Different Roles of Sex Steroid Hormones in the Pathogenesis of Vascular Dysfunction and the Development of Cardiovascular Disease in Men and Women

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ABSTRACT

In this review an overview of current literature on the topic of the relation between sex steroid hormones and cardiovascular diseases (CVDs) is presented. The influence of the mentioned hormones on the three levels has been analyzed: their interaction with the blood vessel receptors, their modulation of the vascular function, and finally their role in the pathogenesis of CVDs. This review is focused not only on already known facts of the protective role of estrogens and the inceptive role of testosterone, but attempts to give examples of their opposite effects on vascular function and development of CVDs.

Key words: estrogens, progesterone, sex steroid hormones, testosterone, androgens, hypertension, and cardiovascular diseases

Introduction

Cardiovascular diseases (CVDs), such as myocardial infarction and cerebral insult, are the major cause of death in the developed societies with approximately 50% of all mortality. There are two major groups of risk factors involved in the pathogenesis of CVDs: constitutional (e.g. age, gender, heredity) and acquired (e.g. hyperlipidemia, hypertension, smoking, diabetes). It should be mentioned that obesity by itself plays its role as well as an independent risk factor for coronary artery disease.

Epidemiological studies have shown the same morbidity and mortality of CVDs between men and postmenopausal women of the same age, but also great differences in these two parameters between men and premenopausal woman of the same age. These differences could be attributed to the specific effects of sex steroid hormones on vascular function. Estrogens and progesterone are commonly considered as protectors against CVDs, while the role of androgens and testosterone in etiopathogenesis of CVDs has not been fully established yet, although some studies suggest that androgens have protective role in the development of cardiovascular diseases.

Molecular Actions of Sex Hormones on the Blood Vessel Receptors

Receptors for estrogens, progesterone, and testosterone are expressed in varying numbers in both the endothelium and vascular smooth muscle cells (VSMCs) of multiple vascular systems. There are two subtypes of estrogens receptor (ER) in human body; ER-α and ER-β. The protective effects of estrogens in a response to a vascular injury are mediated by ER-α, although the ER-β is the receptor which is more widely expressed in human VSMCs, especially in female gender. There are two types of progesterone receptor as well; A and B. Progesterone receptor type B mediates the regulation of gene transcription and VSM cell proliferation.

Two general signaling pathways are activated by sex hormones. The common one is genomic pathway, which involves binding of a sex hormone to an intracellular receptor. After binding between a sex hormone and its specific receptor, two hormone/receptor complexes are bind together and undergo phosphorylation, which enables them to act as a transcription factor. This means that the complex binds to specific sites on the regulatory region of
a target gene. The final result is an increase or decrease in the synthesis of the protein coded by that gene.

The second, much faster pathway, is non-genomic sex hormone signal transduction pathway, where the binding between sex hormones and the receptors occurs on the surface of the cells, and could directly and indirectly affects membrane ion channels, induce the elevation of intracellular calcium as a second messenger, or is involving the interaction of sex steroids with the other signal transduction pathways such as the tyrosine kinase and mitogen – activating protein (MAP) kinase pathways. Li et al. reported that the ER co-activator steroid receptor co-activator 3 (SRC3) is also a co-activator for the major VSM transcription factor myocardin, which is required for VSM differentiation to the non-proliferative, contractile state. The SRC3-myocardin interaction identifies a site of convergence for nuclear hormone receptor-mediated and VSM-specific gene regulation and suggests a possible mechanism for the vascular protective effects of estrogens on vascular injury. Nakamura et al. examined the relative levels of prostaglandin PR isoform (PR-A and PR-B) expression in VSM. PR-B is cell-specific and transcriptionally more active than PR-A. The PR-A isoform has been demonstrated to repress the transcriptional activities of other steroid hormone receptors. The relative level of PR-A expression was more abundant in VSMCs of the female aorta than in those of the male aorta, but the relative level of PR-B expression was not different between male and female aortas. This suggests that PR-A isoform may have protective role against development of CVDs in women.

### Significant Changes in Vascular Function Due to Sex Hormones

A fine balance between vasoconstrictor signals, such as catecholamines, endothelium 1 (ET-1), tromboxane A2 (TXA2), prostaglandin F2α, (PGF2α), and angiotensin II; and vasodilator mediators, primarily NO, endothelium-derived hyperpolarizing factors (EDHF; known as metabolite of arachidonic acid – epoxyeicosatrienoic acids, EET), and PGI2 determines vascular tone and subsequently blood flow to organs and tissue perfusion. Some prostaglandins, such as PGE2, can function as both, vasoconstrictor and vasodilator, depending on the type of receptor they bound at, i.e. EP1 or EP3 prostaglandin receptors. Nitric oxide is the principal mediator of endothelium-dependent vasodilatation. Signals such as ATP, bradykinin, histamine, adenosine, acetylcholine, cytokines, vessel wall distension and shear stress (caused by blood flow and increased by turbulent flow) stimulate the production of nitric oxide. EDHF are factors that activate Ca2+-activated K+ channels (BKCa) and cause hyperpolarization and relaxation of the smooth muscle independently of NO-cGMP and the PGI2-cAMP pathways.

Endothelium-dependent relaxation is greater in females compared to males, which may be related to differences in the endothelium-dependent hyperpolarization of VSM in response to EDHF. In estrogen-deficient states relaxation in response to EDHF is attenuated. Interestingly, testosterone may also release endothelium-derived substances that cause hyperpolarization of the cells partially by a mechanism that involves voltage-dependent and BKCa channels, and partially, by endothelium-independent way that may involve ATP-sensitive K+ channels. One could speculate that the sensitivity to EDHF could be changed, or that some other pathways could be activated when estrogen levels are decreased, as in post-menopausal period of woman’s life, leading to impaired vascular function and increased risks for CVDs.

Changes in vascular function are crucial pathogenic factors in many complex multifactor diseases, such as hypercholesterolemia, ischemia-reperfusion injury, diabetes and hypertension. In these conditions, reactive oxygen species (ROS) are known to play an important role as well. However, the exact mechanism by which oxidative stress exerts its effects is not yet fully elucidated. There probably exists a role for oxidant signaling in physiological (sensing of pO2 changes) and pathophysiological (vascular proliferate processes, attenuation of vasodilator mechanisms) responses. Observations suggest that super-oxide anions can affect physiological vascular reactivity or impair blood flow auto-regulation.

Taking into account the differences in cardiovascular morbidity between men and women, as well as the fact that vascular dysfunction is essential in the pathogenesis of diseases like diabetes and hypertension, it is plausible that steroid sex hormones may have a direct influence on vascular reactivity and function. Gender differences in endothelium, meaning dependent vascular responses to various vasodilator stimuli are widely demonstrated in animal models and in human studies. For example, experiments on aortic rings confirmed that there were sex-specific differences in aortic sensitivity to vasoactive stimuli in consomic rat strains on high-salt diet. In addition, a study by Subakir et al showed that arteries from women exhibit greater flow – mediated dilation compared to man in response to reactive hyperaemia. Majmudar et al found that the vasoconstrictive response to a nitric oxide synthase (NOS) inhibitor (1-NG-nomomethyl-arginine; L-NMMA) was greater in premenopausal women than age-matched men suggesting reduced basal nitric oxide production in men compared with women.

Studies on a group of premenopausal women who underwent bilateral ovariectomy were performed by measuring changes in forearm blood flow induced by intra-brachial administration of acetylcholine before ovariectomy, one month after ovariectomy and three months after the start of estrogen replacement therapy. Compared with the normal values before ovariectomy, acetylcholine-induced vasodilatation was significantly reduced after ovariectomy and was restored after use of exogenous 17β-estradiol. Another such group was studied by examining the effect of intra-brachial administration of vitamin C (an antioxidant that scavenges super-oxide free radicals) on changes in forearm blood flow. Before ovariectomy there was no difference in vasodilatory effects.
response to acetylcholine, whereas one month after ovariec- tomy vitamin C significantly corrected the response to acetylcholine18. These results suggest that ovariec- tomy could be associated with an increase in oxidative stress and that the beneficiary effects of hormonal replacement therapy might be a result of vascular oxidative stress reduction.

The effects of estrogens/testosterone on vascular function were studied in male to female transsexuals taking oral estrogen therapy during 5 months and compared with age-matched men and premenopausal women. Transsexuals had plasma testosterone reduced to the concentration in premenopausal women. Measurement of flow-mediated vasodilation showed that it was lower in men than in estrogens-treated male to female transsexuals or in premenopausal women. Tran- sexuals showed that castrated male to female transsexuals treated with estrogen for an average of 5 years had significantly greater endothelium-dependent vasodilation compared with male control subjects20. Taken together, these studies suggest that endothelial dependent vasodilation is improved in the condition with chronic estrogens supplementation or testosterone levels reduc- tion3.

Crucial Role of Estrogens and Progesterone

Great majority of contemporary studies highlights the protective role of estrogens and progesterone against the development of CVDs. Many studies have demonstrated that estrogen stimulates endothelium-dependent mechanism of vascular smooth muscle cell (VSMC) relaxation by two different pathways. In the genomic pathway, estrogen binds to endothelial cytosolic/nuclear estrogen receptors, increases gene transcription, endothelial cell proliferation, and increases endothelial nitric-oxide production21–39. In the non-genomic pathway, estrogen binds to membrane receptors on endothelial cell surface and causes an increase of endothelial nitric oxide production. Nitric oxide diffuses into the VSMC, binds to guanylate cyclase and increases cGMP, which subsequently causes relaxation by decreasing calcium concentration. Endothelial estrogen receptors may activate cyclo-oxygenases and increase PG12 production. PG12 leads to relaxation of VSMC through the activation of potassium channels5.

Estrogens have a protective role in the development of atherosclerosis by interacting with various pathogenetic factors. They decrease levels of total plasma cholesterol and low density lipoproteins (LDL) and increase high density lipoproteins (HDL) and triglycerides by influenc- ing expression of hepatic apoprotein genes. Estrogens modify LDL receptors on hepatocytes, increasing thereby LDL intake and subsequently decreasing plasma LDL level21. Due to the presence of a phenol ring structure in 17β-estradiol, estrogen may act as an antioxidant suppressing the uptake of LDL-cholesterol by the arterial wall, or enhancing endothelial degradation of LDL-cholesterol22. Estrogens with a phenol structure protect LDL from cellular and calcium ion mediated oxidation in vitro23,24. The mechanisms of LDL oxidation in vivo are still unknown. It has been hypothesized that vascular cells modify LDL into its atherogenic form25,26 but reduction-oxidation active metals in the vascular wall may act on sub-endothelial lipoproteins27. Short-term exposure to physiological concentrations of estradiol had the potential to increase LDL resistance to calcium ion mediat- ed modification28. Furthermore, estrogens interfere with monocyte adherence to the intima surface of endo- thelum and with the sub-endothelial migration of monocytes29.

Lower estrogen levels, lower sex hormone binding globulin (SHGB) and higher androgen levels have been hypothesized by Rexrode et al to predict higher risk of CVD in postmenopausal women30. They discovered that postmenopausal women who are not using HRT have lower SHBG and higher free androgen index (FAI) and that they have increased risk of CVD. Postmenopausal women who are current HRT users have no clear associations between estrogen, androgen, or SHBG levels and risk of CVD. Liu et al31 implied that there are three phases of hormonal milieu changes. The first is pre-men- opause, occurring before estrogens levels start to de- cline, which is approximately two years before meno- pause, the second is inter-menopause, which occurs ap- proximately around the age of 55 years, and the third is post-menopause. During inter-pause, estrogens levels de- cline rapidly around menopause, while there is a more gradual decline of androgen levels up to age 55. The aromatization of androgens to estrogens increases with age and androgens may be the only source of estradiol in post-pause. It has been discovered that early menopause is associated with increased CVD risk. In the inter-menopause hormonal milieu is relatively more androgenic than in either pre-menopause or post-menopause. They hypothesized that if the inter-menopause period in women lasts longer, the CVD risk will be higher.

Acute (short-term) administration of estrogens can cause rapid vasodilation and increased blood flow. The rapid time-course of this estrogens-induced response rules out modulation of gene expression as a potential mechanism. Instead, the acute effects of estrogens are likely to be mediated through the novel (non-genomic) signal transduction pathway. The results of some investiga- tions have suggested that estrogens elicit rapid effects by modulating VSM ion channels. For example, studies have shown that estrogens act like a calcium channel antagonists, thereby decreasing the influx of calcium into VSM. Inhibition of calcium influx would inhibit con- traction3.

Studies in primates and other animal models support evidence that the beneficial effects of HRT in preventing atherosclerosis occur only if HRT is initiated before the development of advanced atherosclerosis (the time hypothesis)21. The Heart and Estrogens/progestin Replacement Study (HERS) was a randomized trial involving nearly 3000 postmenopausal women under 80 years of age (mean 66.7 years) who had a history of coronary ar-
ccular effects in younger women while it may have detri-
mental effect on coagulative balance and vascular inflam-
mation and has little effect on cardiovascular functions
in older women (34). Estrogen exerts their protective ef-
fects in CVD by changes in lipoproteins; decreasing LDL-
cholesterol, apolipoprotein B and lipoprotein(a) and in-
creasing HDL-cholesterol and apolipo- protein A1. In
post-menopause, there are also evident changes in homo-
cysteine (independent risk factor for CVD which homeo-
stasis is influenced by sex hormones) and carbohydrate
metabolism, as well as unfavorable alterations in lipid
profile, and in haemostasis, all related to atherosclerosis
and identified as a part of a metabolic syndrome(22). The
protective effects of HRT may be exerted by changes of
the profile of coagulation factors to more physiological
(pre-menopausal) profile, and by affecting serum glucose
and insulin concentration, as well as by decrease in
homocysteine concentration22. Oral contraceptives, which
are suppressing ovarian production of endogenous estro-
gens, increase the risk of various CVDs, which are re-
lated to impaired endothelial function. Synthetic estro-
gens have less effective function than endogenous one on
endothelial cells(35–37), but this can be disputed. John et al
have proved that there were no significant differences
between vascular vasodilatation in response to acetyl-
choline and sodium nitroprusside between healthy pre-
menopausal women taking oral contraceptives and wo-
men not taking them. In the other hand, there was a
highly significant difference in response to L-NMMA ad-
ministration with a greater vasoconstrictive response af-
ter stimulation with acetylcholine in women with oral
contraception than in those without therapy. Conclusion
was that increased basal production and release of nitric
oxide in premenopausal women receiving oral contracep-
tives had protective effect of estrogens on vascular relax-
ation mechanisms38.

Use of oral contraceptives has long been associated
with increased risk of venous thromboembolism. This
thrombotic risk was attributed only to the estrogens in
the pills. This theory was challenged after 1995 by impli-
cating the progesterone role. The first-generation oral
contraceptives of the 1960s and 1970s were associated
with both ischemic and hemorrhagic stroke, which is al-
estimately in young women who do not smoke using
the second-generation oral contraceptives with their
lower dose of estrogens39. However, one should be aware,
that there could be increased risk of stroke in smokers
and in those with high blood pressure, even among those
women using second-generation oral contraceptives. In-
terestingly, the usage of third-generations oral contra-
ceptives is associated with significantly higher risk of ve-
 nous thromboembolism compared with the usage of
levonorgestrel-containing second-generation oral contra-
ceptives, and even higher risk of venous thrombosis com-
pared with non-users. Third-generation oral contracep-
tives with their low androgenic activity increase HDL
and decrease LDL. Association between third-generation
oral contraceptives and a smaller risk of stroke compared

In early postmenopausal women, like the ones in-
cluded in the observational studies, ovarian hormone re-
placement may be cardio protective because of the re-
sponsiveness of the endothelium to estrogens that also
buffer the detrimental effects of coagulation. In late
postmenopausal women ovarian hormones have either a
null effect or even a detrimental effect on the risk of vas-
cular disease because of the predominance of the procoa-
gulant or plaque-destabilizing effects over the vasopro-
tective effects. Therefore, HRT has beneficial cardiovas-
	ery disease (CAD)30. The women were treated with ei-
ther placebo or combination hormone therapy (0.625 mg
of conjugated estrogens and 2.5 mg of medroxyprogester-
one daily). Interestingly, no significant differences in
primary outcome (CVD death or nonfatal myocardial in-
farction) or secondary outcome (stroke, peripheral arte-
rial disease, congestive heart failure, resuscitated arrest,
unstable angina) were noted between the hormone-trea-
ted groups and those treated with placebo after a 4-year
follow-up, despite a favorable effect of hormone therapy
on lipid profiles30. It was found, however, that more women
in the hormone-treated group suffered coronary events
during the first year of treatment than those taking
the placebo. Women in the hormone-treated group
also experienced more thrombosis events, such as pulmo-
nary embolism. The Estrogens in the Prevention of Ath-
erosclerosis Trial was organized to assess estrogens abil-
ity to attenuate the progression of sub clinical atheroscle-
rotic plaques, and the protocol included postmenopausal
women with no history of CVD receiving unopposed
doses of β-estradiol to ensure no interference from pro-
gestosterone. This trial concluded that unopposed estradiol
treatment can slow the progression of sub clinical ath-
erosclerosis to much the same extent as traditional li-
id-lowering therapy. It assumed that estrogens bind to
alpha and betha intracellular receptors influencing NO,
cytokine and growth factors production (30), thus affect-
ing vascular endothelial function. Much research atten-
tion has been focused on the effects of estrogens and
HRT on blood coagulation and the formation of emboli,
because these are major risk factors for CVD and myo-
cardial infarction, and it has been demonstrated that lev-
els of several coagulation factors such as factors VII and
VIII as well as fibrinogen increase after menopause. It
has been shown that estrogens may exert anticoagulant
effects by interfering with platelet aggregation. After a
blood-vessel wall is injured, collagen fibres allow for
platelets to adhere to the injury site, and the platelets si-
multaneously produce several compounds involved with
coaugulation32. Faraday et al.33 found that the number of
platelet GPIIb/IIIa receptors was the same between
healthy young men and women, but in premenopausal
women these receptors were more responsive to platelet-
activating endogenous signals and platelet-activating
drugs compared with age-matched men. This finding
would tend to increase platelet aggregation in women3.
ET-1 levels were found to be significantly lower in wo-
men compared with men, and were lowest in pregnant
women1.

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with second-generation oral contraceptives remains to be established.

Diverse Role of Testosterone and Other Androgens

Contemporary studies about the role of testosterone and other androgens in the development of CVDs could be divided into three groups: first incentive, second diverse, and third protective. From literature analysis one can see early enthusiasm for use of testosterone in cardiac patients, subsequent disappointment with androgens due to negative effects on lipid metabolism, and recent renewed interest as new technologies has led to re-examination of the adverse effects of androgens.

Studies that highlight the incentive role of testosterone in CVDs are overwhelmingly made in female population. It is proven that visceral fat accumulation occurring in postmenopausal women is connected with hyperestrogenism, deceased production of sex-hormone binding globulin (SHBG) and with rise in free testosterone. Adipose tissue produces adipocytokines: adiponectin, leptin and resisting. All three hormones are connected with insulin resistance, increased pressure and hypertriglyceridaemia. All these conditions lead to CVDs.

Population based study on 513 naturally postmenopausal women aged between 54 and 67 years has shown positive connection between high dose estrogen –testosterone therapy and severe atherosclerosis of the aorta, but only after one year of therapy. Studies have also shown that long-term treatment with high-dose androgens is associated with impaired vascular reactivity in genetic females, consistent with a deleterious effect of androgen excess on arterial physiology. This proatherogenic action of androgens could be explained through an elongation of GAG (glycosaminoglicane) chains on proteoglycans in an androgen receptor-dependent manner. It is proven that adolescent girls with polycystic ovary syndrome (PCOS) have increased levels of factors making the Metabolic syndrome (MetS) than adolescent girls with regular cycles and that overweight women with PCOS have increased cardiovascular risk factors and evidence of early CVD, compared with weight-matched controls.

There is also number of studies that shows diverse effects of androgens. They claim that hyperandrogenism, as isolated androgen excess, has not been clearly recognized as a risk factor for cardiovascular diseases. Long-term studies examining the prevalence of cardiovascular diseases among women with PCOS have not demonstrated a clear increased risk of CVDs. Their risk factors are mainly dependant on the metabolic components, insulin resistance and adiponectin hypo-secretion. Community based cross-sectional study on 587 non-health-care-seeking women has shown that endogenous testosterone and the adrenal pre-androgens per se are not significantly independent determinants of circulating high sensitivity CRP and or lipoprotein lipids. Literature research conducted at Mayo Clinic has shown that testosterone use in men with low testosterone levels leads to inconsensuional changes in blood pressure, glycaemia and all lipid fractions (cholesterol, triglycerides, LDL, HDL). Prospective cohort community-based study in Framingham, Massachusetts, USA has shown that serum testosterone and DHEA-S levels were not statistically significantly associated with incident CVD.

Androgens have important biological roles in young women, with good effects on bone, muscle mass, mood, well-being and libido, but also negative effects like hirsutism and acne, which reverse with discontinuation of treatment. Fair evidences exist that the use of testosterone in combination with hormone therapy has both benefits and risks. The benefits are an improvement in sexual function, an improved sense of well-being and a reduction in triglyceride levels. The most consistent risk is a reduction in high-density lipoprotein (HDL) cholesterol.

Studies that prove protective role of testosterone in CVDs are the most numerous. They show that androgens in general and testosterone in particular may have some protective effects on the cardiovascular system through their metabolic and direct effects upon human vasculature. In study of ex vivo vascular reactivity of fresh subcutaneous resistance arteries in men suffering from heart failure, testosterone induced an acute concentration – dependent vasodilatation of resistance arteries at concentrations over 1 micromole/L. Results of various studies suggest that testosterone can alter vascular tone through in both, endothelium-dependent and endothelium-independent mechanisms. Testosterone’s endothelium-dependent effects are likely mediated at least in part through nitric oxide (NO) release, whereas mechanisms of endothelium-independent effects involve activation of one or more types of smooth muscle ion conductance channels. Testosterone can either activate K+ channels or block Ca2+ channels. Because vascular cells contain sex steroid hormone receptors, testosterone can exert effects on the vascular wall, either by itself or through aromatization in estrogens. The interaction of testosterone with its specific receptors may trigger not only long-term genomic effects, but also acute non-genomic vasodilator responses. Testosterone may activate the endothelium and stimulate the nitric oxide-cGMP and the hyperpolarization-mediated vascular relaxation pathway. It may also inhibit the signaling mechanisms of smooth muscle contraction such as [Ca2+] and protein kinases.

Numerous studies have shown that in ageing men testosterone levels decline together with cognitive function, muscle and bone mass, sexual hair growth, libido and sexual activity, but the risk of cardiovascular risk increases. The Baltimore Longitudinal Study of Aging suggests that influence of low testosterone levels on the cardiovascular system in men may be mediated in part via the effects of testosterone on vascular structure and function. Population based cross sectional study has shown negative correlation between total testosterone and sex hormone binding globulin serum levels and intimae-media thickness (IMT) in men. The Massachusetts Male Aging Study, a population based cohort of
1709 men observed at three time points (T1= 1987–1989; T2= 1995–1997; T3= 2002–2004) has shown that low serum sex hormone binding globulin (SHBG), low total testosterone and clinical androgen deficiency are associated with increased risk of developing MetS (central obesity, lipid and insulin dysregulation and hypertension), particularly in non-overweight, middle-aged men (BMI under 25), that can lead to development of cardiovascular diseases$^{61}$. Hypoandrogenaemia (hypogonadism, hypo-testosteronemia) may be a common accompanying factor in men with the MetS (Raven’s syndrome or syndrome X). When they are present together they may be considered as a specific entity, the hypo-androgen-metabolic (HAM) syndrome$^{62}$. Healthy men with low testosterone levels have increased cardiovascular risk factors, including high fasting and 2-hour plasma glucose, serum triglycerides, total cholesterol and low-density lipoprotein (LDL) cholesterol, and apo-A-I lipoprotein. Injections of testosterone decrease total cholesterol and LDL cholesterol, while increasing high-density lipoprotein (HDL) cholesterol. Testosterone affects the clotting system by increasing thromboxane A2 receptor activity and platelet aggregability. Testosterone also augments the fibrinolytic system and antithrombin III activity, has antiinflammatory effects, and an inverse relationship to systolic blood pressure$^{63}$. Aging in men is accompanied by a progressive, but individually variable decline of serum testosterone production and the clinical picture of aging in men is reminiscent of that of hypogonadism in young men$^{65}$. Middle-aged men with symptoms of andropause, together with absolute or compensated testosterone deficiency, show increased carotid IMT$^{65}$. It was proven that low free testosterone coexists with inflammation and they both affect the process of atherosclerosis in old-age male$^{66}$.

Although, there are numerous studies showing the negative impact of testosterone on women regarding CVDs development, there are also results proving its positive impact. According to them development of CVDs in postmenopausal women is due to not only estrogen, but also testosterone decline$^{67}$. Meta analysis of 101 non-obese postmenopausal women through medical histories, physical examinations and biochemical analysis has shown possible protective role of endogenous androgens at least on carotid atherosclerosis$^{68}$.

There are also results showing higher total testosterone and SHBG to be inversely related to carotid atherosclerosis, suggesting their potential importance in reducing atherosclerotic risk in postmenopausal women not using hormonal replacement therapy (HRT)$^{69}$. In postmenopausal women endogenous steroid precursors and androgens are inversely related to IMT, an established marker of atherosclerosis$^{70}$.

These studies have thus revealed an estrogen-androgen paradox: those endogenous sex hormones may relate both to atherosclerotic cardiovascular disease and its risk factors oppositely in women and men$^{71}$. In the case of androgens, hypo-androgenemia in men and hyper-androgenemia in women are associated with increased risk of coronary artery disease, but also with visceral obesity, insulin resistance, low high-density lipoprotein (HDL) cholesterol, elevated triglycerides, low-density lipoprotein (LDL) cholesterol and plasminogen activator inhibitor (PAI-1). Exogenous androgens, on the other hand, induce both apparently beneficial and deleterious effects on cardiovascular risk factors by decreasing serum levels of HDL-C, plasminogen activator inhibitor (PAI-1), lipoprotein (a), fibrinogen, insulin, leptin and visceral fat mass in men as well as in women$^{72}$. Testosterone treatment is reported to reduce serum levels of the proinflammatory cytokines interleukin (IL)-1β and tumour necrosis factor (TNF)-α, and to increase levels of the anti-inflammatory cytokine IL-10; to reduce vascular cell adhesion molecule (VCAM)-1 expression in aortic endothelial cells; to promote vascular smooth muscle and endothelial cell proliferation; to induce vasodilatation and to improve vascular reactivity; to reduce serum levels of the pro-thrombotic factors PAI-1 and fibrinogen; to reduce LDL-C; to improve insulin sensitivity; and to reduce body mass index and visceral fat mass$^{73}$.

**Conclusion**

In this review we have attempted to evaluate the role of the sex steroid hormones in the development of the cardiovascular diseases (CVDs). The interaction of sex hormones on the blood vessel receptors, the vascular reactivity and the pathogenesis of CVDs were examined. We have highlighted not just the protective role of estrogens, but also the protective role of testosterone, on one side, and the incentive role of both of them on the other side, which is gender dependent. It is clear that sex steroid hormones are important in physiological function of vasculature, as well as in pathogenesis of vascular diseases, but to fully understand all the complex interactions of sex hormones with pathogenesis factors and processes, further research is necessary. If one intends to effectively use the known facts of sex hormone physiology to influence cardiovascular diseases, to safely manipulate the sex hormone system and thereby to improve therapy, one has to elucidate all important mechanisms before we can possibly modify them to our advantage at first.

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RAZLIČITE ULOGE SPOLNIH STEROIDNIH HORMONA U PATOGENEZI VASKULARNE DISFUNKCIJE I RAZVOJU KARDIOVASKULARNIH BOLESTI KOD MUŠKARACA I ŽENA

S A Z E T A K

U ovom radu predstavljen je pregled najnovije literature, koja analizira odnose između spolnih steroidnih hormona i kardiovaskularnih bolesti. Analiziran je utjecaj spomenutih hormona na tri razine: njihovu interakciju s krvilosnim receptorima, njihovu modulaciju vaskularne funkcije, te ulogu u patogenezi kardiovaskularnih bolesti. U radu su istaknute ne samo poznate činjenice protektivne uloge estrogena i poticajnog utjecaja testosterona, već su dani pojedinačni primjeri njihovog suprotnog učinka.