Serum sex hormones in premenopausal women with coronary heart disease

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Key words: sex hormones; coronary heart disease; serum lipoprotein; premenopausal women

Abstract

OBJECTIVES: The objectives of this study were to investigate the relationship between the incidence of coronary heart diseases in premenopausal women and plasma level of total and free testosterone, estrogen, androstenedione and sex hormone binding globulin with coronary risk factors: fasting plasma concentration of glucose, triglyceride, total cholesterol, and low density lipoproteins.

METHODS: The study was conducted in Faculty of Medicine, Jordanian University of Science/Irbid Jordan and Technology and department of cardiology in Queen Alia Heart Institute /Amman Jordan during the period from April 2003 to March 2004. Serum sex hormones levels were measured in fifty-three premenopausal women; 25 women with coronary heart disease who had hypertension and / or diabetes mellitus and 28 women without coronary heart disease. Ages ranged from 34 to 48 years. Blood samples were collected just before performing coronary angiography and serum was obtained and frozen at –70 °C until use.

RESULTS: We found that the mean triglyceride, fasting blood sugar total cholesterol, and low density lipoprotein concentration were significantly higher in coronary heart disease patients than in patients with normal coronaries. We also found that the low levels of sex hormone binding globulin and high levels of free testosterone are associated with development of coronary heart disease. No significant correlation could be established between other plasma sex hormones level and coronary heart disease.

CONCLUSION: In young women, in the presence of coronary risk factors and normal level of serum estrogen, the high levels of serum free testosterone and low levels of serum sex hormone binding globulin are associated with development of atherosclerosis and increased incidence of coronary heart disease.

Key words: sex hormones; coronary heart disease; serum lipoprotein; premenopausal women
Introduction

Increased risk for myocardial infarction in men more than in women is related to differences in unhealthy behavior more than inherent sex differences in physiology [1,2]. These behaviors include smoking, eating more red meat, heavy alcohol and physical hazard. Results from the Framingham studies [3,4] found that low-level work (e.g. clerical jobs, with subordinate status) and limited education were associated with an increased risk for myocardial infarction in women. While Barrett-Conner observed that the incidence of cardiovascular disease differs significantly between men and women, in part because of differences in risk factors and hormones [5]. The protective effect of estrogen in cardiovascular disease remains controversial. Several studies on the estrogen therapy in postmenopausal women have provided inconsistent results. Some studies of hormone replacement therapy in postmenopausal women showed a reduction in risk of coronary heart disease in women using oral estrogen [6–8]. While other studies showed opposite effect [9–11]. Recently, Herrington et al [12] showed that estrogen although produced significant reduction in low-density lipoprotein (LDL) and significant increases in high-density lipoprotein (HDL) but it did not affect the progression of coronary atherosclerosis in women with angiographically vitrified coronary disease. On the other hand, the incidence of ischemic heart is uncommon in premenopausal women and this is attributed to the abundance of the endogenous ovarian hormones specially estrogen [13]. The atheroprotective effects of estrogen are mainly by its direct action on blood vessel [14,15]. Estrogen increases vasodilatation and inhibits the response of blood vessels to injury and the development of atherosclerosis [8]. Estrogen produces acute vasodilatation in healthy post menopausal but not in patients with vascular dysfunction who have, hypertension, diabetes, and atherosclerosis [16,17]. Also estrogens have numerous actions on many systems that could influence the risk for coronary heart disease. These actions include lipid metabolism, Carbohydrate metabolism, coagulation parameters and blood pressure [18,19]. Between 25% and 50% of the beneficial effect of estrogen in reducing coronary heart disease (CHD) development is through changes in lipoprotein mainly cholesterol, HDL and LDL [20, 21]. Estrogen, particularly when taken orally, lowers the levels LDL and raises those of HDL [22].

Although the average age of menopause is about 50 years, still many young women can have coronary artery disease [23]. The effect of endogenous sex hormones level on the development and presentation of coronary artery disease has been less examined than the effect of hormonal use after menopause. However the nurse's health study conducted on more than 35000 menopausal women showed that early natural menopause was not a risk factor for cardiovascular disease [24].

The aim of this study is to explore the relationship of endogenous sex hormones levels to the development of coronary ischemic heart disease in young women. These hormones include estrogen, total testosterone, free testosterone and androstenedione. Also we look at the level of serum total cholesterol, HDL, LDL and triglyceride, and glucose level in the presence or absence of coronary artery disease risk factors, i.e. hypertension and diabetes mellitus. All those values are compared to the values obtained from control group of young women with normal coronary arteries.

Methods

Study population

Premenopausal women with normal regular menses presenting with episodes of chest pain were included in this study. Fifty-three patients were admitted to the department of cardiology in Queen Alia Heart Institute for diagnostic coronary angiography. Twenty five women, aged from 34 to 48 (mean, 43.3; SD±4.2) years, have demonstrated stenosis of one or several coronary arteries by over 70% on coronary angiography. This group is designated women with coronary heart disease (CHD). Of this group, 18 women (72%) had both hypertension and diabetes mellitus, 5 women (20%) had diabetes mellitus alone and 2women (8%) had only hypertension.

Twenty eight women aged 35 to 48 (mean, 43.8; SD±4.1) years failed on coronary angiography to demonstrate significant changes in the coronary arteries. This group is designated women with normal coronaryography (NC). Four women of this group (14%) had only diabetes mellitus. These patients admitted for cardiac catheterization because of frequent attack of chest pain without significant ECG changes and found to have normal coronaries and they were considered as control group. None of the women included in this study reported drinking alcohol or using contraceptives. All had normal renal, hepatic and thyroid function.

Cardiac catheterization procedure

All patients had left heart catheterization and coronary angiography performed from femoral approach. Coronary artery disease was defined when there was more than 70% diameter stenosis in one or more of the major coronary artery as assessed by quantitative angiography. For each artery the view showing the most severe degree of stenosis was used for analysis. Patients with valvular heart disease, congenital heart disease were excluded from the study.

Analysis of blood samples

Blood samples were taken after fasting 14 hours and before coronary angiographic procedure for determinations of lipoproteins, fasting blood glucose and sex hormones (including total and free testosterone, estrogen, androstenedione and sex hormone binding globulin).

Blood samples were withdrawn from all subjects between 8 and 9 am. Serum samples for determination hormones were frozen at −70 °C until analyzed. Androstenedione, estrogen, both total and free testosterone were quantified using coat – a-count radioimmunoassay.
kits. Sex hormone binding globulin was analyzed using immunoradiometric assay (IRMA) – count kits. All kits were purchased from diagnostic products corporation, Los Angeles, CA. Blood samples were collected in 0.1% EDTA tubes, centrifuged for 20 minutes at 1000 × g at 4°C to obtain plasma for assessment lipid profile and blood glucose.

Statistical analysis
Data are expressed as mean ±SD. Significant test were carried out using one-way ANOVA and unpaired student t-test for inter group analyses. Statistical significance was defined as a P values less than 0.05.

Results
The characteristics of the two groups of study participants are shown in Table 1. Women in the two groups had similar mean age and other anthropometric measures. No significant difference was seen between the two groups regarding age, height, weight and body mass index (BMI). BMI in both groups was high in both groups (< 30 kg/m²). Table 2 shows plasma lipid profile and serum hormones concentration in both groups. Triglyceride, total cholesterol and LDL concentrations in women with CHD were significantly higher than in NC patients. Although plasma HDL levels tended to be higher in women with NC but this difference was not statistically significant. Serum hormones levels showed that women with CHD compared with those of women with NC have higher free testosterone and lower sex hormone binding globulin (SHBG). There were no significant differences between the two groups of women in relation to estradiol, androstenedione and total testosterone.

Discussion
Women before menopause have a significantly lower incidence of CHD than men of similar age [25]. If the main risk factors for CHD; hypertension, smoking, obesity, diabetes, and hyperlipidemia are controlled for gender, then the most obvious cause for this finding is the difference in sex hormone pattern in men and women. The hypothesis that endogenous ovarian hormones offer a protective effect on the development of CHD is supported by epidemiological study that shows women suffer coronary heart disease 10 to 20 years later than men [26]. In female, sex hormones mainly estrogen has specific effects on cardiovascular system, particularly the vasculature. It is clear that estrogen reduces atherosclero-

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<th>Table 1: Characteristics of women participated in the study</th>
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<td><strong>Women with CHD</strong></td>
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<td>(n=25)</td>
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<tr>
<td>Age (yr)</td>
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<td>Height (cm)</td>
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All values are mean ±SD

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<th>Table 2: Fasting blood sugar, lipid profile and serum hormones in women with coronary stenosis (CHD), and in women with normal coronaries (NC).</th>
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<td><strong>Women with CHD</strong></td>
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<td>(n=25)</td>
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<tr>
<td>Fasting blood glucose (mg/dl)</td>
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<td>Triglyceride (mg/dl)</td>
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<td>Total cholesterol (mg/dl)</td>
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<td>Androstenedione (ng/ mL)</td>
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<td>Sex hormone-binding globulin(nmol/L)</td>
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All values are mean ±SD
sis through lipoprotein metabolism, which is responsible for up to 40% of the cardiovascular protection exerted by the estrogen [27]. Estrogen is also a vasodilator and hypotensive agent, which can induce vascular relaxation by stimulating release of endothelium-derived vasodilatory substances (e.g., nitric oxide [NO]) or by acting directly on the vascular smooth muscle [28]. In addition, some beneficial action of estrogen is mediated through the estrogen receptors [29]. In spite of the beneficial effects of estrogen on the vasculature, the clinical trials have shown that hormone replacement therapy neither reduces the risk of coronary disease in postmenopausal women [30] nor affects the progression of coronary atherosclerosis in women with established disease [12]. The protective effects of estrogen seemed to be mainly on healthy blood vessels and not in the presence of atherosclerosis [31]. Estrogen therapy has no beneficial effect in the treatment of unstable angina [32]. Many studies have found low level of endogenous estrogen in premenopausal [33] and postmenopausal [34] women with CHD compared with control women. Also there were more frequent episodes of myocardial ischemia associated with low endogenous estrogen [35] and post exercise myocardial ischemia was more easily induced when estrogen concentration was low [36]. In this study we found no significant differences in estrogen level between the two groups of women. 72% of women in CHD group have diabetes mellitus and hypertension. So it seems that normal level of estrogen (Table 2) in CHD group does not protect coronary vessels. These findings demonstrate that in premenopausal women with normal concentration of estrogen, stenosis of one or more coronary arteries can develop in the presence of risk factors for ischemic heart disease i.e. hypertension and/or diabetes mellitus. This was also reported in postmenopausal women by Barrett-Connor and Goodman-Gruen [37].

Few studies with no conclusive results have investigated the relationship between endogenous levels of androgens and CHD. Free testosterone and androstenedione concentration did not differ significantly in 651 women with or without history of heart disease and did not predict death from ischemic heart disease during subsequent 19 years [37]. In contrast, serum levels of free testosterone were correlated with the maximum percentage reduction of the luminal diameter of coronary arteries in postmenopausal women with chest pain. This correlation was independent of age, BMI, systolic blood pressure, smoking, or levels of cholesterol, insulin, and estradiol [38]. However, Bernini et al found that higher free testosterone and androstenedione within the physiological range had been correlated with less carotid artery atherosclerosis in premenopausal and postmenopausal women [39]. In this study we found that free testosterone levels were significantly higher in women with CHD compared with women with NC. This finding is in agreement with the findings of Sutton-Tyrrell et al in 3297 premenopausal and perimenopausal multiethnic women [40] and in postmenopausal women [41]. The high free testosterone levels could be a risk factor for coronary atherosclerosis in our premenopausal women as in postmenopausal women [38].

High serum levels of triglyceride and LDL are known risk factors for ischemic heart disease. CHD group, compared with NC group, had higher serum levels of Cholesterol, LDL. This lipid profile can not attributed to change in sex hormones serum level since such profile is more to fit with low estrogen level [42] and with administration of exogenous anabolic androgen [43] and also such lipid profile is not associated with low serum levels of SHBG [41]. A major limitation of our study is that the hormone levels were not measured at fixed day of menstrual cycle. Although the hormones assessments were done during follicular phase, nevertheless there may be some fluctuations in the levels of ovarian hormones during different days of follicular phase of menstrual cycle.

**Conclusion**

Through multiple mechanisms estrogen has beneficial effects on cardiovascular system through multifactorial mechanisms including effects on serum lipoprotein, NO, smooth muscle calcium homeostasis and specific binding receptors. Our study showed that these effects act mainly in healthy coronary blood vessels but not in the presence of risk factors (hypertension, diabetes, hyperlipidemia) and CHD. We also found that CHD develop in the presence of low SHBG and high free testosterone and this could explain the possible role of these hormones in the development of atherosclerosis in young women.

**REFERENCES**


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