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Review

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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A B S T R A C T

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[1]. 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[1]. 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[1]. 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[2], while the role of androgens and testosterone in ethiopathogenesis of CVDs has not been fully established yet, although some studies suggest that androgens have protective role in the development of cardiovascular diseases[3].

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[2].

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

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a target gene. The final result is an increase or decrease in the synthesis of the protein coded by that gene[3].

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[3]. Li et al.[4] 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[5] examined the relative levels of prostaglandin PR isoform (PR-A and PR-B) expression in VSM. PR-B is cell-specific and transcriptional 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 A_2 (TXA2), prostaglandin $F_{2\alpha}$, ($PGF_{2\alpha}$), and angiotensin II; and vasodilator mediators, primarily NO, endothelium-derived hyperpolarizing factors (EDHF; known as metabolite of arachidonic acid – epoxyeicosatrienoic acids, EET), and PGI_2, determines vascular tone and subsequently blood flow to organs and tissue perfusion. Some prostaglandins, such as PGE_2, can function as both, vasoconstrictor and vasodilator, depending on the type of receptor they bound at, i.e. EP1 or EP3 prostanoid receptors[2]. 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[6]. EDHF are factors that activate Ca^{2+}-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[2]. 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[7–10]. 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 pO_2 changes) and pathophysiological (vascular proliferate processes, attenuation of vasodilator mechanisms) responses[10]. Observations suggest that super-oxide anions can affect physiological vascular reactivity or impair blood flow auto-regulation[11–13].

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[14]; 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[15]. 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[3]. Majmudar et al found that the vasoconstrictive response to a nitric oxide synthase (NOS) inhibitor (1-NG-monomethyl-arginine; L-NMMA) was greater in premenopausal women than age-matched men suggesting reduced basal nitric oxide production in men compared with women[16].

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[17]. 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 not difference in vasodilatatory

response to acetylcholine, whereas one month after ovariectomy vitamin C significantly corrected the response to acetylcholine[18]. These results suggest that ovariectomy 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/testosteron 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 concentrations found in premenopausal women. Measurement of flow-mediated vasodilatation showed that it was lower in men than in estrogens-treated male to female transsexuals or in premenopausal women[19]. Another study showed that castrated male to female transsexuals treated with estrogen for an average of 5 years had significantly greater endothelium-dependent vasodilatation compared with male control subjects[20]. Taken together, these studies suggest that endothelium dependent vasodilatation is improved in the condition with chronic estrogens supplementation or testosterone levels reduction[3].

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 production[21–39]. 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 PGI_2 production. PGI_2 leads to relaxation of VSMC through the activation of potassium channels[2].

Estrogens have a protective role in the development of atherosclerosis by interacting with various pathogenic factors. They decrease levels of total plasma cholesterol and low density lipoproteins (LDL) and increase high density lipoproteins (HDL) and triglycerides by influencing expression of hepatic apoprotein genes. Estrogens modify LDL receptors on hepathocytes, increasing thereby LDL intake and subsequently decreasing plasma LDL level[21]. Due to the presence of a phenol ring structure in 17-β-estradiol, estrogen may act as an antioxidant suppressing the uptake of LDL-cholesterol by the arterial wall, or enhancing endothelial degradation of LDL-cholesterol[22]. Estrogens with a phenol structure protect LDL from cellular and calcium ion mediated oxidation in vitro[23,24]. The mechanisms of LDL oxidation in vivo are still unknown. It has been hypothesized that vascular cells modify LDL into its atherogenic form[25,26] but reduction-oxidation active metals in the vascular wall may act on sub-endothelial lipoproteins[27]. Short-term exposure to physiological concentrations of estradiol had the potential to increase LDL resistance to calcium ion mediated modification[28]. Furthermore, estrogens interfere with monocyte adherence to the intimae surface of endothelium and with the sub-endothelial migration of monocytes[29].

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 women[30]. 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 al[31] implied that there are three phases of hormonal milieu changes. The first is pre-menopause, occurring before estrogens levels start to decline, which is approximately two years before menopause, the second is inter-menopause, which occurs approximately around the age of 55 years, and the third is post-menopause. During inter-pause, estrogens levels decline 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 vasodilatation 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 investigations 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 contraction[3].

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-

tery disease (CAD)[30]. The women were treated with either placebo or combination hormone therapy (0.625 mg of conjugated estrogens and 2.5 mg of medroxyprogesterone daily). Interestingly, no significant differences in primary outcome (CVD death or nonfatal myocardial infarction) or secondary outcome (stroke, peripheral arterial disease, congestive heart failure, resuscitated arrest, unstable angina) were noted between the hormone-treated groups and those treated with placebo after a 4-year follow-up, despite a favorable effect of hormone therapy on lipid profiles[30]. 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 pulmonary embolism. The Estrogens in the Prevention of Atherosclerosis Trial was organized to assess estrogens ability to attenuate the progression of sub clinical atherosclerotic plaques, and the protocol included postmenopausal women with no history of CVD receiving unopposed doses of β-estradiol to ensure no interference from progesterone. This trial concluded that unopposed estradiol treatment can slow the progression of sub clinical atherosclerosis to much the same extent as traditional lipid-lowering therapy. It assumed that estrogens bind to alpha and betha intracellular receptors influencing NO, cytokine and growth factors production (30), thus affecting vascular endothelial function. Much research attention 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 myocardial infarction, and it has been demonstrated that levels 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 simultaneously produce several compounds involved with coagulation[32]. 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 women[3]. ET-1 levels were found to be significantly lower in women compared with men, and were lowest in pregnant women[3].

In early postmenopausal women, like the ones included in the observational studies, ovarian hormone replacement may be cardio protective because of the responsiveness 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 vascular disease because of the predominance of the procoagulant or plaque-destabilizing effects over the vasoprotective effects. Therefore, HRT has beneficial cardiovascular effects in younger women while it may have detrimental effect on coagulative balance and vascular inflammation and has little effect on cardiovascular functions in older women (34). Estrogen exerts their protective effects in CVD by changes in lipoproteins; decreasing LDL-cholesterol, apolipoprotein B and lipoprotein(a) and increasing HDL-cholesterol and apolipo- protein A1. In post-menopause, there are also evident changes in homocysteine (independent risk factor for CVD which homeostasis 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 concentration[22]. Oral contraceptives, which are suppressing ovarian production of endogenous estrogens, increase the risk of various CVDs, which are related to impaired endothelial function. Synthetic estrogens 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 acetylcholine and sodium nitroprusside between healthy premenopausal women taking oral contraceptives and women not taking them. In the other hand, there was a highly significant difference in response to L-NMMA administration with a greater vasoconstrictive response after 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 contraceptives had protective effect of estrogens on vascular relaxation mechanisms[38].

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 implicating the progesterone role. The first-generation oral contraceptives of the 1960s and 1970s were associated with both ischemic and hemorrhagic stroke, which is almost eliminated in young women who do not smoke using the second-generation oral contraceptives with their lower dose of estrogens[39]. 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. Interestingly, the usage of third-generations oral contraceptives is associated with significantly higher risk of venous thromboembolism compared with the usage of levonorgestrel-containing second-generation oral contraceptives, and even higher risk of venous thrombosis compared with non-users. Third-generation oral contraceptives with their low androgenic activity increase HDL and decrease LDL. Association between third-generation oral contraceptives and a smaller risk of stroke compared

with second-generation oral contraceptives remains to be established[39].

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 hypoestrogenism, deceased production of sex-hormone binding globulin (SHBG) and with rise in free testosterone. Adipose tissue produces adipocytokines: adiponectin, lepton and resisting[40]. All three hormones are connected with insulin resistance, increased pressure and hypertriglyceridaemia. All these conditions lead to CVDs (40). 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[41]. 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[42]. This proatherogenic action of androgens could be explained through an elongation of GAG (glycoseaminoglicane) chains on proteoglycans in an androgen receptor-dependent manner[43]. 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[44] and that overweight women with PCOS have increased cardiovascular risk factors and evidence of early CVD, compared with weight-matched controls[45].

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[46]. 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[46]. 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[47]. Literature research conducted at Mayo Clinic has shown that testosterone use in men with low testosterone levels leads to inconsenquentional changes in blood pressure, glycaemia and all lipid fractions (cholesterol, triglycerides, LDL, HDL)[48]. 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[49]. 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[50]. 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[51].

Studies that prove protective role of testosterone in CVDs are the most numerous[53–73]. 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[52]. 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[53]. 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[54]. Testosterone can either activate K+ channels or block Ca^{2+} channels[55]. Because vascular cells contain sex steroid hormone receptors, testosterone can exert effects on the vascular wall, either by itself or through aromatization in estrogens[56]. 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 [Ca^{2+}] and protein kinases[57].

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[58]. 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[59]. 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[60]. 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, hypotestosteronaemia) 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 A_2 receptor activity and platelet aggregability. Testosterone also augments the fibrinolytic system and antithrombin III activity, has antianginal 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[64]. 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 proinflamatory 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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REFERENCES

1. KUMAR V, COTRAN RS, ROBBINS SL, Basic Pathology (W. B. Saunders Company, Philadelphia, 1992). — 2. ORSHAL JM, KHALIL RA, Am J Physio Regul Integr Comp Physiol, 286 (2004) R233. — 3. SCHWERTZ DW, PENCKHOFER S, Heart and Lung, 30(6) (2001) 401–428. — 4. LI HJ, HAQUE Z, LU Q, LI L, KARAS R, MENDELSOHN M, Proc. Natl Acad Sci USA, 104 (2007) 4065. — 5. NAKAMURA Y, SUZUKI T, INOUE T, TAZAWA C, ONO K, MORIYA T, SAITO H, ISHIBASHI T, TAKAHASHI S, YAMADA S, SASANO H, Endrocine Journal, 52 (2005) 245. — 6. HUANG A, WU Y, SUN D, KOLLER A, KALEY GJ, Appl Physiol, 91(6) (1998) 2561. — 7. KUGA T, TAGAWA H, TOMOIKE H, MITSOUKA W, EGASHIRA S, OHARA Y, TAKESHITA A, NAKAMURA M, Circulation. 87(2) (1993) 573. — 8. BOLLI, A, Basic Res Cardiol. 93(3), (1998) 156. — 9. DIEDRICH D, SKOPEC J, DIEDRICH A, DAI FX, Am J Physiol, 266 (1994) H1153. — 10. WOLIN MS, Arterioscler Thromb Vasc Biol, 20 (2000) 1430. — 11. HUANG A, SUN D, KALEY G, KOLLER A, Circ Res 83 (1998) 960. — 12. LENDA DM, SAULS BA, BOEGEHOLD MA, Am J Physiol, 279 (2000) H7. — 13. ZAGORAC D, YAMURA K, ZHANG C, ROMAN RJ, HARDER DR, Stroke 36 (2005) 2589. — 14. KUNERT MP, DRENJANCEVIC-PERIC I, DWINELL MR, LOMBARD JH, COWLEY AW JR, GREENE AS, KWITEK AE, JACOB HJ, Physiol Genomics, 26(3) (2006) 218. — 15. KUNERT MP, DWINELL MR, DRENJANCEVIC-PERIC I, LOMBARD JH, Am J Physiol Regul Integr Comp Physiol, 295(2) (2008) R516. — 16. MAJMUDAR NG, ROBSON SC, FORD GA, J Clin Endocrinol Metab, 85 (2000) 1577. — 17. PINTO S, VIRIDIS A, GHIADONI L, BERNINI G, LOMBARDO M, PETRAGLIA F, GENAZZANI AR, TADDEI S, SALVETTI A, Hypertension, 29 (1997) 268. — 18. VIRIDIS A, GHIADONI L, PINTO S, LOMBARDO M, PETRAGLIA F, GENNAZZANI A, BURALLI S, TADDEI S, SALVETTI A, Circulation, 101 (2000) 2258. — 19. NEW G, TIMMINNS KL, DUFFY SJ, TRAN BT, O'BRIEN RC, HARPER RW, J Am Coll Cardiol, 29 (1997) 1437. — 20. McCROHON JA, WALTERS WAW, ROBINSON JTC, McCRADIE RJ, TURNER L, ADAMS MR, J Am Coll Cardiol, 29 (1997) 1432. — 21. MENDELSOHN ME, KARAS RH, Science, 308(5728) (2005) 1583. — 22. PINES A, MIJATOVIC V, VAN DER MOOREN MJ, KENEMANS P, Eur J Obstet Gynecol Reprod Biol, 71 (1997) 193. — 23. HUBER L, SCHEFFLER E, POLL R, ZEIGLER R, DRESEL HA, Free Radic Res Comm, 8 (1990) 167. — 24. TANG M, ABPLANALP W, AYRES S, SUBBIAH MTR, Metabolism, 45 (1996) 411. — 25. STEINBRECHER UP, PARTHASARATHY S, LEAKE DS, WITZUM JL, STEINBERG D, Proc Natl Acad Sci USA, 81 (1984) 3883. — 26. PARTHASARATHY S, PRINTZ DJ, BOYD, JOY L, STEINBERG D, Arteriosclerosis, 6 (1986) 505. — 27. EHRENWALD E, CHISOLM GM, FOX PL, J Clin Invest, 93 (1994) 1493. — 28. SHAWAERY GT, VITA JA, KEANEY JF JR, Circulation, 95 (1997) 1378. — 29. NATHAN L, PERVINE S, SINGH R, ROSENFELD M, CHANDHUN G, Circ Res, 85 (1999) 377. — 30. REXRODE KM, MANSON JE, LEE I, RIDKER PM, SLUSS PM, COOK NR, BURING JE, Circulation, 108 (2003) 1688. — 31. LIU Y, DING J, BUSH TL, LONGENECKER JC, NIETO FJ, GOLDEN SH, SZKLO M, American Journal of Epidemiology, 154 (2001) 489. — 32. BAKER L, MELDRUM KK, WANG M, SANKULA R, VANAM R, RAIESDANA A, TSAI B, HILE K, BROWN JW, MELDRUM D, Journal of Surgical Research, 115 (2003) 325. — 33. FARADAY N, GOLDSCHMIDT-CLERMONT PJ, BRAY PF, Thromb Haemost, 77 (1997) 748. — 34. ROSANO GM, VITALE C, FINI M, Ann NY Acad Sci, 1092 (2006) 341. — 35. CARR BR, GRIFFINN JD, Fertility control and its complications. In: Wilson JD, Foster DW (Eds) (WB Saunders, Philadelphia, 1985). — 36. PEEK MJ, MARKHAM R, FRASER IS. Hum Reprod, 10 (1995) 2238. — 37. SUBAKIR SB, HADISAPUTRA W, SIREGAR B, IRAWATI D, SANTOSO DI, CORNAIN S, Hum Reprod, 10 (1995) 2579. — 38. JOHN S, JACOBI J, SCHIAH MP, DELLES C, SCHNIEDER RE. Am J Obstet Gynecol, 183(1) (2000) 28. — 39. LeBLANC ES, LAWS A, J Gen Intern Med, 14 (1999) 625. — 40. MOHAMAD MJ, KARAYYEM M, MOHAMMAD MA, Al-ALAMI J, Al-HADER A. Neuro Endocrinol Lett, 6(2006) 758. — 41. HAK AE, WESTENDROP IC, POLS HA, HOFMAN A, WITTEMANN JC. Mauritas, 56(2) (2007) 153. — 42. McCREDIE RJ, McCROHON JA, TURNER L, GRIFFITHS KA, HANDELSMANN DJ, CELERMAJER DS, J Am Coll Cardiol, 32(5) (1998) 1331. — 43. HASHIMURA K, SUDHIR K, NIGRO J, LING S, WILLIAMS MR, KOMESAROFF PA, LITTLE PJ, Endocrinology, 146(4) (2005) 2085. — 44. GLUECK CJ, MORRISON CJ, FRIEDMAN LA, GOLDENBERG N, STROOP DM, WANG P, Metabolism, 55(4) (2006) 508. — 45. MEYER C, McGRATH BP, TEEDE HJ, J Clin Endocrinol Metab, 90(10) (2005) 5711. — 46. RIZZO M, RINI GB, CARMINA E, Minerva Endocrinol, 32(1) (2007) 67. — 47. BELL RJ, DAVISON SL, PAPALIA MA, McKENZIE DP, DAVIS SR, Menopause, (2007). — 48. HADDADD RM, KENNEDY CC, CAPLES SM, TRACZ MJ, BOLONA ER, SIDERAS K, URAGA MV, ERWIN PJ, MONTORI VM, Mayo Clin Proc, 82(1) (2007) 29. — 49. ARNLOV J, PENCINA MJ, AMIN S, NAM BH, BENJAMIN EJ, MURABITO JM, WANG TJ, KNAPP PE, D'AGOSTIONO RB SR, BHASIN S, VASAN RS, Ann Intern Med, 145(3) (2006) 176. — 50. KALANTRIDOU SN, CALIS KA, Semin Reprod Med, 24(2) (2006) 106. — 51. SOMBOONPORN W, Semin Reprod Med, 24(2) (2006) 115. — 52. ROSANO GM, CORNOLDI A, FINI M, J Endocrinol Invest, 28(3) (2005) 32. — 53. MALKIN CJ, JONES RD, JONES TH, CHANNER KS, Clin Sci (Lond), 111(4) (2006) 265. — 54. LITTLETON-KEARNEY M, HURN PD, Biol Res Nurs, 5(4) (2004) 276. — 55. YILDIZ O, SEYREK M, Exp Clin Endocrinal Diabetes, 115(1) (2007) 1. — 56. SHABISGH R, KATZ M, YAN G, MAKSHIDA N, Am J Cardiol, 96(12B) (2005) 67M. — 57. WYNNE FL, KHALIL RA, J Endocrinol Invest, 26(2) (2003) 181. — 58. NAKHAI POUR HR, EMMELOT-VONK MH, SUKEL-HELLEMAN M, VERHAAR HJ, GROEBEE D, VAN DER SCHOUW YT, Trials, 7 (2006) 24. — 59. HOUGHAKU H, FLEG JL, NAJJAR SS, LAKATTA EG, HARMAN SM, BLACKMAN MR, METTER EJ, Am J Physiol Endocrinol Metab, 290(2) (2005) E234. — 60. SVARTBERG J, VON MUHELN D, MATHIESEN E, JOAKIMSEN O, BONAA KH, STENSLAND-BUGGE E, J Intern Med, 259(6) (2006) 576. — 61. KUPELIAN V, PAGE ST, ARAUJO AB, TRAVISON TG, BREMNER WJ, McKINLAY JB, J Clin Endocrinol Metab, 91(3) (2006) 843. — 62. GOULD DC, KIRBY RS, AMOROSO P, Int J Clin Pract, 61(2) (2007) 341. — 63. SHAPIRO J, CHRISTIANA J, FRISHMAN WH, Am J Ther, 6(3) (1999) 167. — 64. KAUFMAN JM, VERMEULEN A, Endocr Rev, 26(6) (2005) 833. — 65. MAKINEN J, JARVISALO MJ, POLLANEN P, PERHEENTUPA A, IRJALA K, KOSKENVUO M, MAKINEN J, HUHTANIEMI I, RAITAKARI OT, J Am Coll Cardiol, 45(10) (2005) 1603. — 66. YANG YM, LY XY, HUANG WD, XU ZR, WU LJ, J ZHEJIANG, Univ Sci B, 6(9) (2005) 931. — 67. MONTALCINI T, GORGONE G, GAZZARUSO C, SESTI G, PERTICONE F, PUJIA A, Coron Artery Dis, 18(1) (2007) 9. — 68. MONTALCINI T, GORGONE G, GAZZARUSO C, SESTI G, PETRICONE F, PUJIA A, Nutr Metab Cardiovasc Dis, (2007). — 69. GOLDEN SH, MAGUIRE A, DING J, CROUSE JR, CAULEY JA, ZACUR H, SZKLO M, Am J Epidemiol, 155(5) (2002) 437. — 70. BERNINI GP, MORETTI A, SGRO M, ARGENIO GF, BARLASCINI CO, CRISTOFANI R, SALVETTI A, Menopause. 8(1) (2001) 43. — 71. PHILLIPS GB, J Clin Endocrinol Metab, 90(5) (2005) 2708. — 72. ECKARDSTEIN A, WU FC, Growth Horm IGF Res, A (2003) S72. — KAPOOR D, JONES RD, NETTLESHIP JE, JONES HT, CHANNER KS, Am J Cardiovasc Drugs, 5(3) (2005) 141.

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

S A Ž 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 krvožilnim 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.