Review Article

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Sex Hormones and Cardiovascular Diseases

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Abstract

Cardiovascular diseases (CVD) are the leading cause of mortality in men and women both in developed as well as developing countries like India with an estimate of 20 million people dying, mainly from heart disease and stroke each year as per WHO. It is well established that men tend to develop cardiovascular diseases one decade earlier as compared to females. The loss of female sex hormones after menopause contributes to the striking increase in the incidence of cardiovascular morbidity and mortality in menopausal women. The biological explanations for the gender differences underlie the importance of sex hormones. The endogenous sex hormones are testosterone, dehydroepiandrosterone sulfate, estradiol and progesterone. In this article we have discussed sex hormones and their influence on cardiovascular disease risk factors, cardiac risk and vascular function.

Keywords: Estrogen; Testosterone; CVD.

Introduction

Male sex is one of the strongest risk factors predicting the risk of cardiovascular disease with several case-control studies confirming role of one or more endogenous sex hormones related to cardiovascular disease risk in men [1,2]. In one study in white men followed for 12 years showed that testosterone levels were significantly inversely associated with levels of blood pressure, fasting plasma glucose, and triglyceride and body mass index [3]. Sex hormones of importance in men are testosterone, dihydrotestosterone, estradiol and androstenedione. Testosterone is produced in the testis, dihydrotestosterone and estradiol mainly produced in the adrenal glands and androstenedione produced by both testicles and adrenal glands [4]. Most of the Androgens and estrogens circulating is bound to serum proteins, albumin (binds 40–60% of Testosterone) and sex hormone binding globulin (binds 40–80% of Testosterone) with only 1-2% in free form. Androstenedione and DHEA are weakly bound to albumin whereas DHEA-S binds strongly to albumin [5].

Effect of Sex Hormones on Cardiovascular Risk Factors

Testosterone [6]

It has modulating effect on risk factors such as insulin resistance, obesity, hypercholesterolemia, and hypertriglyceridemia. Testosterone causes an increase in triglyceride through effect on hepatic triglyceride lipase, improve HDL-cholesterol by increasing the hepatic production of apolipoprotein A-I. In animal studies castration of male rats produced insulin resistance which was reversed after testosterone supplementation. Androgen receptors are distributed throughout the cardiovascular system including aortic, coronary, pulmonary and carotid arteries. Complex action on vascular system occurs through various receptors like vasodilatation through potassium channels and calcium antagonism whereas vasoconstriction through thromboxane

release. It may also have direct actions like vasodilatation by direct effects on vascular smooth muscle and by increasing nitric oxide (NO) synthase activity in vascular endothelium. Testosterone causes coronary, aortic, and brachial vasculature dilatation through both endothelial-dependent and independent mechanisms. In isolated rabbit coronary artery and porcine coronary myocytes testosterone has shown to cause prostaglandin I2 or cyclic GMP independent relaxation probably by altering potassium conductance and thus also implicating potassium channels in the mechanism of testosterone induced relaxation. Testosterone may also acts as a coronary vasodilator by a calcium antagonistic action. However in some studies testosterone was shown to cause vasoconstriction. In experimental studies of isolated perfused rat heart model vasoconstriction effect of testosterone was postulated due to thromboxane release which is a strong vasoconstrictor and a platelet aggregator. So any vascular effect of testosterone is likely to be a balance between vasodilatation occurring through endothelial and nonendothelial effects and vasoconstriction due to thromboxane and possibly other mediators. Testosterone also upregulates the expression of arterial androgen receptor mRNA and is associated with a significant reduction in neointimal plaque development. Testosterone may have beneficial role to influence development of atherosclerosis by inhibiting smooth muscle migration and proliferation. Androgen receptors are also present in peripheral vascular, ventricular and atrial mammalian cells and normal human megakaryocytes and platelets. Androgen receptors on the megakaryocyte lineage needs further research to assess prothrombotic effects of androgens. Androgens also have anabolic effect on cardiac myocytes responsible higher left ventricular mass in males. Adrenal androgens like Dihydroepiandrostanediones (DHEAS) may have beneficial effects through actions like prevention of platelet aggregation, inhibition of macrophage accumulation in the intima, inhibition of proliferation of smooth muscle cells from the media into the intima , interference with arterial uptake of cholesterol , suppression of superoxide radical formation, conversion of DHEA to estrogen, and binding of DHEA metabolite (androstenediol) to vacant estrogen receptors, and enhanced estrogen like effects in men [7].

A meta-analysis of 70 studies indicated that patients with CV disease demonstrated significantly lower T and higher 17-b estradiol levels, which remained significant markers after adjusting for age and body mass index.

Estrogen and Estrogen Receptors in Cardiovascular Tissue [9]

The estrogen receptor (ER), a member of the nuclear receptor super family, is associated with heat shock proteins. Estrogen binding causes conformational changes in the ER, dissociation of the heat shock protein complex and homodimerization of the receptor which then binds to specific DNA sequence. The hormone-bound ER also interacts with transcriptional coactivators. The result is a change in the level of transcription of specific genes, leading to altered messenger ribonucleic acid (mRNA) levels and the types and levels of cellular proteins. Estrogen receptors are found in myocardial, vascular smooth muscle cells (VSMC) and endothelial cells in both humans and animals. Heterogeneity of ER distribution has been noted among various vascular beds, between female and male animals, and between normal and atherosclerotic vascular beds, different phases of menstrual cycle and pre and postmenaopause. Antiatherogenic effects of estradiol are in part mediated through cardiovascular ER, and atherosclerosis is associated with diminished ER expression. Testosterone by being converted to estradiol by the enzyme aromatase in endothelial cells may attenuate early atherogenesis. Estrogen is also produced in a number of extragonadal sites like vascular endothelium, aortic smooth muscle cells and numerous other sites. Within these sites, aromatase action can generate high levels of estradiol locally without significantly affecting circulating levels. The ability of estradiol to augment basic fibroblast growth factor-induced angiogenesis is lost in transgenic mice lacking functional ER-a receptors providing strong evidence for receptor dependence. The absence of a functional estrogen receptor is associated with an impaired flow-mediated endothelium dependent peripheral vasodilatation, glucose intolerance, hyperinsulinemia, and lipid abnormalities as seen in patients with aromatase deficiency causing estrogen deficiency or estrogen receptor mutation resulting in estrogen resistance.

Biological Effects of Estradiol on Vascular Smooth Muscle Cells (VSMC) [9]

Vasodilatory effects are mediated through indirect actions exerted through the endothelium and directly through effects on VSMC. Estrogen increases nitric oxide (NO) synthase activity in the vascular endothelium and causes vasodilatation through release of NO. Increase of NO lead to increased

production of cGMP via guanylate cyclase and subsequent activation of protein kinase G, which phosphorylates and stimulates BKCa channels. Estradiol also stimulates vascular endothelial cell secretion of NO. Long term estradiol replacement was shown to improve endothelium-dependent relaxation in ovariectomized rabbits and endothelium dependent vasodilation in coronary arteries of ovariectomized monkeys. Low-dose oral estrogen in men reduces very low-density lipoprotein and LDL subclass levels. Low-dose oral estrogen also has shown to reduce fibrinogen and plasminogen activator inhibitor-1 concentrations without increasing markers of thrombotic risk. Estrogens may also limit lipid accumulation in the presence of an intact endothelium and releases NO. NO also inhibits platelet aggregation, leukocyte adhesion to endothelium, vascular smooth muscle cell migration and growth, and LDL-cholesterol oxidation. Estradiol acutely attenuates voltage-dependent T- and L-type calcium channel currents in VSMC contributing to the hyperpolarization and also causes activation of potassium (K) channels and attenuation of myocardial and vascular contractility. Antiatherogenic effects of estradiol are partially due to inhibition of VSMC growth and proliferation. Estradiol was shown to inhibit neointimal VSMC proliferation and extracellular matrix formation after balloon injury of iliac arteries of rabbits. Myointimal proliferation after balloon injury of the carotid artery in rats and the abdominal aorta of rabbits was attenuated by estradiol in experimental studies. Estradiol exerts its effects through alterations in gene expression and synthesis of proteins involved in the regulation of the VSMC cell cycle. Estradiol may also affect endothelial cell regeneration and angiogenesis. It promotes neovascularization as well as migration, proliferation, and differentiation of endothelial cells in vitro and in vivo. Estradiol enhances transcription of the genes for endothelial cell leukocyte adhesion molecules and integrins. Estradiol may also stimulate expression of endothelial growth factors such as fibroblast growth factor, vascular endothelial growth factor, and tumor necrosis factor.

Progesterone Effects on the Vasculature [9]

Like estradiol, progesterone acts by binding to a specific, high affinity receptor protein, The progesterone receptor (PR) which like the ER, is a member of the nuclear receptor superfamily of ligand-activated transcription factors. The PR exists in two forms A and B. A form is an N-terminal truncation of the B form. These two forms differentially modulate gene expression with the A form can repress the ability of the B form to activate transcription from some promoters. PR expression can be induced by estrogen, therefore the action of progesterone is generally studied in combination with estrogen. In the uterus, progesterone inhibits estrogen-induced growth, whereas in the breast, both estrogen and progesterone promote growth. The cardiovascular effects of progesterone are not clear. Progestins inhibit estradiol-induced endothelium-mediated vascular relaxation, may negate estradiol effect on intimal plaque size and cellular proliferation in atherosclerotic plaque, increase LDL and decrease HDL cholesterol levels. However Progesterone also stimulates thrombospondin-1 expression by both endothelial cells and VSMC which potentially inhibits endothelial cell adhesion, migration, proliferation, and angiogenesis. Effects of combination hormonal replacement on CAD risk experimental studies suggested that addition of a progestin to prevent potential neoplastic effects of unopposed estrogen on the endometrium, would negate some of the cardiovascular protective effects of estrogen. Estrogen replacement therapy (ERT) has shown beneficial effects on the lipoprotein profile like increase in high density lipoprotein (HDL) and decreases in low density lipoprotein (LDL) cholesterol, decrease in LDL oxidation, and lipoprotein(a) level. Though progestins raise LDL and reduce HDL cholesterol levels and attenuate vascular estrogen- induced nitric oxide (NO) production and vasorelaxation the protective effects of ERT against CAD are preserved when progestins are added. The Nurses' Health Study showed a substantial reduction in the risk of major CAD among women who used combined HRT compared with women who took estrogen alone or did not use HRT. Similarly in the PEPI trial, the combination of a progestin with estrogen did not negate the LDL-lowering effects of estrogen. Combination therapy is also associated with a lowering of fibrinogen, and no increases in either blood pressure or glucose intolerance. Plasma levels of plasminogen activator inhibitor type I were reduced to similar levels and significant increases in cross-liked fibrin partly explaining protective effects of HRT. Overall, cardiovascular protection can be maintained with appropriate combination therapy.

Summary

Due beneficial effects of testosterone on cardiovascular risk factors androgen therapy should be prescribed if male patients have both the presence of clinical symptoms and reduced testosterone levels

indicating hypogonadism avoiding supraphysiologic levels due to concerns about the effect of supplemental T on cardiac mass and blood pressure and should be monitored for hematocrit, prostate-specific antigen, and cardiac mass due to possible adverse effects like prostate carcinoma, increased hematocrit and water retention. There is a need for large-scale prospective randomized trials involving men with low serum levels of androgens to firmly establish role of androgens in the prevention and treatment of CVD. Estrogen appears to reduce the risk of CVD through a combination of effects, including changes in lipid profile, endothelial NO generation, cell proliferation and angiogenesis and regulation of VSMC Ca21 and K channel mediated through genomic and/or nongenomic mechanisms. Progesterone does not negate beneficial effects of estrogen in postmenopausal females. Estradiol-induced NO release is probably an important mechanism underlying the cardioprotective effects. The cardiovascular effects and the mechanisms underlying the biological effects of sex hormones are complex and need further investigation and studies before advocating their prophylactic use.

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