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Sex hormone ratio changes in men and postmenopausal women with coronary artery disease

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Abstract

Objective: The goal of this study was to investigate the potential role of sex hormones in coronary atherosclerosis in both men and postmenopausal women.

Design: A total of 258 male and 236 female postmenopausal participants with angiographically defined stable coronary artery disease (CAD) were enrolled. We measured the levels of estradiol (E_2), progesterone (P), testosterone (T), follicle-stimulating hormone, and luteinizing hormone in the participants and in 156 male and 132 female disease-free and age-matched controls using commercially available radioimmunoassay kits.

Results: In the male study participants and control subjects, the levels of E_2 and P differed slightly in opposing directions; however, these differences were not significantly different, nor were there significant differences in T. However, the ratio of E_2 to P in participants was significantly ($P < 0.01$) lower (even after adjustments for age and body mass index) than in the control subjects (mean ± SEM: 70.2 ± 56.4 vs 90.7 ± 59.5, respectively). In the postmenopausal women, a slight decrease in E_2 and increases in P and T in participants were not significantly different from levels in the control group. However, the E_2 to P and E_2 to T ratios were significantly ($P < 0.01$) lower (before and after adjustments for age and body mass index adjustments) in the participants relative to the control subjects (38.7 ± 28.4 vs 49.6 ± 36.3 and 46.5 ± 37.6 vs 60.6 ± 40.8, respectively). Correlation analyses demonstrated that the sex hormone ratio changes in both men and postmenopausal women were related with atherogenic blood lipoprotein changes. In both the male and female groups, levels of follicle-stimulating hormone and luteinizing hormone did not differ significantly between the participants and controls, and correlation analyses revealed no association between these hormones and the ratio of E_2 to P in males and the ratios of E_2 to P and E_2 to T in females ($r < 0.2$, $P > 0.05$). Multiple regression analyses demonstrated that age and the presence of CAD were significantly and independently associated with the E_2-to-P ratio in men and the E_2-to-P and E_2-to-T ratios in women and that E_2-to-P ratio and low-density lipoprotein cholesterol level were significant independent predictors of CAD in males; E_2-to-P and E_2-to-T ratios and low-density lipoprotein cholesterol level were significant predictors of CAD in women.

Conclusions: In both men and postmenopausal women with angiographic CAD, there were significant differences (relative to age-matched control subjects) in sex hormone ratios, suggesting an abnormality that could influence coronary health. A lower E_2-to-P ratio may be associated with the male disposition to coronary atherosclerosis, whereas lower E_2-to-P and E_2-to-T ratios may be associated with the same condition in females.

Key Words: Estrogen – Testosterone – Progesterone – Coronary atherosclerosis.

Coronary artery disease (CAD) is a leading cause of death among both men and women in most industrialized countries. Premenopausal women have a far lower incidence of CAD than men of the same age. After menopause, however, the incidence in women increases rapidly and approaches that in men. The timing of this change suggests that alterations of sex hormone levels and/or ratios may play a key role in the development of the disease.[1,2]

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Estrogen, a major sex hormone for females, was previously believed to play a central role in atheroprotection. Numerous in vitro and in vivo studies have identified at least a dozen estrogen effects that would be expected to prevent or delay CAD.[3-5] However, recent clinical trials have failed to demonstrate any beneficial effects of hormone therapy with estrogen and progestin when these were administered for the primary and secondary prevention of CAD in postmenopausal women.[6-8] In the majority of observational studies, unopposed estrogen was used, whereas clinical trials such as the Heart and Estrogen/progestin Replacement Study and Women's Health Initiative used a combination of estrogen and progestin. Although the role of progestin remains poorly defined according to data until now,[9] it is possible that progestin may have some influence on the cardiovascular effect of estrogen. However, the primary focus of studies investigating the role of sex hormones on CAD has been limited to estrogen. The role played by another female sex hormone, progesterone, especially its influence on estrogen, has been mostly overlooked.

In the case of the male hormone androgen, observational data suggest testosterone levels are associated with atherogenic profiles in lipid metabolism.[10] Although male gender is believed to be one of the classic risk factors for CAD,[11] some investigators have reported, for example, that testosterone may have some beneficial cardiovascular effects, such as inhibiting the calcium channel of smooth muscle cells and suppressing activation of proinflammatory cytokines.[12,13] The vascular properties of the principal mammalian androgen testosterone are complex, and the precise role it plays in atherosclerosis remains unclear.

We conducted a study to investigate the potential role of sex hormones in the development of coronary atherosclerosis. Our results showed both men and postmenopausal women with CAD had significant differences in sex hormone ratios when compared to age-matched control subjects.

METHODS

Participants

The participants were enrolled prospectively in the study as follows: (1) The male participant group consisted of 258 individuals undergoing clinically ordered coronary angiography for suspected ischemia (but without unstable myocardial ischemia) who had at least one atherosclerotic luminal narrowing (>50% diameter stenosis) on angiography. The male control group consisted of 156 age-matched healthy participants who, after a complete medical history and physical examination before the investigation, indicated no history of CAD and had a normal electrocardiogram. (2) The female participant group included 236 postmenopausal women with stable angina pectoris who had no menstrual period for at least 1 year and had one or more atherosclerotic luminal narrowings on angiography. The female control group included 132 age-matched healthy postmenopausal women who had no history of CAD and also had a normal electrocardiogram. Written informed consent was obtained from all participants before entry into the study, and the study protocol was approved by the institutional review committee of the University of Shandong. Exclusion criteria included chronic hepatic, renal, or endocrine diseases and a recent history of taking medication that influenced sex hormones or plasma lipid levels. Furthermore, because diseases such as hypertension and diabetes mellitus were reported to promote abnormal sex hormone levels,[14-16] participants with these conditions were also excluded from the study.

Sex hormone and lipoprotein analyses

Blood samples were drawn with the subject at rest from a large antecubital vein at 7 AM after overnight fasting and were immediately centrifuged for 20 minutes at 4°C. The serum was separated into aliquots and stored at −80°C before analysis. Estradiol (E_2), progesterone (P), testosterone (T), follicle-stimulating hormone (FSH), and luteinizing hormone (LH) concentrations were determined by their specific immunoassays (Diagnostic Products Corp, Los Angeles, CA) according to the manufacturer's instructions. Total cholesterol, low-density lipoprotein cholesterol (LDL-C), high-density lipoprotein cholesterol (HDL-C), and triglyceride concentrations were determined by conventional enzymatic methods.

Data analyses

Means with their SEM values of baseline characteristics were presented for the participant group and control group. Differences between the participant and control groups were tested using the independent Student's *t* test for continuous data. The frequency of current smokers in the participant and control groups was compared with a standard χ^2 test. Ratios of E_2 to P and E_2 to T were calculated for each participant and control subject. Concentrations of sex hormones and the ratios of E_2 to P and E_2 to T were logarithmically transformed to produce approximately normal distributions. To make the results easily interpretable, the means were transformed back to their original scale, resulting in geometric means. Geometric mean levels were calculated for each sex hormone (FSH, LH, E_2, P, T) and the E_2-to-P and E_2-to-T ratios. Comparisons of sex hormone levels and the ratios of E_2 to P and E_2 to T between the participant and control groups were performed using the independent *t* test. Correlation analyses were performed to investigate the association between the sex hormone ratios of E_2 to P and E_2 to T and blood lipoprotein levels and to determine whether the changes in E_2/P and E_2/T were thalamic in origin. Stepwise multiple regression analysis was used to identify the independent determinants of the sex hormone ratios, and stepwise logistic regression analysis was used to model CAD as a function of the sex hormone ratios and other cardiovascular risk factors. All analyses were

TABLE 1. *Clinical characteristics of study participants*

Variable	Men			Postmenopausal women		
	Participant	Control	*P*	Participant	Control	*P*
No. of participants	258	156		236	132	
Age (y)	61.5 ± 9.84	61.3 ± 11.2	NS	64.7 ± 7.5	62.4 ± 6.8	NS
Time since menopause (y)	–	–	–	12.1 ± 6.3	11.8 ± 7.2	NS
Current smoker (%)	25	21	NS	8	6	NS
Body mass index (kg/m^2)	25.1 ± 2.4	23.8 ± 1.76	NS	24.9 ± 2.4	23.6 ± 2.5	NS
Total cholesterol (mg/dL)	198 ± 36	177 ± 32	<0.01	195 ± 38	175 ± 34	<0.01
LDL-C (mg/dL)	126 ± 30	107 ± 26	<0.01	134 ± 29	110 ± 27	<0.01
HDL-C (mg/dL)	40 ± 10	49 ± 11	<0.05	42 ± 11	50 ± 12	<0.05
Trigycerides (mg/dL)	127 ± 53	121 ± 50	NS	130 ± 55	128 ± 56	NS

Data are mean ± SEM or percentage. NS, not significant ($P > 0.05$); LDL-C, low-density lipoprotein cholesterol; HDL-C, high-density lipoprotein cholesterol.

performed using SAS software (version 6.12). A P value of 0.05 or less was considered statistically significant (two sided).

RESULTS

Both men and postmenopausal women tended to have a slightly higher body mass index (BMI) and smoking rate than the control subjects, although the differences were not significant (Table 1). Participants had significantly higher total cholesterol and LDL-C levels. HDL-C levels were significantly lower in the participant groups.

In male participants, levels of FSH, LH, and P were somewhat higher than in the control subjects, whereas E_2 and T were lower, although none of these differences were significant (Table 2). P and T were higher in female participants, and FSH, LH, and E_2 were lower, although, as in men, these differences were not significant. Accordingly, the ratios of E_2 to P in both male and female participant groups were significantly lower than in the control groups. In postmenopausal women, the E_2-to-T ratio was also significantly lower in participants; the ratio was not significantly different in men. Significant differences between the participant and control groups were still present after adjustment was made for age and BMI (data not shown).

Correlation analyses were performed to investigate the relationship between sex hormone ratios and blood lipoprotein levels. In men, significant negative correlations were found between the E_2-to-P ratio and total cholesterol ($r = -0.47$, $P < 0.01$) and LDL-C ($r = -0.60$, $P < 0.05$) levels. A moderate positive correlation was found between the E_2-to-P ratio and HDL-C level ($r = 0.35$, $P < 0.05$). In postmenopausal women, significant negative correlations were found between both the E_2-to-P and E_2-to-T ratios and total cholesterol (E_2-to-P ratio: $r = -0.45$, $P < 0.01$; E_2-to-T ratio: $r = -0.37$, $P < 0.05$) and LDL-C (E_2-to-P ratio: $r = -0.62$, $P < 0.01$; E_2-to-T ratio: $r = 0.51$, $P < 0.01$) levels and positive correlations were found between these ratios and HDL-C level (E_2-to-P ratio: $r = 0.38$, $P < 0.05$; E_2-to-T ratio: $r = 0.40$, $P < 0.05$). Correlation analyses demonstrated no relationship between FSH and LH levels and the E_2-to-P ratio in men, as well as E_2-to-P and E_2-to-T ratios in postmenopausal women ($r < 0.2$, $P > 0.05$).

Independent variables initially included in the multivariate model to predict sex hormone imbalance were age, BMI, blood lipids, smoking, and the presence or absence of CAD. In men, only age ($P < 0.01$, regression coefficient = 0.0062, adjusted $R^2 = 0.027$) and the presence of CAD ($P < 0.05$, −0.046, 0.010) were significant predictors of the log-transformed E_2-to-P ratio after the model was reduced through stepwise regression. In postmenopausal women, age (E_2-to-P ratio: $P < 0.01$, 0.0058, 0.026; E_2/T ratio: $P < 0.01$, 0.006, 0.021) and the presence of CAD (E_2-to-P ratio: $P < 0.01$, −0.031, 0.014; E_2-to-T ratio: $P < 0.01$, −0.027, 0.012) also showed significant and independent associations with the log-transformed E_2-to-P and E_2-to-T ratios. In a separate multivariate model to predict CAD, age, time since menopause (in postmenopausal women), BMI, current smoking, blood lipids, and sex hormones and their ratios

TABLE 2. *Sex hormone levels in study participants*

Variable	Men			Postmenopausal women		
	Participant	Control	*P*	Participant	Control	*P*
FSH (mIU/mL)	14.2 ± 8.1	13.5 ± 7.7	NS	65.5 ± 26.2	66.7 ± 24.3	NS
LH (mIU/mL)	11.2 ± 6.1	10.7 ± 5.8	NS	42.7 ± 20.5	45.6 ± 20.2	NS
E_2 (pg/mL)	85.6 ± 43.7	92.7 ± 35.2	NS	52.7 ± 35.8	58.2 ± 34.5	NS
P (ng/mL)	1.48 ± 1.14	1.27 ± 1.06	NS	1.5 ± 1.02	1.29 ± 0.93	NS
T (ng/mL)	7.32 ± 2.96	7.4 ± 1.92	NS	1.12 ± 0.87	0.95 ± 0.61	NS
E_2-to-P ratio (×1,000)	70.2 ± 56.4	90.7 ± 59.5	<0.01	38.7 ± 28.4	49.6 ± 36.3	<0.01
E_2-to-T ratio (×1,000)	12.5 ± 7.8	13.1 ± 7.6	NS	46.5 ± 37.6	60.6 ± 40.8	<0.01

Data are mean ± SEM. NS, not significant ($P > 0.05$); FSH, follicle-stimulating hormone; LH, luteinizing hormone; E_2, estradiol; P, progesterone; T, testosterone.

TABLE 3. *Significant predictors of coronary artery disease*

	Men			Postmenopausal women		
	OR	CI	*P*	OR	CI	*P*
E_2-to-P ratio	5.4	2.1-16.7	<0.01	5.7	1.8-17.4	<0.01
E_2-to-T ratio	–	–	–	4.6	1.56-15.8	<0.01
LDL-C	4.8	1.69-17.2	<0.01	5.1	2.2-16.4	<0.01

R^2 = 0.42 in men; R^2 = 0.46 in postmenopausal women. OR, odds ratio; E_2, estradiol; P, progesterone; T, testosterone; LDL-C, low-density lipoprotein cholesterol.

were evaluated initially. In men, E_2-to-P ratio and LDL-C were the only remaining significant predictors after the model was reduced through stepwise logistic regression; E_2-to-P and E_2-to-T ratios and LDL-C were the only remaining significant predictors in postmenopausal women (Table 3).

DISCUSSION

We measured and compared the levels of serum E_2, P, T, FSH, and LH levels in men and postmenopausal women with angiographically proven CAD and age-matched control subjects with no clinical evidence of atherosclerosis. Our main observations were as follows: (1) There were significant differences in sex hormone ratios in both men and postmenopausal women with angiographically proven CAD. The ratio of E_2 to P in the male CAD group was significantly lower than in the control group; in the case of postmenopausal women, the ratios of both E_2 to P and E_2 to T were significantly lower in the CAD group. The differences were still significant after adjustments for confounding variables. (2) In both men and postmenopausal women, the sex hormone ratio changes were associated with atherogenic profiles in lipid metabolism and especially highly related with LDL-C level. (3) Age and the presence of CAD were significant independent variables in determining the E_2-to-P ratio in men as well as the E_2-to-P and E_2-to-T ratios in postmenopausal women. The E_2-to-P ratio and LDL-C were significant independent predictors of CAD in men, and the ratios of E_2-to-P and E_2-to-T, as well as LDL-C, were significant predictors of CAD in postmenopausal women. (4) The sex hormone ratio changes were not thalamic in origin. No significant correlation was found between FSH and LH levels and the E_2-to-P ratio or the E_2-to-P and E_2-to-T ratios in men and women, respectively.

Estrogen is widely regarded as protective against atherosclerosis. The beneficial effects induced by estrogen are well described and include reductions in LDL, lipoprotein (a), plasma fibrinogen and plasminogen activator inhibitor activity, an increase in HDL, decreased LDL oxidation, enhanced glucose metabolism, and enhanced insulin sensitivity.[17-19] In the arterial wall, estrogen increases nitric oxide synthase activity and the secretion of nitric oxide, inhibits the secretion of endothelin-1, and decreases calcification and the secretion of a number of inflammatory cytokines, including fibroblast growth factor, intercellular adhesion molecule, and vascular cell adhesion molecule; estrogen reduces atherosclerosis itself in animal models.[20-22]

The effects of progesterone often counter those of estrogen in multiple physiological systems, including cardiovascular health. Progesterone can down-regulate the E_2 receptor in the arterial wall. In plasma, under the influence of progesterone, LDL levels are increased as a result of the down-regulation of LDL receptor activity, HDL levels decrease in association with increased hepatic lipase activity, LDL oxidation is enhanced, and plasma levels of glucose, insulin, and fibrinogen tend to increase.[23,24] In addition, it has been reported that progesterone is antagonistic to estrogen effects in nitric oxide formation and arterial vasodialation.[25] In animal models, combined progesterone/estrogen treatment is associated with reduced protection against arterial atherosclerosis.[26]

The effects of testosterone on cardiovascular health are complex and gender specific. Under the influence of testosterone, beneficial, neutral, and detrimental effects on vascular reactivity have been observed. Testosterone influences cardiovascular risk factors by decreasing serum levels of HDL-C, plasminogen activator type 1 (apparently deleterious), lipoprotein (a), fibrinogen, insulin, and leptin (apparently beneficial). Relative to macrophage function, testosterone exerts proatherogenic effects by facilitating the uptake of modified lipoproteins and an antiatherogenic effect by stimulating efflux of cellular cholesterol to HDL.[27,28] Bruck et al[29] demonstrated that in castrated male and female rabbits fed an atherogenic diet, testosterone treatment increased plaque size in female but not male rabbits. Similarly, in female ovariectomized cynomolgus monkeys fed an atherogenic diet for 24 months, the extent of coronary atherosclerosis doubled in the testosterone-treated group compared with the intact and untreated ovariectomized controls.[30] Data from clinical studies have not shown an association between endogenous testosterone levels and coronary events in men. Although some studies have reported lower levels of testosterone in male participants with CAD compared to healthy control subjects, others have found no difference.[31-34] In women, however, observational studies indicate that androgen replacement may exacerbate existing hypertension, increase the risk of cardiovascular events, or promote atherogenesis; women with polycystic ovarian syndrome have high endogenous T levels and potentially increased CAD risk.[35,36]

In our study, however, individual sex hormone levels did not differ significantly between the participants with angiographic CAD and control subjects in both genders. However, the E_2-to-P ratio in men and E_2-to-P and E_2-to-T ratios in

women differed significantly according to the status of the coronary atherosclerosis. These findings demonstrate, for the first time, the potential significance of the proportion of estrogen to progesterone in men and the proportions of estrogen to progesterone and androgen in postmenopausal women as novel markers for atherogenicity.

Although some observations have been made on the relationship between sex hormones and atherosclerosis, most of these are anecdotal or are derived from small-scale clinical studies with limited information on the effects in women. One of the potential confounding factors in some earlier studies was the inclusion of participants with hypertension or diabetes mellitus, which have been reported to contribute to abnormal sex hormone levels.[14-16] In the current investigation, which to our knowledge is the largest prospective study that included both men and postmenopausal women simultaneously, participants with hypertension or diabetes mellitus were excluded, thus eliminating the influence of those diseases. Based on the results of this study and relying on accumulated knowledge of the effects of sex hormones on the cardiovascular system, we hypothesize that the functions of hormone-secreting glands decrease gradually with age, and during this process, fluctuations in sex hormone levels disrupt normal hormone ratios, especially estrogen to progesterone and estrogen to androgen, which may exert a detrimental effect on lipid metabolism and cause adverse effects on cardiovascular health, even in situations where individual sex hormone levels do not appear to be significantly affected. It is possible that progesterone is atherogenic in men and both progesterone and androgen are atherogenic in postmenopausal women. However, levels of peripheral E_2 may ameliorate the atherogenicity, possibly as a result of the antagonistic or synergistic interactions among sex hormones. In light of data that indicate no benefit of the estrogen/progestin combination in preventing cardiovascular events in the Heart and Estrogen/progestin Replacement Study and the Women's Health Initiative, it may be prudent to consider the impact of the use of progestin and changes to the estrogen-to-progestin ratio.

Correlation analysis of the data obtained in this study demonstrated no relationship between FSH or LH levels and the E_2-to-P ratio in men, as well as the E_2-to-P and E_2-to-T ratios in postmenopausal women. This suggests the abnormal ratios of sex hormones in all study participants are not thalamic in origin. It is known that FSH and LH levels are controlled by gonadotropin-releasing hormone which can also directly control the secretion of estrogen, progesterone, and androgen. Secretion of ganadotropin-releasing hormone is influenced by several neurochemical factors, including dopamine, norepinephrine, and even the cerebral cortex; it is therefore possible that nervous system disruptions might influence the proportion of sex hormones. Furthermore, the genesis of sex hormones can be directly affected in several ways. For example, cell culture studies have shown that high doses of prolactin can inhibit progesterone production by corpus luteum cells.[37,38] It is apparent that, given the influence that multiple factors can have on sex hormone production, additional research will be necessary to identify and understand the control mechanisms behind hormone levels and overall sex hormone balance.

CONCLUSIONS

In conclusion, significant differences in sex hormone ratios were detected in both male and postmenopausal female participants with angiographically proven CAD. Correcting these changes might be beneficial in the prevention and/or treatment of CAD; however, additional research is needed to verify the results reported here. Also, in this study, we could not determine whether altered sex hormone ratios cause or are the results of CAD; only an association was supported. Thus, further longitudinal studies should be done to define the temporal relationships between the sex hormone ratios and CAD.

REFERENCES

1. Barrett-Connor E, Grady D. Hormone replacement therapy, heart disease and other considerations. *Annu Rev Public Health* 1998;19: 55-72.
2. Kannel WB, Hortland MC, McNamara PM, Gordon T. Menopause and the risk of cardiovascular disease. The Framingham Study. *Ann Intern Med* 1976;85:447-452.
3. Subbiah MT. Mechanisms of cardioprotection by estrogens. *Proc Soc Exp Biol Med* 1998;217:23-29.
4. Mendelsohn ME, Karas RH. The protective effects of estrogen on the cardiovascular system. *N Engl J Med* 1999;340:1801-1811.
5. Merz C, Johnson BD, Sharaf BL, et al. Hypoestrogenemia of hypothalamic origin and coronary artery disease in premenopausal women: a report from the NHLBI-sponsored WISE study. *J Am Coll Cardiol* 2003;41:413-419.
6. Writing Group for the Women's Health Initiative Investigators. Risks and benefits of estrogen plus progestin in healthy postmenopausal women. *JAMA* 2002;288:321-333.
7. Grady D. Cardiovascular disease outcomes during 6.8 years of hormone therapy: Heart and Estrogen/progestin Replacement Study follow-up (HERS II). *JAMA* 2002;288:49-57.
8. Manson JE, Hsia J, Johnson KC, et al. Estrogen plus progestin and the risk of coronary heart disease. *N Engl J Med* 2003;349:523-534.
9. Stefanick ML, Cochrane BB, Hsia J, Barad DH, Liu JH, Johnson SR. The Women's Health Initiative postmenopausal hormone trials: overview and baseline characteristics of participants. *Ann Epidemiol* 2003;13(9 Suppl):S78-S86.
10. Asscherman H, Gooren LIG, Megens JAJ, Nauta J, Kloosterboer HJ, Eikelboom F. Serum testosterone is the major determinant of male-female differences in serum levels of high-density lipoprotein-cholesterol and HDL-2 cholesterol. *Metabolism* 1994;43:935-939.
11. Assmann G, Cullen P, Jossa F, Lewis B, Mancini M. Coronary heart disease: reducing the risk. The scientific background to primary and secondary prevention of coronary heart disease. A worldwide view. International Task Force for the Prevention of Coronary Heart Disease. *Arterioscler Thromb Vasc Biol* 1999;19:1819-1824.
12. Scragg JL, Jones RD, Channer KS, Jones TH, Peers C. Testosterone is a potent inhibitor of L-type Ca (2+) channels. *Biochem Biophys Res Commun* 2004;318:503-506.
13. Malkin CJ, Pugh PJ, Jones TH, Channer KS. Testosterone as a protective factor against atherosclerosis immunomodulation and influence upon plaque development and stability. *J Endocrinol* 2003;178: 373-380.
14. Khalil RA. Sex hormones as potential modulators of vascular function in hypertension. *Hypertension* 2005;46:249-254.
15. Mayes JS, Watson GH. Direct effects of sex steroid hormones on adipose tissues and obesity. *Obes Rev* 2004;5:197-216.
16. Durant S, Christeff N, Coulaud J, Nunez EA, Dardenne M, Homo-Delarche F. Basal concentrations of various steroids in the nonobese

diabetic (NOD) mouse and effect of immobilization stress. *Autoimmunity* 1998;28:249-258.
17. Mendelsohn ME, Karas RH. The protective effects of estrogen on the cardiovascular system. *N Engl J Med* 1999;340:1801-1811.
18. Knopp RH. Multiple beneficial effects of estrogen on lipoprotein metabolism. *J Clin Endocrinol Metab* 1997;82:3952-3954.
19. Sack MN, Rader DJ, Cannon RO III. Oestrogen and inhibition of oxidation in low-density lipoproteins in postmenopausal women. *Lancet* 1994;342:269-270.
20. Hayashi T, Yamada K, Esaki T, et al. Estrogen increases endothelial nitric oxide by a receptor-mediated system. *Biochem Biophys Res Commun* 1995;214:847-855.
21. Blum A, Cannon RO III. Effects of estrogens and selective oestrogen receptor modulators on serum lipoproteins and vascular function. *Curr Opin Lipidol* 1998;9:575-586.
22. Adams MR, Kaplan JR, Manuck SB, et al. Inhibition of coronary artery atherosclerosis by 17β-estradiol in ovariectomized monkeys: lack of an effect of added estrogen. *Arteriosclerosis* 1990;10: 1051-1057.
23. Zhu X, Bonet B, Gillenwater H, Knopp RH. Opposing effects of estrogen and progestins on LDL oxidation and vascular wall cytotoxicity: implications for atherogenesis. *Exp Bio and Med* 1999;222: 214-221.
24. The Writing Group for the PEPI Trial. Effects of estrogen or estrogen/progestin regimen on heart disease risk factors in postmenopausal women. The Postmenopausal Estrogen/Progestin Intervention Trial. *JAMA* 1995;273:199-208.
25. Nickenig G, Strehlow K, Wassmann S, et al. Differential effects of estrogen and progesterone on AT(1) receptor gene expression in vascular smooth muscle cells. *Circulation* 2000;102:1828-1833.
26. Hanke H, Hanke S, Finking G, et al. Different effects of estrogen and progesterone on experimental atherosclerosis in female versus male rabbits: quantification of cellular proliferation by bromodeoxyuridine. *Circulation* 1996;94:175-181.
27. Wu FC, Eckardstein A. Androgens and coronary artery disease. *Endocr Rev* 2003;24:183-217.
28. Little-Kearney M, Hurn PD. Testosterone as a modulator of vascular behavior. *Biol Res Nurs* 2004;5:276-285.
29. Bruck B, Brehme U, Gugel N, et al. Gender-specific differences in the effects of testosterone and estrogen on the development of atherosclerosis in rabbits. *Arterioscler Thromb Vasc Biol* 1997;17:2192-2199.
30. Adams MR, Williams JK, Kaplan JR. Effects of androgens on coronary artery atherosclerosis and atherosclerosis-related impairment of vascular responsiveness. *Arterioscler Thromb Vasc Biol* 1995;15:562-570.
31. Zhao SP, Li XP. The association of low plasma testosterone level with coronary artery disease in Chinese men. *Int J Cardiol* 1998;63:161-164.
32. Lichtenstein MJ, Yamell JW, Elwood PC, et al. Sex hormones, insulin, lipids, and prevalent ischemic heart disease. *Am J Epidemiol* 1987;126: 647-657.
33. Harman SM, Metter EJ, Tobin JD, Pearson J, Blackman MR. Longitudinal effects of aging on serum total and free testosterone levels in healthy men. *J Clin Endocrinol Metab* 2001;86:724-731.
34. Feldman HA, Johannes CB, McKinlay JB, Longcope C. Low dehydroepiandrosterone sulfate and heart disease in middle-aged men: cross-sectional results from the Massachusetts Male Aging Study. *Ann Epidemiol* 1998;8:217-228.
35. Phillips GB, Pinkernell BH, Jing TY. Relationship between serum sex hormones and coronary artery disease in postmenopausal women. *Arterioscler Thromb Vasc Biol* 1997;17:695-701.
36. Amowitz LL, Sobel BE. Cardiovascular consequences of polycystic ovary syndrome. *Endocrinol Metab Clin North Am* 1999;28:439-458.
37. Bambino TH, Schreiber JR, Hsueh AJ. Gonadotropin-releasing hormone and its agonist inhibit testicular luteinizing hormone receptor and steroidogenesis in immature and adult hypophysectomized rats. *Endocrinology* 1980;107:908-917.
38. Meston CM, Frohlich PF. The neurobiology of sexual function. *Arch Gen Psychiatry* 2000;57:1012-1030.

