

Cardiovascular and metabolic effects of estrogen in men

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Abstract

Although in men with an inherited mutation of gene encoding ER α (estrogen resistance) the occurrence of premature coronary artery disease was documented, and in men with inherited lack of aromatase (estrogen deficiency) an unfavorable lipid milieu was reported, the predominant number of both epidemiological and interventional studies suggests that in men estrogens may either not influence or may promote the development of coronary artery disease. It is possible therefore the beneficial effect of estrogen administration on the lipid milieu in patients with estrogen deficiency is limited only to this unique situation.

There may exist a sex-specific difference in the response to estrogen action. In contrast to women where estrogens generate nitric oxide (NO) production in the vascular endothelium, they do not do so in men. NO is responsible for vascular dilation and inhibits lipoprotein oxidation and monocyte adhesion to the endothelium. There may exist also a difference between short-term, non-genomic effect of estrogen and the effects of a long-term exposition to the hormone. Several reports are available indicating that estrogen administration may have an unfavourable effect not only on blood lipid profile but also on venous thromboembolism in both sexes. In this context the role of estrogens in the regulation of the cardiovascular system gains a special importance and needs further studies.

Key words: estradiol, coronary artery disease, human male.

Introduction

Differences in the clinical course of coronary artery disease (CAD) between men and women have been observed for years. Lower incidence of CAD in premenopausal women led to conclusion that female sex hormones, including estradiol (E2) are responsible for this difference. This assumption leads to a wide use of the estrogen replacement therapy in postmenopausal women, between others to decrease the risk of CAD. Nevertheless, the results of recent studies have negatively verified this assumption [1].

Estrogens are produced by the ovary and are traditionally considered as exclusively female sex hormones. For years it has been considered that these hormones have no influence in men or induce the malfunctioning of the testes. However, it has been found that in men estrogens are produced in the testes, adipose tissue brain, adrenals, liver, breast, and hair. Daily production rate and serum concentration of E2 in men is higher than in

postmenopausal women. Even though the role of sex hormones in the pathogenesis of CAD was postulated years ago, little is known about the link between sex steroids secretion or action and CAD spectrum in men.

Why estrogens, the “female” sex hormones, are supposed to have biological and clinical significance in men?

The initial revealing that E2 may be physiologically important for male gonadal function was published at the end of the 80s [2] and was confirmed recently [3, 4]. The classical point of view considering estrogens as female hormone exclusively was changed also due to the discovery of estrogen receptors (ER) in the male. First papers on transgenic mice with ER gene deprivation (ER knock out – ERKO) or with knock out of the gene coding aromatase, necessary for conversion of testosterone to estrogen (ARKO), were published in the 90s [5]. Subsequently, the first studies on men with inherited mutations of gene encoding aromatase showed that in the human male, estrogens are mainly responsible for pubertal spurt in bone growth and epiphyseal closure after puberty, the effects that were previously attributed to the testosterone action [6]. Estrogen may contribute to the human male pathology as well. Estrogens are risk factors for prostatic cancer. Increased biosynthesis of estrogen in tissues unfavorably aggravates the cell proliferative potential in autoimmune diseases [for review see 7].

Recent data indicate a possible role of estrogens and ER in the cardiovascular system function. Two types of estrogen receptors have been discovered in men: ER α and ER β [8]. In a 31-year-old man with inherited mutation of ER α premature CAD was documented, suggesting a possible preventive role of estrogens for CAD [9]. Furthermore, as in women, also in men a nongenomic influence of estrogens on the cardiovascular system has been reported. In men with inherited mutation of ER α resulting in the lack of estrogen activity (estrogen resistancy), a rapid (within 5 minutes) relaxation of brachial artery after administration of E2 was observed pointing to nongenomic, ER-independent action of E2 [10]. This is related to the stimulation by E2 of calcium-dependent potassium channels in the vascular smooth muscles. Further parts of this paper will deal with clinical correlations to ascertain a potential role of estrogens in the pathogenesis of ischemic heart disease in men.

Estrogens and the metabolic risk factors for CAD

Lipid profile

It has been documented that physiological levels of E2 may influence serum lipoprotein concentration in healthy men [11, 12]. Nevertheless, the results of these studies are contradictory. Shono et al. [12]

demonstrated that E2 negatively correlates with the levels of low density lipoproteins fraction of cholesterol (LDL), suggesting a beneficial effect of E2. Kiel et al. [13] correlated blood E2 level with lipid profile both in healthy men and in men with angiographically confirmed CAD and showed a plausible, positive correlation between E2 level and the level of high density lipoproteins fraction of cholesterol (HDL) in both groups of men. The same study showed however, also an unfavorable (positive) correlation between the blood level of E2 and total cholesterol. Other investigators did not find any correlations between E2 and lipoprotein serum concentration in healthy men [14, 15].

In our prospective study on 111 men in the mean age of 55 years with angiographically confirmed CAD, the unfavorable correlations between E2 and total cholesterol, LDL cholesterol and triglycerides were found. Significant positive correlations between E2 blood levels and total cholesterol, LDL, total cholesterol/HDL ratio or triglycerides were present. All lipid factors are considered as important measures of atherosclerotic milieu. These correlations remained significant after adjustment for clinical covariates like age, hypertension, diabetes or prior hypertension in the multivariate logistic regression model. No associations were found between levels of the blood lipids and total testosterone or dehydroepiandrosterone sulphate (DHEAS) levels. These results indicated a possible role of E2 in the promotion of atherogenic lipid milieu development in men with CAD [16, 17].

Our studies were not in accordance with the findings based on the case reports of young men lacking E2 due to the inherited mutations of the gene encoding aromatase, where the unfavorable increased levels of LDL were associated with decreased levels of HDL [6, 18, 19]. Supplementation of E2 in these patients resulted in the normalization of lipoprotein profile [6, 19], indicating a favorable effect of estrogen. The discrepancy can be explained by the profound difference in the clinical material. Namely, while in men with inherited estrogen deficiency increased susceptibility of ER to estrogen can be present because ER is unsaturated, this unique prepubertal-like state is not present in adult men with normal secretion of E2 [17]. Thus, it seems that observations of men with inherited estrogen deficiency (due to mutation of the gene encoding aromatase), representing physiology during development, may have limited application to clinical practice that represents pathology, where estrogens are available and acts through functional ER.

Obesity and glucose levels

Overweight and obesity are well recognized risk factors for CAD in both men and women. The distribution of fatty tissue in humans shows sexual dimorphism. Females in the reproductive period of

life tend to show gynoidal distribution of adipose tissue (hips, buttock), while androidal distribution predominates in men and in postmenopausal women. The former phenotype, with predominant androidal (trunk or visceral) obesity, is related to the higher risk of diabetes, insulin resistance, CAD and breast cancer development.

The relationship between estrogen deficiency and the development of visceral obesity may arise from the findings that both in females and in males with inherited estrogen deficiency, androidal obesity with coexisting insulin resistance, hypercholesterolemia and hypertriglyceridemia were observed [18, 19]. Mendoza et al. [20, 21] showed higher E2 levels in healthy but obese men as compared to healthy men with normal body weight. These authors conclude that the profile of endogenous sex hormones observed in obese men (high E2, low testosterone and high E2/testosterone ratio) is similar to one found in young postinfarction men, suggesting a possible unfavorable role of E2, predisposing for CAD.

Coexistence of obesity and diabetes is frequent and unfavorable for cardiovascular system. Nevertheless, the results of few studies assessing a role of E2 in the metabolism of glucose are contradictory. There are data showing that in healthy men E2 levels negatively correlate with basal blood level of glucose [12], while other authors did not confirm these results. Tchernhof et al. [15] did not find any relationship between E2 and glucose level or the degree of visceral obesity (detected on the computerized tomography). Just the opposite, in men with angiographically documented CAD an unfavorable correlation between E2 and impaired glucose tolerance was observed [11].

Endogenous estrogens versus the occurrence, clinical stage and prediction of CAD in men

Higher levels of E2 and low testosterone/E2 ratio were observed in men with CAD as compared to healthy controls, appearing together with signs of metabolic syndrome [22]. In a study of Philips et al. [23, 24] higher levels of E2 in men with CAD than in healthy men were found. Girndt et al. [25] documented higher E2 levels in men with angiographically documented CAD as compared to healthy subjects. Srzednicki et al. [26] also found significantly increased E2 levels in patients with stable and unstable CAD.

Several other studies did not support the association between higher E2 and CAD. Goldberg et al. [27] and Lichtenstein et al. [28] showed that blood E2 did not differentiate healthy men and men with CAD. Hauner et al. [29] did not find any difference in E2 levels between men with angiographically documented CAD and in subjects with no coronary atherosclerosis on angiography. The lack of correlation between E2 and CAD is also supported by a study of Barrett-Connor and Khaw [30] who evaluated a cohort of over 1000 healthy men during 12 years follow up and did not find

E2 level to be predictive for CAD. Similar results based on over 10 years follow up were showed by Contoreggi et al. [31]. Our recent data revealed that although in men with CAD the variability of plasma E2 is predictive for the variability of total cholesterol, LDL and HDL/total cholesterol ratio and through this way E2 may predispose toward atherogenic lipid profile, E2 blood level is not predictive for the degree of coronary artery stenosis in men [32].

Clinical administration of estrogens to men

Chronic administration of estrogens in male-to-female transsexualism resulted in the reduction of total cholesterol, LDL and Apo-lipoproteins B levels, suggesting a plausible effects of estrogens in men [33].

The influence of E2 on vascular endothelium, causing blood vessels relaxation, indicates another plausible effect of estrogens. Chester et al. [34] observed that E2 provoked *in vitro* relaxation of coronary arteries which was less expressed in the arteries taken from men than from women. The direct effect of E2 on coronary arteries was also studied. Both relaxation and no influence were described [35, 36]. In the randomized, double-blind, placebo controlled crossover study on 30 healthy men, vasodilation was not increased by E2 administration [37]. On the other hand, intracoronary injection of E2 in men undergoing coronary angioplasty significantly attenuated vasoconstriction by reducing endothelin levels [38].

“The Coronary Drug Project” [39], a clinical study with the administration of estrogens in men with CAD after myocardial infarction, was stopped before the study was complete due to increased incidence of mortality and myocardial infarctions after estrogens as compared to controls. Similarly, in men with male-to-female transsexualism treated orally with estrogens and anti-androgens venous thrombo-embolism was found as one of the most frequent side effects [40]. Recent clinical experience based on the hormonal “replacement” therapy in postmenopausal women and studies with the administration of oral hormonal contraceptives to women showed an increase in thrombotic events related to estrogen therapy [1].

It can not be excluded, however, that there may exist a difference between the effects of long-term estrogen therapy, which may represent unfavorable effects of estrogen [1, 39, 40] and the effects of short term estrogen administration, that may account for non-genomic stimulation of vascular dilation [34, 35, 38].

Much less is known about the influence of estrogen therapy in men on the risk factors of CAD, that are other than lipids. It was observed that estrogen administration to men results in a decrease in homocystein level [41, 42]. In turn, a favorable effect of estrogen treatment on procoagulation activity in a human male was also shown. A decrease in the inhibitor of plasminogen activation and fibrinogen levels as well as a decrease in platelet activating factor activity were seen after estrogen treatment [42].

Sex-specific differences in estrogen influence on vascular endothelium

In 2003 Gong et al. [43] showed that in contrast to women where estrogens generate nitric oxide (NO) production in the vascular endothelium, they do not do so in men. NO is responsible for vascular dilation and inhibits lipoprotein oxidation, monocyte adhesion to the endothelium, as well as production of the inflammation mediators. All these mechanisms of NO action prevent development of arteriosclerosis. Endothelial NO synthase (eNOS) is stimulated by HDL. However, according to Gong et al. [43] eNOS is stimulated only by HDL separated from females. Female HDL is a carrier of E2 and acts together with E2 in the vascular endothelium stimulating eNOS through HDL receptor, called scavenger receptor class B type I, localised in the sinuses of vascular endothelium. As HDL separated from males is not a carrier of E2 it does not stimulate eNOS in men. This difference may explain the lack of the relaxation effect of estrogen administration on coronary blood vessels [36, 37] or lack of correlations between blood E2 concentration and the severity of CAD spectrum in men [27-32].

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