Sex Hormone Levels – Estradiol, Testosterone, and Sex Hormone Binding Globulin as a Risk Marker for Atherosclerotic Coronary Artery Disease in Post-menopausal Women

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Abstract

Context: Sex hormones levels determine the risk of occurrence of coronary artery disease (CAD) in post-menopausal (PM) women. Aims: To investigate the relationship between sex hormones (estradiol and testosterone)/sex hormone binding globulin (SHBG) and cardiovascular risk factors in PM women. In addition, we learned the association between these sex hormones/SHBG and the occurrence of atherosclerotic CAD event in PM women. Settings and Design: Cross-sectional case-control study. Subjects and Methods: Subjects recruited in the present study were from the cardiology outpatient clinic or Emergency department Gauhati Medical College and Hospital, Assam. The subjects were grouped into two categories after appropriate exclusion criteria: Cases – PM women with documented CAD (n = 40) and controls – Healthy PM women (n = 30). The medical history, clinical examination, and investigations including serum estradiol, total testosterone, SHBG, free testosterone index (FTI), high-sensitivity C-reactive protein (hs-CRP), lipid profile, carotid intima-media thickness (CIMT), fasting plasma glucose (FPG), and postprandial plasma glucose (PPPG) were done and analyzed. Statistical Analysis Used: Pearson correlation between sex hormones and CAD risk factors was done. The association between sex hormones and CAD risk factors among PM women was analyzed by multiple logistic regression. The statistical significance was set at the 0.05 level. Results: The mean age of all the subjects was 62.27 ± 6.9 years. Among the cases, a significant positive correlation was found between total testosterone/FTI and waist circumference, W/H ratio, triglyceride levels, hs-CRP, and CIMT (P < 0.01). In addition, a significant negative correlation was found between total testosterone and FTI with high-density lipoprotein-cholesterol levels (P < 0.01). The multiple logistic regression analysis showed that total testosterone levels (P < 0.01) and SHBG (P < 0.01) are independently associated with the occurrence of atherosclerotic CAD in PM. Conclusion: We conclude that increased serum testosterone levels and low SHBG in PM women are associated with the development of atherosclerotic cardiovascular risk factors.

Keywords: Coronary artery disease, estradiol, post-menopausal women, SHBG, testosterone

Introduction

Cardiovascular disease (CVD) is the leading cause of death among women worldwide.

Studies examining associations between endogenous estrogen levels and CVD risk factors have yielded conflicting results.[1-4] Indirect evidence for a role of androgens comes from findings of clinical studies showing an unfavorable cardiovascular risk profile, relating to imbalance in estradiol to testosterone ratio.[7-10] The present study was planned to analyze the influence of endogenous sex hormones (estradiol and testosterone) and sex hormone binding globulin (SHBG) on the risk factors for coronary artery disease (CAD) in post-menopausal (PM) women.
The study subjects were divided into two groups. Cases that included PM women of age between 50 and 75 years attending the Cardiology outpatient department/Emergency department of Gauhati Medical College Hospital with CAD (Atherosclerotic) defined as subjects who have had documented myocardial infarction as per clinical presentation, Electrocardiogram, and elevated cardiac enzymes, or subjects who have a documented angiography showing 70% occlusion of any of the major coronary vessels not on prior treatment. The controls were age, gender, and body mass index (BMI) matched healthy PM women. The PM status was defined as cessation of menses for more than 12 months in presence of natural menopause. CAD was excluded among controls by symptom analysis (angina or angina equivalent), physical examination, ECG, and chest X -ray. The patients with history of endocrine diseases, hepatic disease, renal failure, diabetes mellitus or on statins or hormonal replacement medications, smokers, alcoholism, and who have undergone oophorectomy were excluded from the study. The patients who fulfilled the study criteria underwent a detailed medical history and clinical examination.

Risk factors for atherosclerotic CAD as defined by metabolic syndrome criteria International Diabetes Federation (IDF) criteria for Asian population. The cut-off for Asian population are summed below:

- Waist circumference (WC) >80 cm in Asian population women
- BMI >23 (Asian cut-off for obesity)
- Waist and hip circumference ratio >0.8 women suggestive of android obesity.

All subjects underwent detailed history and thorough physical examination. Weight, height, BMI, and waist and hip circumference were measured with standard techniques. Blood sample for high-sensitivity C-reactive protein (hs-CRP) and lipid profile was taken from cases from the emergency department patients once they were diagnosed to have myocardial infarction irrespective of the time of presentation before starting high doses of statins or aspirin or heparin. For those patients with documented CAD angiographically not on medications, blood samples were taken in fasting state. Venipunctures for hormonal assay (estradiol, total testosterone, and SHBG) were performed in the morning after subjects had fasted for at least 8 h. The blood samples were subjected to biochemical and hormonal assay. The samples were immediately centrifuged, and the serum was stored at −20°C until hormonal assayed. The subjects were designated to have metabolic syndrome as per IDF criteria.

**Assay of hormones**

Serum estradiol was estimated by Elecsys Estradiol II assay (ROCHE COBAS) that employs a competitive test principle using a polyclonal antibody specifically directed against 17β-estradiol. Intra-assay and inter-assay coefficient of variation varies from 5.6 to 6.5% to 3.1 to 5.0%. The testosterone assay (ROCHE COBAS) was also according to a competitive test principle using a monoclonal antibody specifically directed against testosterone. Intra-assay and inter-assay coefficient of variation varies from 5.2 to 6.8% to 3 to 4.5%. The SHBG assay (ROCHE COBAS) employed sandwich assay using two monoclonal antibodies specifically directed against human SHBG. Intra-assay and inter-assay coefficient of variation varies from 2.1 to 2.7% to 2.5 to 4% for SHBG.

**Assay of biochemical markers**

Fasting plasma glucose (FPG) and postprandial plasma glucose (PPPG) were measured using glucose oxidase method, and lipid profile was measured by enzymatic colorimetry, using Vitros 5600 automated analyzer. Low-density lipoprotein cholesterol (LDL-C) was calculated using Friedewald formula. Non-high-density lipoprotein cholesterol (HDL-C), calculated as the difference between total cholesterol and HDL-C, has been documented to be equivalent to LDL-C in predicting CVD. Triglyceride (TG) to HDL-C ratio was calculated as an additional predictor of CVD risks. The hs-CRP was measured from stored serum samples using a solid phase chemiluminescent assay with the immulite 1000 (Siemens Healthcare Diagnostics) and intra-assay coefficient of variation of 5.0%. The cardiovascular risk assessment cut-offs for hs-CRP have been recommended by American Heart Association (AHA) as low risk: (<1.0 mg/L), average risk: (1.0 ~ 3.0 mg/L), and high risk: (>3.0 mg/L). Carotid intima media thickness (CIMT) was estimated in both cases and control by an Advanced Technology Laboratories High Definition Imaging (ATL HDI) 1500 ultrasound system (B-mode ultrasound) using a 10–12 MHz linear transducer (Siemens), which is considered as a accepted surrogate marker of atherosclerosis. In healthy middle-aged adults, CIMT values between 0.6 and 0.7 mm have been considered normal, whereas CIMT of 1 mm or more has been associated with significant increased absolute risk of CHD. The measurement of CIMT varies with age and values >0.8 mm are considered abnormal in younger population and confer increased absolute risk of CHD.

**RESULTS**

As seen in Table 1, the mean age of the cases and control were 62.27 ± 6.81 and 63.03 ± 5.24 years, respectively ($P = 0.49$). There were no significant differences between the mean BMI, blood pressures, and serum estradiol levels among the cases and controls. However, the cases had significant higher mean WC, waist/hip (W/H) ratio, total cholesterol, TGs, non-HDL-C total testosterone, free testosterone index (FTI), estradiol/total testosterone (E2/T) ratio, hs-CRP, and CIMT. There was also a significant low HDL-C and SHBG levels among the cases in comparison to controls.

**DISCUSSION**

The relationship between estrogen and coronary heart disease has been widely described. Estrogen has been known to have...
Among the baseline lipoprotein profile, the mean HDL-C was 35.75 ± 8.95 and 40.34 ± 9.12 mg/dl in the cases and controls, which is far below the desired level. We also found that the cases had higher serum TGs and lower HDL-C than that in control groups \( (P < 0.01) \). These findings were similar to both the Los Angeles atherosclerosis study and the Study of Women’s Health Across the Nation Heart women (SWAN) heart women, which demonstrated that the antithrombotic effect of HDL diminishes in women around the age of menopause,\(^{22,23}\) and it was suggested that it is possibly related to changes in the lipoprotein sub-class profile observed during the menopausal transition. From these initial results, we can firmly infer that the PM state is a state of metabolic syndrome where the body composition and lipid profile changes. Indian studies in pre- and PM women have found that the prevalence of metabolic syndrome had varied from 31% to 60% in different regions.\(^{24}\) The prevalence of metabolic syndrome in north India was 45% in premenopausal and 55% in PM women according to various studies.\(^{25}\) The components of metabolic syndrome in Indian women that was most prevalent among the subjects having metabolic syndrome was abnormal WC (94%) followed by hypertension (71.14%), low-HDL (55.14%), abnormal TG (40%), and diabetes (35.71%).\(^{26,27}\) The prevalence of metabolic syndrome among PM women was significantly higher \( (P < 0.001) \) than that in premenopausal women as per IDF criteria (premenopausal 45% and PM 55%). In our study, we found 47% patients with abnormal WC, 91% low-HDL-C, 47% high TG, and 8% hypertension among all the subjects including cases and controls. Out of those, metabolic syndrome was seen in 60% cases and 16% of the controls as IDF criteria.

Sex hormone levels showed a comparable estradiol levels among the both groups with significant elevated total testosterone, FTI, and E2/T ratios. The SHBG levels were lower among the cases \( (P < 0.01) \). hs-CRP and CIMT are considered as peripheral markers of atherosclerosis in cardiovascular system were elevated among the cases \( (P < 0.01) \). Several studies in PM women have shown a positive correlation between serum testosterone levels and occurrence of CAD.\(^{8-13}\) In the current study, we found total testosterone levels and FTI are related with central adiposity as evident from its significant association with WC and W/H ratio. Although the relationship between testosterone on body composition in women remains controversial, it has been shown that serum level of estradiol and testosterone possibly affects body fat distribution in PM women. Söderberg et al. in his study has elaborated a similar finding to ours.\(^{28}\) The study characterized the relationship between biologically active testosterone and leptin after careful stratification for gender and adiposity among the men and pre- and PM women. The study showed the women (both pre-menopausal and PM) with increased central obesity (as evident by increased W/H ratio and WC) had a positive correlation with serum total testosterone levels \( (r = 0.59, P < 0.01) \).\(^{26}\) Few other studies also has supported similar association among PM women.
suggesting abdominal adiposity is associated with a relatively more androgenic sex hormone profile. It is well-known that central distribution of adiposity such as WC and waist to hip ratio (WHR) show stronger associations with CVD and its CVD risk factors. Phillips et al. reported a positive correlation between free testosterone and visceral fat mass (visceral fat mass in the abdominal cavity was assessed by Computerized Tomography) in healthy PM women. Two studies reported an inverse association between SHBG and visceral fat tissue. In another study, including pre-, peri-, and PM women, high Bioavailable testosterone, and low SHBG levels were also found to be associated with an increase in visceral fat, independently of age, insulin resistance, and estradiol.

In the present study, we found a correlation and association between total testosterone (and FTI), estradiol levels, and SHBG with lipoprotein profiles among the cases. We found that the elevated levels of TGs among cases and correlated with high testosterone and low estradiol levels among the cases [Tables 2 and 3]. Such relations were not seen with LDL-C or total cholesterol. However, our study also revealed HDL-C levels were positively dependent on SHBG concentrations [Tables 4 and 5] and negatively related to total testosterone levels. The relationship seen in the above study is similar to the lipid profile seen among women with hyperandrogenic polycystic ovary syndrome. They have an abnormal lipid profile, characterized by elevated TG and reduced HDL-C levels. Moreover, in female to male transsexuals, testosterone administration has been associated with a reduction in HDL-C and an increase of TG levels. In a study with obese PM women, the administration of androstenol decanoate causes a decrease in HDL-C (purpose of this study was to assess the effects on fat distribution of administering androstenol decanoate in obese PM women). The mechanisms explained through which testosterone and SHBG affect lipid metabolism are not completely understood, although direct regulatory effects on hepatic lipase (HL) and lipoprotein lipases (LPLs) have been reported. HL and LPL are key enzymes involved in the regulation of TG and HDL-C levels. The LPL activity causes a decrease in TG and an increase in HDL-C levels, whereas HL activity is associated with a decrease in HDL-C. The sensitivity of lipolytic enzymes for androgens is further supported by findings from the HERITAGE study showing a strong inverse association between SHBG and HL activity and a positive association between SHBG and LPL activity. The study included subjects of both sexes between 17 and 64 year. In this study, the hypotheses were that there are significant associations between SHBG, sex steroid hormone levels, and post-heparin lipolytic enzyme activities, and that these associations are independent of concomitant variation in adiposity and the metabolic profile. In women of the present study, after statistical adjustment for fasting insulin and adiposity measures, the negative association between HL and SHBG level did not change. Thus, the regulation of HL by free androgens and/or estrogens may be presumably independent from concomitant variations in insulin levels or abdominal

### Table 2: Distribution of various components of metabolic syndrome in the study population (n=70)

| Components of metabolic syndrome | Percentage (%) of patients (n=70) |
|---------------------------------|----------------------------------|
| Abnormal waist circumference(cm) | 47% (n=33)                         |
| Low HDL-C (mg/dl)               | 91% (n=63)                         |
| High triglycerides (mg/dl)      | 47% (n=33)                         |
| Systemic hypertension (mm Hg)   | 8% (n=6)                           |

### Table 3: Correlation between total testosterone levels and free testosterone index with lipoprotein profile/waist circumference/W/H ratio/CIMT, and hs-CRP among the cases (n=40)

| Components | Pearson correlation coefficients, n=40 (P) |
|------------|------------------------------------------|
| Cholesterol | r1=0.16, r2=0.09, P=0.38, P=0.48          |
| LDL-C      | r1=0.08, r2=0.04, P=0.58, P=0.6            |
| Triglyceride | r1=0.64, r2=0.84, P<0.01, P=0.01       |
| HDL-C      | r1=-0.29, r2=-0.36, P=0.04, P=0.02        |
| Waist circumference | r1=0.58, r2=0.8, P<0.01, P=0.01 |
| Waist/ Hip (W/H) ratio | r1=0.48, r2=0.30, P=0.01, P=0.03       |
| CIMT       | r1=0.78, r2=0.91, P<0.01, P=0.01          |
| hs-CRP     | r1=0.68, r2=0.80, P<0.01, P=0.01          |
| Non-HDL-C  | r1=0.48, r2=0.50, P<0.01, P<0.01          |

1: Total testosterone correlation, 2: Free testosterone index correlation. Among the post-menopausal women with CAD, a significant positive correlation was found between total testosterone and free testosterone index with waist circumference, W/H ratio, serum triglyceride levels, Non-HDL-C, hs-CRP, and CIMT. The negative correlation of significance was found between total testosterone and free testosterone index with HDL-C levels. The linear regression analysis showed association between total testosterone and free testosterone index with waist circumference, W/H ratio, serum triglyceride levels, Non-HDL-C, hs-CRP, and CIMT. (P<0.01). No such correlations were seen among the controls.

### Table 4: Correlation between estradiol levels and lipoprotein profile/Waist circumference/W/H ratio/CIMT and hsCRP among the cases (n=40)

| Estradiol | Pearson correlation coefficients, n=40 (P) |
|----------|------------------------------------------|
| Cholesterol | 0.01, P=0.48                           |
| LDL-C     | 0.07, P=0.34                           |
| Triglyceride | -0.39, P<0.01            |
| HDL-C     | 0.02, P=0.7                          |
| Waist circumference | 0.08, P=0.4          |
| Waist/ Hip (W/H) ratio | 0.02, P=0.3   |
| CIMT      | 0.11, P=0.91                       |
| hs-CRP    | -0.64, P<0.01                     |
| Non-HDL-C | 0.2, P=0.6                         |

Among the post-menopausal women with CAD, a significant negative correlation was found between estradiol levels and serum triglyceride levels with hs-CRP. The linear regression analysis showed association between estradiol levels and serum triglyceride levels with hs-CRP (P=0.01). No such correlations were seen among the controls.
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The present study also showed that mean hs-CRP levels were significantly higher among the cases than that in controls group (cases 5.68 ± 3.39 vs. control 2.70 ± 0.9). The estradiol levels negatively correlated with hs-CRP levels among the cases. Similar finding were also found in few studies where a significant differences in the levels of hs-CRP were found regarding pre- and PM women with approximately 3-fold increase of hs-CRP in the serum of PM healthy women when compared to pre-menopausal women. An elevated level of hs-CRP in PM is due to estrogen shortage. Apparently, besides being directly involving in low-grade chronic systemic inflammation, hs-CRP is emerging as the strongest and most independent predictive risk factor for atherosclerosis and CVD. The cardiovascular risk assessment cut-offs for hs-CRP have been recommended by AHA 2004 as low risk: (<1.0 mg/L), average risk: (1.0 – 3.0 mg/L), and high risk: (>3.0 mg/L). In our study, the cardiovascular risk assessment from hs-CRP was found to be high in cases and average risk in controls. It is known that hs-CRP binds to oxidized LDL which leads to an increase in adhesion molecules promoting complement proteins and trigger inflammation in atherosclerotic plaques. Furthermore, CRP promote the induction of tissue factor, the remarkable factors on monocyte surface which is considered to be one of the important coagulation factors, also increase adhesion molecules and manipulate the production of nitric oxide. The removal of the regulatory effect of estrogens up on hs-CRP leads to an increase of hs-CRP level in PM women accumulating the increased risk of CVD. It has to be understood that the menopausal state itself is a cardiovascular risk, and women who have an elevated testosterone levels among the menopausal state will further add a risk as evident from our study population. In this study, we were able to find a relationship between increased total testosterone levels and FTI with elevated hs-CRP levels.

We found a significant positive correlation between CIMT and testosterone levels in the cases but not in the controls. The measurement of CIMT is an accepted surrogate marker of atherosclerosis. Ouyang et al. in his study focused on a population of PM women without clinically evident CVD and found that high total testosterone and bioavailable testosterone levels were associated with carotid atherosclerosis. Total and bioavailable testosterones were positively associated with common CIMT independent of age, BMI, hypertension, smoking, HDL-C, LDL-C, and insulin sensitivity. We can make a strong comment from above study that in PM women, testosterone may be independently associated with greater common CIMT and increases the risk of cardiovascular events in PM women. Further, elevated hs-CRP and altered lipoprotein profile/waist circumference/W/H ratio/CIMT and hs-CRP among the cases (n=40) (P)

| Variables          | Odds ratio (OR) | 95% Confidence interval (CI) | P   |
|--------------------|----------------|-----------------------------|-----|
| Model              | Estradiol      | 0.23                        | 0.34-0.92 | 0.7 | 0.01 |
|                    | Testosterone   | 6.76                        | 2.385-19.170 | <0.01 |
| Multiple logistic regression | SHBG | -0.82 | 0.74-0.98 | <0.01 |

The multiple logistic regression analysis showed that total testosterone levels [OR 6.76 (CI -2.34-19.42) P<0.01] and SHBG [OR -0.825 (CI -0.74-0.91), P<0.01) are independently association with the occurrence of atherosclerotic CAD in PM women.
levels as seen in our study per se can also alter the caliber of vessels.

Finally, we did multi-variance logistic analysis to find the role of estradiol, testosterone, and SHBG independently in the occurrence of CAD event in PM women [Table 6]. After adjusting for age, BMI, blood pressure, lipid profile, and hs-CRP, we found that total testosterone levels [OR 6.76 (CI -2.34-19.42) P < 0.01 ] and SHBG [OR –0.825 (CI -0.74-0.91), P < 0.01 ] are independently associated with the occurrence of atherosclerotic CAD in PM women.

We would like to emphasize that Freudwald index may not be useful if TG levels are above 400 mg%. In our study, none of the patient had Triglyceride above this value. An equal number of case and controls are always considered better, but because of the paucity of study period, we could not attain an equal number that may be a limitation of our study.

**Conclusion**

The PM state itself is considered a risk factor for CAD. There is a relative change in body composition particularly the fat mass of centripetal distribution is owing to the hypogestrogenemia in the menopausal state. Moreover, hs-CRP levels were higher in all patients with menopause. This central obesity is involved in multiple metabolic events that proceed to the occurrence of CAD. Higher serum testosterone levels with low SHBG and comparable serum estradiol levels were seen in the cases. This characteristic sex hormone profile seen in cases were also found to alter the lipoprotein pattern, and further, raise inflammatory markers such as hs-CRP which are risk factors for CAD. The higher chances of a coronary artery event were further demonstrated by an elevation of CIMT as seen among the cases, which is considered as a peripheral marker of atherosclerosis. It was also found that testosterone and SHBG independently associated with the occurrence of atherosclerotic CAD in PM women.

Hence, we can conclude that high testosterone levels and low SHBG directly or indirectly by altering lipid profile and inflammatory markers increase the risk of atherosclerotic CAD among the menopausal women.

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**Conflicts of interest**

There are no conflicts of interest.

**References**

1. Stampfer MJ, Colditz GA, Willett WC. Menopause and heart disease. A review. Ann N Y Acad Sci 1990;592:193-03.
2. Tunstall-Pedoe H. Myth and paradox of coronary risk and the menopause. Lancet 1998;351:1425-27.
3. Gorodeski GI. Impact of the menopause on the epidemiology and risk factors for coronary artery heart disease in women. ExpGerontol 1994;29:357-75.
4. Kuller LH, Gutai JP, Meilahn E, Matthews KA, Plantinga P. Relationship of endogenous sex steroid hormones to lipids and apoproteins in postmenopausal women. Arteriosclerosis 1990;10:1058-66.
5. Lambrinoudaki I, Christodoulakis G, Rizos D, Economou E, Argeitis I, Vlachou S, et al. Endogenous sex hormones and risk factors for atherosclerosis in healthy Greek postmenopausal women. Eur J Endocrinol 2006;154:907-16.
6. Muladi S, Dobs AS, Ding J, Cauley JA, Szkl M, Golden SH. Endogenous postmenopausal hormones and serum lipids: The atherosclerosis risk in communities study. J ClinEndocrinolMetab 2005;90:1202-09.
7. Rexrode KM, Manson JE, Lee IM, Ridker PM, Sluss PM, Cook NR, et al. Sex hormone levels and risk of cardiovascular events in postmenopausal women. Circulation 2003;108:1688-93.
8. Barnett-Connor E, Goodman-Gruen D. Prospective study of endogenous sex hormones and fatal cardiovascular disease in postmenopausal women. BMJ1995;311:1193-6.
9. Bush TL. The epidemiology of cardiovascular disease in postmenopausal women. Ann N Y AcadSci 1990;592:263-71.
10. Alberti KG, Zimmet P, Shaw J, Grundy SM. The IDF consensus worldwide definition of the metabolic syndrome. Lancet 2005;366:1059-62.
11. Roberts WL. CDC/AHA Workshop on Markers of Inflammation andCardiovascular Disease: Application to Clinical and Public Health Practice. Laboratory tests available to assess inflammation-performance and standardization: A background paper. Circulation 2004;110:572-6.
12. Hansa G, Bhargava K, Bansal M, Tandon S, Kasiwal RR. Carotid intima-media thickness and coronary artery disease: An Indian perspective. AsianCardiovascThorac Ann 2003;11:217-21.
13. Kasiwal RR, Bansal M, Desai D, Sharm M. Carotid intima-media thickness: Current evidence, practices and Indian experience. Indian J Endocr Metab 2014;18:13-22.
14. Thomas GN, McGhee SM, Schooling M, Ho SY, Lam KS, Janus ED, et al. Impact of sex-specific body composition on cardiovascular risk factors: The Hong Kong Cardiovascular Risk Factor Study. Metabolism 2006;55:563-69.
15. Schneider HJ, McGhee SM, Schooling M, Ho SY, Lam KS, Janus ED, et al. The predictive value of different measures of obesity for incident cardiovascular events and mortality. JClinEndocrinolMetab2010;95:1777-85.
16. Greenberg AS, Obin MS. Obesity and the role of adipose tissue inflammation and metabolism. Am J ClinNutr 2006;83:461-5.
17. Flegal KM, Carroll MD, Ogden CL, Johnson CL. Prevalence and trends inobesity among US adults. JAMA 2002;288:1723-7.
18. Williamson DF. Descriptive epidemiology of body weight and weight change in U.S. adults. Ann Intern Med 1993;119:646-9.
19. Noppa H, Andersson M, Bengtsson C, Bruce A, Isaksson B. Longitudinalstudies of anthropometric data and body composition. The population study of women in Gotenberg, Sweden. Am J ClinNutr 1980;33:155-62.
20. Wilson PW, D’Agostino RB, Sullivan L, Parise H, Kannel WB. Overweightand obesity as determinants of cardiovascular risk: The Framingham experience. Arch Intern Med 2002;162:1867-72.
21. Stevens J, Cai J, Eveson KR, Thomas R. Fitness and fatness as predictors of mortality from all causes and from cardiovascular disease in men and women in the lipid research clinics study. Am J Epidemiol 2002;156:832-41.
22. Fan AZ, Dwyer J. Sex differences in the relation of HDL cholesterol topgression of carotid intima-media thickness: The Los AngelesAtherosclerosis Study. Atherosclerosis 2007;195:191-6.
23. Woodard GA, Brooks MM, Barinas-Mitchell E, Mackey RH, Matthews KA, Sutton-Tyrrell K. Lipids, menopause, and nearly atherosclerosis in Study of Women’s Health Across the Nation Heart women. Menopause 2011;18:376-84.
24. Packard CI, Saito Y. Non- HDL Cholesterol as a measure of atherosclerotic cardiovascular risk. J AtherosclerThromb 2004;11:6-12.
25. Pandey S, Srinivas M, Agashe S, Joshi J, Galvankar P, Prakasam CP, et al. Menopause and metabolic syndrome: A study of 498 urban women fromwestern India. J Midlife Health 2010;1:63-9.
26. Marjani A, Moghasemi S. The metabolic syndrome among postmenopausal women in Gorgan. Int J Endocrinol 2012;95:36-27.
27. Sawant A, Mankeshwar R, Shah S, Raghavan R, Dhongde G, Raje H, et al. Prevalence of metabolic syndrome in urban India. Cholesterol
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2011:2011.doi: 10.1155/2011/920983.

28. Söderberg S, Olsson T, Eliasson M, Johnson O, Brismar K, Carlström K, et al. A strong association between bio logically active testosterone and leptin in non-obese men and women is lost with increasing (central) adiposity. Int J Obes Relat Metab Disord 2001;25:98-105.

29. Tanko LB, Bagger YZ, Qin G, Alexandersen P, Larsen PJ, Christiansen C. Enlarged waist combined with elevated triglycerides is a strong predictor of accelerated atherogenesis and related cardiovascular mortality in postmenopausal women. Circulation 2005;111:1883-90.

30. Baglietto L, English DR, Hopper JL, MacInnis RJ, Morris HA, , et al. A strong association between biologically active testosterone and leptin in non-obese men and women is lost with increasing (central) adiposity. Int J Obes Relat Metab Disord 2001;25:98-105.

31. Kaye SA, Folsom AR, Soler JT, Prineas RJ, Potter JD. Associations of body mass and fat distribution with sex hormone concentrations in postmenopausal women. Int J Epidemiol 1991;20:151-6.

32. Phillips GB, Jing T, Heymsfield SB. Does insulin resistance, visceral adiposity or a sex hormone alteration underlie the metabolic syndrome? Studies in women. Metabolism 2008;57:838-44.

33. Turcato E, Zamboni M, De Pergola G, Armellini F, Zivelonghi A, Bergamo-Andreis IA, et al. Interrelationships between weight loss, body fat distribution and sex hormones in pre- and postmenopausal obese women. J Intern Med 1997;241:363-72.

34. Hajamor S, Despres JP, Couillard C, Lemieux S, Tremblay A, Prud’homme D, et al. Relationship between sex hormone binding globulin levels and features of the metabolic syndrome. Metabolism 2003;52:724-30.

35. Valkenburg O, Steegers-Theunissen RP, Smedts HP, Dallinga-Thie GM, Fauser BC, Westerveld EH, et al. A more atherogenic serum lipoprotein profile is present in women with polycystic ovary syndrome: A case–control study. J Clin Endocrinol Metab 2008;93:470-6.

36. Fruzzetti F, Perini D, Lazzarini V, Parrini D, Genazzani AR. Adolescent girls with polycystic ovary syndrome showing different phenotypes have a different metabolic profile associated with increasing androgen levels. Fertil Steril 2009;92:626-34.

37. Elbers JM, Giltay EJ, Teerlink T, Scheffer PG, Asscheman H, Seidell JC, et al. Effects of sex steroids on components of the insulin resistance syndrome in nonsexual subjects. Clin Endocrinol 2003;58:562-71.

38. Lovejoy JC, Bray GA, Bourgeois MO, Maciavielli R, Rood JC, Greason C, et al. Exogenous androgens influence body composition and regional body fat distribution in obese postmenopausal women — a clinical research center study. J Clin Endocrinol Metab 1996;81:2198-203.

39. Desmeules A, Coulard C, Tchernof A, Bergeron J, Rankinen T, Leon AS, et al. Post-heparin lipolytic enzyme activities, sex hormones and sex hormone binding globulin (SHBG) in men and women: The HERITAGE Family Study. Atherosclerosis 2003;171:343-50.

40. Yasui T, Uemura H, Irahara M, Arai M, Kojimahara N, Okabe R, et al. Associations of endogenous sex hormones and sex hormone-binding globulin with lipid profiles in aged Japanese men and women. Clin Chim Acta 2008;398:43-7.

41. Bell RJ, Davison SL, Papalia MA, McKenzie DP, Davis SR. Endogenous androgen levels and cardiovascular risk profile in women across the adult lifespan. Menopause 2007;14:630-8.

42. Janssen I, Powell LH, Kazlauskaite R, Dugan SA. Testosterone and visceral fat in midlife women: The Study of Women’s Health Across the Nation (SWAN) pat terning study. Obesity 2009;18:604-10.

43. Espeland MA, O’Leary DH, Terry JG, Morgan T, Evans G, Mudra H. Carotid intimal-media thickness as a surrogate for cardiovascular disease events in trials of HMG-CoA reductase inhibitors. Curr Control Trials Cardiovasc Med 2005;6:30-9.

44. Haffner SM, Newcomb PA, Marcus PM, Klein BE, Klein R. Relation of sex hormones and dehydroepiandrosteronesulfate (DHEA-SO4) to cardiovascular risk factors in postmenopausal women. Am J Epidemiol 1995;142:925-34.

45. Ding EL, Song Y, Manson JE, Hunter DJ, Lee CC, Rifai N, et al. Sex hormone binding globulin and risk of type 2 diabetes in women and men. N Engl J Med 2009;361:1152-63.