To Study Correlation of Body Fat and Blood Lipids with Autonomic Nervous System Activity in Postmenopausal Indian Women

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ABSTRACT

Background: Obesity, physical inactivity, and altered estrogen metabolism play integrated role contributing to the disease risk profiles of postmenopausal women (PMW). Aim: To study the correlation of body fat and blood lipids with autonomic nervous system activity in PM Indian women. Subjects and Methods: A total of 60 PM sedentary women without any gross systemic disease were selected as a control group and 23 PMW, who were regularly doing morning walk for 1-year was selected as a study group. Body mass index (BMI), waist/hip (W/H) ratio were recorded; lipid profile analyzed, and conventional autonomic function tests were carried. Results were analyzed using SPSS version 16. Results: There was a significant difference in BMI, W/H ratio, lipid profile, autonomic function tests between the two groups. Aging and menopausal duration (MD) were positively correlated with pulse rate, systolic blood pressure, total cholesterol (TC), low-density lipoprotein (LDL) cholesterol, orthostatic tolerance test (OTT), and negatively correlated with Valsalva ratio (VR), deep breath test (DBT), 30:15 relative risk (RR) intervals ratio, isometric hand-grip test (HGT), cold pressor test (CPT). BMI and W/H ratio were positively correlated with TC, triglyceride, LDL cholesterol, OTT, and negatively correlated with isometric HGT, CPT. TC and LDL were negatively correlated with VR, deep breath difference test, 30:15 RR interval ratios, isometric HGT, CPT, and positively correlated with OTT. Multiple regression analysis revealed LDL cholesterol as the only significant independent explanatory variable of DBT. LDL cholesterol and age were the significant independent explanatory variables of 30:15 RR interval ratios, CPT. TC, LDL cholesterol, and age were the significant independent explanatory variables of isometric HGT. Conclusions: Aging, MD, BMI, and W/H ratio all contribute significantly to worsening of autonomic functions and lipid profile. Multiple regression analysis revealed LDL cholesterol as the most significant contributor of worsening of autonomic functions in PM females and regular exercise can improve these parameters significantly.

KEY WORDS: Autonomic functions, blood lipids, body fat, menopause

INTRODUCTION

Menopause is associated with higher prevalence of obesity. 44% of postmenopausal women (PMW) are overweight, among them, 23% are obese of the adult world population. Menopausal transition leads to weight gain, and physiological withdrawal of estrogen brings about changes in fat distribution. These same risk factors also affect the modulation of the autonomic nervous system (ANS). Higher activity of the sympathetic nervous system and higher levels of leptin in women after menopause may suggest their participation in the pathogenesis of hypertension in this group of patients. Women with abdominal obesity have high vasomotor scores, sleeping disorders, lack of energy and several chronic diseases (e.g., cardiovascular disease, diabetes, cancer, hypertension, depression, and osteoporosis), and premature death.

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How to cite this article: Chaudhuri A, Ray M, Hazra SK, Ghosh S. To study correlation of body fat and blood lipids with autonomic nervous system activity in postmenopausal Indian women. J Basic Clin Reprod Sci 2015;4:58-63.
Stress influences health and disease which might be of special relevance for ageing and age-associated changes of the hypothalamic-pituitary-adrenal axis.\(^1\)\(^-\)\(^3\) The possible modulatory role of estradiol and the influence of rising stress hormone levels for the ageing brain.\(^1\)\(^-\)\(^3\)

The role of estrogen on autonomic nerve function has not yet been clearly indicated. Estrogen is known to be a vagotonic and sympatholytic hormone. A metabolite of progesterone is known to have sympatholytic activity.\(^4\) It has been suggested that estrogen may have some effects on the central baroreflex mechanism. It facilitates the glutamatergic neurotransmission in the nucleus tractus solitarius. It also increases baroreflex sensitivity as well as vagal tone. Therefore, decrease in baroreflex sensitivity, heart rate variability (HRV); parasympathetic activity may be the consequences of estrogen deficiency in PMW.\(^4\)\(^-\)\(^10\)

The present study was undertaken to correlate body fat and blood lipids with ANS activity in (PM) in an urban population of eastern India. Early detection of subclinical autonomic dysfunction may improve the quality of life and longevity in PMW by proper medication and lifestyle modifications as they have a shorter lifespan in a developing country like India as compared to developed countries.

SUBJECTS AND METHODS

The present study was conducted in a tertiary care hospital in a time span of 1-year after taking institutional ethical clearance and informed consent of the subjects.

Inclusion criteria
Sixty PM sedentary women without any gross systemic disease were selected as control group and 23 PMW who were regularly doing morning walk (1-h every day and 5 days/week) for past 1-year were selected as study group.

Exclusion criteria
Patients with tachycardia, cardiac arrhythmias, hypertension, diabetes, ischemic heart disease, retinopathy, nephropathy, and any other chronic disease or associated factors (drugs) that may affect the autonomic reflexes were excluded from the study. Subjects on hormone replacement therapy were also excluded. Subjects practicing yoga were not included.

Determination of the sample size was done taking studies by Tandon et al.\(^1\)\(^-\)\(^3\) in PM Indian women into consideration (In the study by Tandon et al two groups were formed; Group I = 30 was designated as intervention group and Group II, 24 served as control and in the present study 60 PM sedentary women were selected as control group and 23 PMW who were regularly doing morning walk (1-h every day and 5 days/week) for past 1-year were selected as study group).

Methods
On the first appointment, particulars of the subject, chief complaints, personal history, family history, history of past illness, and treatment history of the subjects were carefully recorded. General physical examinations were done, and informed consent was taken. Pretest instructions were given to avoid consumption of any drugs that may alter the autonomic function 48 h prior to the test. The subjects were advised for a good restful sleep. Fasting blood samples were collected followed by anthropometric measurements. Pulse rate (PR) and blood pressure (systolic blood pressure [SBP]; diastolic blood pressure [DBP]) were recorded, followed by conventional autonomic function tests.

Biochemical analyses

Lipid profile
Early morning venous samples were collected in plain bulbs from the subjects for analysis of lipid profile following a 12 h overnight fasting. Samples were collected, centrifuged, and analyzed on the same day.\(^4\)

1. High-density lipoprotein (HDL) analysis: Enzymatic end point method was used. Noninsulin-dependent diabetes mellitus (ASPEN) HDL: Cholesterol test employs a specific antibody and is applied on an automated analyzer.
2. Total cholesterol (TC) analysis: Phenol-free cholesterol reagent was used.
3. Triglyceride (TG) analysis: Dynamic extended stability with lipid clearing agent was used.
4. Low-density lipoprotein (LDL) analysis: Enzymatic end point method was used. ASPEN LDL: Cholesterol test was employed.

Anthropometry

Body weight
A digital weighing scale was used to measure body weight with an accuracy of ± 100 g. Subjects were weighed without their shoes.\(^4\)

Height
Standing body height was measured without shoes to the nearest 0.5 cm with the use of height stand with shoulders in relaxed position and arms hanging freely.

Body mass index
Body mass index (BMI) and waist/hip (W/H) ratio were selected as markers of body fat in the present study. BMI was calculated as body weight in kilograms divided by the square of body height in meters.\(^4\)
Waist/hip ratio
Waist/hip ratio\(^4\) of the subjects was measured. Waist circumference (WC) was measured at the level of umbilicus and hip circumference at the fullest point around buttocks. WC was divided by hip circumference to calculate the W/H.

Lead II of the electrocardiogram (ECG) was selected for recording heart rate. The ECG tracings were screened for any suspected pathological waveform configuration. Autonomic function tests were carried.

Tests reflecting cardiac parasympathetic damage
2. Heart rate variation during deep breathing test (DBT).
3. Heart rate response to Valsalva maneuver (Valsalva ratio [VR]).\(^{11,12}\)

The subjects were made to rest for 15 min in the supine position. The resting time given to subjects in between two tests was 5–10 min.

Tests reflecting sympathetic damage
1. Blood pressure response to postural change.
2. Blood pressure response to sustained (isometric) hand-grip test (HGT).
3. Cold pressor test (CPT).\(^{11,12}\)

Statistical analysis
The computer software “Statistical Package for the Social Sciences (SPSS) version 16.0, SPSS Inc., Chicago, IL, USA”.

Methods of assessing normality
The main tests for the assessment of normality are Kolmogorov–Smirnov (K-S) test, Lilliefors corrected K-S test, Shapiro–Wilk test, Anderson–Darling test, Cramer–von Mises test, D’Agostino skewness test, Ancombe-Glynn kurtosis test, D’Agostino–Pearson omnibus test, and the Jarque–Bera test. Among these, K-S is a much-used test and the K-S and Shapiro–Wilk tests can be conducted in the SPSS Explore procedure (analyze → descriptive statistics → explore → plots → normality plots with tests). We used SPSS K-S test for assessing normality of the data. The data were normally distributed and expressed as mean (standard deviation [SD]).

Unpaired t-test was done to compare different parameters between the two groups.

Pearson’s correlation coefficient was used to find a correlation between independent variables age, BMI, W/H ratio, menopausal duration (MD), and dependent variables, that is, ANS activity and lipid profile. Pearson’s correlation coefficient was also used to find a correlation between independent variables lipid profile and dependent variables that is, autonomic function tests. Stepwise multiple regression was performed with age, MD, BMI, and W/H ratio, TC, TG, LDL cholesterol as independent explanatory variables and VR, DBT, 30:15 RR ratio, OTT, HGT, CPT (S), and CPT (D) as dependent variables. For all analyses, \( P < 0.05^* \) were considered as statistically significant, and \( P < 0.01^{**} \) were considered as statistically highly significant.

RESULTS
Mean and SD of different parameters of the 60 sedentary females and subjects on regular morning walk regime were as follows: Age 53.6 (8.7) years versus 57.7 (9.8) years (\( P < 0.05^* \)); BMI 23.07 (4.4) kg/m\(^2\) versus 20.5 (2.7) kg/m\(^2\) (\( P < 0.001^{**} \)); W/H ratio 0.89 (0.08) versus 0.85 (0.03); MD 8.3 (7.9) years versus 5.7 (4.6) years (\( P < 0.06 \)); pulse 80.3 (5.95) beats/min versus 76.9 (4.7) beats/min (\( P < 0.001 \)); SBP 127.4 (16.7) mm of Hg versus 122.5 (15.7) mm of Hg (\( P = 0.22 \)); DBP 78.3 (9) mm of Hg versus 76.7 (6.9) mm of Hg (\( P = 0.37 \)); TC 178.4 (26.3) mg/dl versus 156.1 (14.1) mg/dl (\( P < 0.001^{**} \)); TG 119.9 (34.1) mg/dl versus 100.3 (22) mg/dl (\( P < 0.01^{**} \)); HDL cholesterol 49.4 (7.5) mg/dl versus 51 (8.4) mg/dl (\( P = 0.43 \)); LDL cholesterol 108.3 (28.3) mg/dl versus 84.3 (20.2) mg/dl (\( P < 0.001^{**} \)); VR 1.2 (0.1) versus 1.3 (0.1) (\( P < 0.001^{**} \)); DBT 13.3 (8.6) beats/min versus 15.7 (2.6) beats/min (\( P = 0.04 \)) and expiration: inspiration ratio 1.2 (0.1) versus 1.3 (0.2); 30:15 RR ratio 1.05 (0.05) versus 1.1 (0.03) (\( P < 0.01^{**} \)); HGT 10.07 (4.2) mm of Hg versus 20.5 (3.5) mm of Hg (\( P = 0.06 \)); OTT 29.2 (8.8) mm of Hg versus 25.4 (7.7) mm of Hg (\( P < 0.01^{**} \)); CPT (SBP) 16.6 (10.1) mm of Hg versus 27.04 (8.1) mm of Hg (\( P < 0.001^{**} \)); CPT (DBP) 9.9 (5.6) mm of Hg versus 15.6 (4.6) mm of Hg (\( P < 0.001^{**} \)) [Table 1].

Aging and MD were positively correlated with PR, SBP, TC, LDL, OTT, and negatively correlated with VR, DBT, 30:15 RR intervals ratio, HGT, CPT. BMI and W/H ratio were positively correlated with TC, TG, LDL, OTT, and negatively correlated with HGT, CPT. No significant correlation was observed between aging, MD with BMI, W/H ratio, DBP, TG, HDL. Pulse, blood pressure, HDL, VR, DBT, 30:15 RR ratios were not significantly correlated with BMI and W/H ratio. Among lipid profile parameters, only TC and LDL had significant positive correlation with age, MD, BMI, W/H ratio, and all autonomic function test results were worsened with the rise in TC and LDL levels.

Total cholesterol and LDL were negatively correlated with VR, DBT, 30:15 RR ratios, HGT, CPT (S), CPT (D), and positively correlated with OTT. HDL was positively correlated with HGT. TG was positively correlated with OTT and negatively
BMI findings in both groups are $9.9 \pm 5.6$ and $5.7 \pm 4.6$ respectively, with $P<0.001$.

WC/HD ratio was $0.17 \pm 0.89$ in the control group and $0.08 \pm 0.85$ in the experimental group, with $P<0.001$.

Mean $HDL = 77.4 \pm 4.3$ in the control group and $78.4 \pm 4.5$ in the experimental group, with $P<0.001$.

CPT (D) was $10.1 \pm 4.2$ in the control group and $10.5 \pm 4.3$ in the experimental group, with $P<0.001$.

BMI = Body mass index, MD = Menopausal duration, SBP = Systolic blood pressure, DBP = Diastolic blood pressure, TC = Total cholesterol, TG = Triglyceride, HLD = High density lipoprotein, LDL = Low density lipoprotein, VR = Valsalva ratio, DBT = Deep breathing test, HGT = Hand-grip test, CPT = Cold pressor test, OTT = Orthostatic tolerance test, RR = Relative risk.

Multiple regression analysis

Low-density lipoprotein cholesterol was the only significant independent explanatory variable of DBT ($P<0.01$) and DBT results worsened with increasing LDL levels. LDL cholesterol and age were the significant independent explanatory variables of 30:15 RR ratios, CPT (D) and 30:15 RR, CPT (D), results worsened with increasing LDL (LDL and 30:15 RR $P<0.04$); LDL and CPT (D) $P<0.02$) levels and ageing (age and 30: 15 RR $P<0.02$; age and CPT [D] $P<0.04$). TC, LDL cholesterol, and age were the significant independent explanatory variables of HGT and HGT results worsened with increasing TC ($P<0.033$), LDL ($P<0.01$) levels, and ageing ($P<0.04$) [Table 3].

**DISCUSSION**

The present study examined the correlation of autonomic functions and body fat and blood lipids in PMW with the progression of MD. Autonomic regulation of heart was assessed by conventional autonomic function tests. There was significant difference in autonomic function tests, lipid profile, and distribution of body fat among study and control group though they were age and MD matched. The findings of this study indicate that healthy ageing is associated with a gradual reduction of overall fluctuation in autonomic input to the heart as well as vagal index. Sympathetic nervous system activity increased significantly with an increase in BMI and W/H ratio in PMW. Previous studies have shown that body composition changes and body weight increases during the menopausal period.[4-8,10] BMI findings in both groups are shown to be within normal levels. We had taken only healthy PM females, but BMI of subjects not doing any exercise were more as compared to subjects who were exercising. We analyzed only 23 subjects in the control group. This small sample size reduces the statistical power for analysis. But the samples were difficult to obtain, as it was very difficult to find PM healthy females doing regular exercise in a rural population of a developing country like India, where consciousness...
about positive effects of exercise is grossly lacking. 60 million women in India are above the age of 65 years. The average lifespan for Indian women is 65 years, while in developed countries, it is 80 years, so women of our country deserve special attention.[11,12]

Menopause may result in endothelial dysfunction and increase in body weight, which causes an increase in sympathetic activation. Decreased baroreflex sensitivity also appears with increasing body mass.[13,14] In PMW, the risk of cardiovascular diseases gradually increases and alterations in autonomic nerve functions commonly affect cardiac vagal control.[15] We observed the significant negative correlation of MD with all autonomic function tests reflecting parasympathetic nervous system activity. A study by Naher et al. in 2009 by regression analysis showed parasympathetic nerve function had significant association with estrogen level but no association with age and it was concluded that parasympathetic nerve function was lower in PMW, which may be related to decreased level of estrogen. Our study showed aging as an important factor for developing autonomic dysfunction. We conducted both sympathetic as well as parasympathetic function tests and age in our study was 53.55 ± 8.68 years, while in the above study, it was 50.53 ± 3.02 years. This may be the result of the variation.

Previous studies have shown that changes in the metabolic rate that occur during menopause may increase serum levels of LDL and TG, which may increase the incidence of cardiovascular disease among PMW.[15] Our study also showed significant positive correlation between MD and TC, LDL. BMI and W/H ratio were also positively correlated to TG, TC, and LDL. TC and LDL were negatively correlated with VR, DBT, 30:15 RR ratios, HGT, CPT (S), CPT (D), and positively correlated with OTT. TG was positively correlated with OTT and negatively correlated with CPT. HDL was positively correlated with HGT in the present study. Stepwise multiple regression analysis by Sevre et al. had revealed gender, age, HDL cholesterol, and blood pressure as independent explanatory variables of baroreceptor sensitivity and HRV. In our study, also autonomic function test results worsened with an increase in TC, TG, LDL levels.

Loss of estrogen in menopause causes dyslipidemia.[8,9] Hypercholesterolemia has been proved to be associated with a decreased 24-h HRV. Baroreceptor sensitivity is negatively correlated with LDL cholesterol levels.[9] In the present study, multiple regression analysis revealed that LDL cholesterol was the only significant independent explanatory variable of DBT (P<0.01) and DBT results worsened with increasing LDL levels. LDL cholesterol and age were the significant independent explanatory variables of 30:15 RR ratios, CPT (D) and 30:15 RR, CPT (D), results worsened with increasing LDL (LDL and 30:15 RR P<0.04); LDL and CPT [D] P<0.02) levels and ageing (age and 30:15 RR P<0.02; age and CPT [D] P<0.04). TC, LDL cholesterol, and age were the significant independent explanatory variables of HGT and HGT results worsened with increasing TC (P<0.03), LDL (P<0.01) levels, and ageing (P<0.04) [Table 3]. Aging was positively correlated with LDL with r value of 0.304 and P 0.02. LDL levels were the most significant contributors of worsening of autonomic functions in the present study.

A study was designed by Fu et al. to test the hypothesis that alteration of cardiovascular autonomic functions by vegetarian diets in healthy PMW is related to lipid metabolism. The vegetarians had statistically significant lowered blood pressure, TC, LDL cholesterol, TG, and fasting glucose levels compared with the omnivores. The vegetarians exhibited a significant higher total power, low-frequency (LF) and high-frequency (HF) of HRV, and increased baroreflex sensitivity measures (Brr [LF] and Brr [HF]) compared with the omnivores. Total power, LF and HF of HRV, Brr [LF], and Brr (HF) were significantly and negatively correlated with LDL cholesterol concentrations (P < 0.01). Similar effects of LDL cholesterol were also demonstrated on autonomic functions in the present study.

Tetsuya Kimura et al. in 2006 indicated an association of PM reduced sympathovagal activity with higher body fat content, blood pressure, and blood lipid concentrations. Body composition, blood pressure, lipid profile, and blood sugar of 175 PM subjects were measured. Resting ANS activity was assessed by HRV power spectral analysis. Subjects were divided into low and high group, based on the total power of HRV. Body fat percentage, blood pressure, and lipid profile were significantly different in the two groups. No significant difference was found in years after menopause between the two groups. These findings are similar to the present study. Multiple regression analysis in our study also excluded MD as a significant contributor to worsening of autonomic functions.

Tandon et al. in 2014 conducted a study to evaluate the effect of lifestyle modification on overweight and obese PM women. Two groups were formed; Group I was designated as an intervention (dietary and exercise group) and Group II as a control. Comparison of weight, WC, and BMI was made and compared among two groups at 4, 8, 16, and 24 weeks. Group I produced a significant reduction in WC from 8 weeks onward up to 24 weeks. BMI was statistically significant in Group I and the effect started at 4th week and the differences in BMI reduction were highly significant at 16th and 24th weeks.

These studies show that lifestyle modifications with diet, exercise, relaxation exercises may significantly improve the worsening autonomic functions by improving dyslipidemia
Limitations and future scope
Percentages of body fat can be measured by different methods including bioelectrical impedance analyzer or magnetic resonance imaging (MRI). But due to lack of infrastructure facilities in our center, we could not use these methods, which is a limitation of the present study. Further studies with larger samples of the population and using MRI or bioelectric impedance analyzer for measuring body fat percentage may prove to be more useful.

CONCLUSIONS
Aging, MD, BMI, W/H ratio all contribute significantly to worsening of autonomic functions and lipid profile. Multiple regression analysis revealed LDL cholesterol as the most significant contributor of worsening of autonomic functions in PM females and regular exercise can improve these parameters significantly.

Financial support and sponsorship
Nil.

Conflicts of interest
There are no conflicts of interest.

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