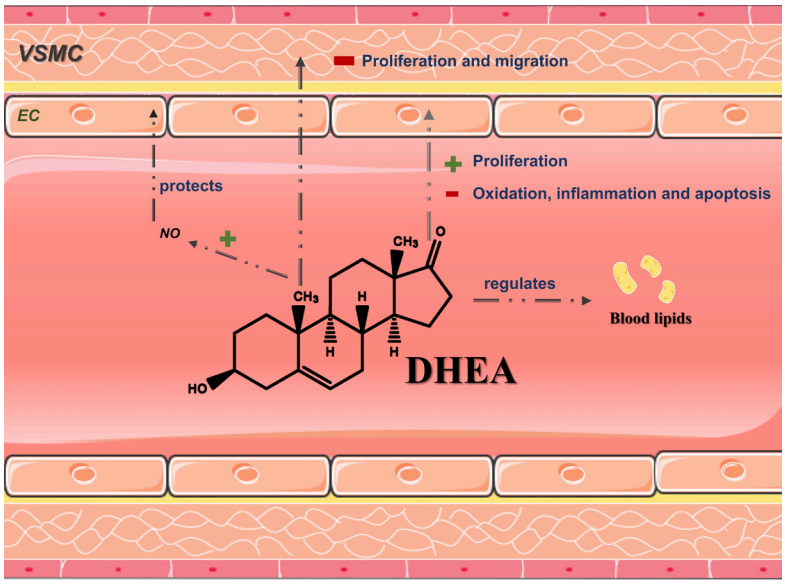

Figure 5. The effects of DHEA on atherosclerosis. First, DHEA affects the development and progression of AS by regulating blood lipid parameters, but substantial differences in results have been noted. Moreover, DHEA preserves EC function by inhibiting the oxidation and inflammation of ECs through NO production and promoting EC proliferation and inhibiting EC apoptosis. In addition, DHEA inhibits the progression of AS by inhibiting the proliferation and migration of VSMCs.

Table 1. The effects of DHEA on AS

Pathophysiological role of DHEA	Specific changes/mechanisms
Effects on blood lipids	A subject of debate
Effects on endothelial function	
Inhibition of EC oxidation	Prevention of LDL conversion to ox-LDL (*47,66,67*) Protection of endogenous vitamin E (*68*) Inhibition of leukocyte adhesion to ECs (*69*) Restoring the level and activity of antioxidant enzymes (*70,72*) Inhibition of MDA release by ECs (*47,70*)
Inhibition of EC inflammation	Inhibition of leukocyte adhesion to ECs: inhibiting the production of MCP-1, ROS, ICAM-1, VCAM-1, PECAM-1, and E-selectin by ECs; decreasing the expression of CCR2, LFA-1, and VLA-4 in the U937 monocyte-like cell line (*47*) Inhibition of IL-8, ICAM-1 and VCAM-1 production induced by TNF-α by blocking the LPS/TNF-α/PPARα/NF-κB signalling pathway (*47,96*) Inhibiting EC adhesion and oxidative stress by blocking AP-1 activity (*67,97,98*)
Protecting ECs through NO production	Inhibitory effect of NO on platelet aggregation and dilation of blood vessels (*86*) Inhibitory effect of NO on the expression of NF-κB, ICAM-1 and VCAM-1; prevention of the invasion and adhesion of leukocytes (*99*) Activation of eNOS *via* a GPCR-ERK1/2 MAPK cascade (*85*) Increasing NO production through the PKC/cGMP/eNOS/NO signalling pathway (*44,86*)
Promotion of EC proliferation and inhibition of EC apoptosis	EC proliferation (*85*) Protecting ECs from apoptosis by activating the DHEAR/Gαi/PI3K/Akt/Bcl-2 signalling pathway (*89*)
Inhibition of VSMC proliferation and migration	Promoting relaxation and inhibiting the proliferation of VSMCs by directly interrupting ROS-dependent ERK1/2 signalling and the p38 MAPK/NF-κB signalling pathway (*30,95*) Inhibiting the phenotypic transition and proliferation of VSMCs by blocking platelet-derived growth factor receptor-β (PDGFR-β) and regulating glutathione/glutathione (GSH/GRX) and low molecular weight protein tyrosine phosphatase (LMW-PTP) (*100*) Causing apoptosis: inducing cell cycle arrest in the G1 phase; upregulating the expression of the cyclin-dependent kinase (CDK) inhibitor $p16^{INK4a}$, activating caspase-3, and inducing PPARα expression in VSMCs (*101*)

take DHEA to treat or prevent forms of CVD such as AS is unclear. In addition, there is no clear standard for its indications and dosage (*117*).

DHEA causes adverse reactions such as hirsutism and acne. DHEA is believed to increase the risk of breast cancer in postmenopausal women (*118,119*). That said, experiments have indicated that the use of DHEA for 52 weeks has no effect on the endometrium (*94*). Evaluating the appropriate dose for patients is difficult because of the possibility of those adverse reactions, and indications for DHEA need to be carefully evaluated (*120*). Timing of use is also important. Treatment should start during menopausal transition, that is, within six years after menopause (*93,121*).

At present, studies on the clinical use of DHEA are still lacking. Therefore, use of DHEA should be carefully considered, the patient's eligibility should be determined, the patient's adrenal function should be considered, and whether the patient can tolerate the drug's adverse effects should be considered.

6. Conclusion

As a hormone precursor, DHEA is an endogenous steroid hormone and important source of estrogen and androgen in postmenopausal women. In addition, DHEA itself has a variety of biological actions that are independent of ER/AR and its conversion into estrogen/androgen, and it functions in almost all systems of the body (*43*). The current review has analyzed the mechanisms of postmenopausal women's susceptibility to AS. It has also discussed how DHEA plays a role in combating AS by countering these mechanisms, which include regulating the blood lipid status, protecting ECs (including coping with OS and inflammatory reactions of the vascular endothelium, inhibiting apoptosis of ECs, and inducing NO production) and inhibiting the proliferation and migration of VSMCs. In addition to its activity against AS, DHEA might have other protective effects on the cardiovascular system, such as preventing and reversing pulmonary hypertension (*55*) and reducing insulin resistance (*122*). However, further studies need to examine the mechanism and long-term effects of DHEA and additional clinical trials need to examine DHEA supplements. DHEA may serve as a better treatment for postmenopausal women and the entire population in the near future.

Acknowledgements

The authors sincerely appreciate the assistance of Peng Li and Suna Tian in preparing the figures.

Funding: This work was supported by grants from the 2018 Program to Guide Medicine ("Yixue Yindao") of the Shanghai Municipal Science and Technology Commission (grant no.18401902200 to L Wang), a project under the Scientific and Technological Innovation Action Plan of the Shanghai Natural Science Fund (grant no. 20ZR1409100 to L Wang), a project of the Chinese Association of Integration of Traditional and Western Medicine special foundation for Obstetrics and Gynecology-PuZheng Pharmaceutical Foundation (grant no. FCK-PZ-08 to L Wang), a project for hospital management of the Shanghai Hospital Association (grant no. X2021046 to L Wang), and a clinical trial project (L Wang) of the Special Foundation for Healthcare Research of the Shanghai Municipal Health Commission.

Conflict of Interest: The authors have no conflicts of interest to disclose.

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Received August 2, 2021; Revised October 28, 2021; Accepted November 5, 2021.

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Released online in J-STAGE as advance publication November 10, 2021.