

Menopause versus aging: The predictor of obesity and metabolic aberrations among menopausal women of Karnataka, South India

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ABSTRACT

Context: Increased incidences of cardiovascular disorder and metabolic syndrome particularly after menopause have raised curiosity for the underlying factors. However, it is still a debate whether age or menopausal transition is a greater contributor.

Aims: To elucidate the inter-relationships of age, menopause, and associated obesity and to assess their independent effects on aggravation of cardio metabolic risk factors in postmenopausal women.

Settings and Design: Four hundred two women aged between 30 and 75 years were recruited in a cross-sectional study from Southern India. Three hundred sixteen participants exempting exclusion criteria, comprising of 169 premenopausal and 147 postmenopausal women were finally included.

Materials and Methods: Anthropometric measurements such as weight, height, waist circumference (WC), hip circumference (HC), fat percentage, basal metabolic rate (BMR), and blood pressure were taken. Fasting plasma glucose, postprandial glucose, glycated hemoglobin (HbA1c), lipid profile, and C-reactive protein (CRP) were also measured.

Statistical Analysis Used: Independent *t*-test, Analysis of covariates (ANCOVA), Pearson's correlation coefficients and multiple stepwise linear regression model analysis were done.

Results: A significant increase in physical and metabolic factors was observed in postmenopausal women compared to premenopausal women except WC and HbA1c. Contrastingly, high-density lipoprotein cholesterol (HDL) levels and BMR were significantly decreased. After adjusting for BMI and age, the significant differences in the variables through the menopausal transition persisted, including an increase in WC. Significant correlation was observed between age and measures of general obesity such as BMI ($P < 0.05$) and fat percentage ($P < 0.001$) but not with central obesity indices. Menopausal status and WC exerted an independent effect on most of the metabolic risk factors ($P < 0.001$ or $P < 0.01$). Fat percentage was the predicting variable for CRP, HbA1c, diastolic blood pressure ($P < 0.001$), and HDL ($P < 0.01$). But Age showed independent effect only on HbA1c.

Conclusions: Menopausal transition brings about anomalies in total body composition characterized by an increased body fat mass and central adiposity. This creates a compatible atmosphere for abnormal metabolism and aggravated cardio metabolic risk factors. Thus, menopausal status and associated obesity is the major predictor of metabolic aberrations over age in menopausal women.

Key Words: Cardiometabolic risk, cardiovascular disease, hormonal transition, menopause, metabolic syndrome, obesity

INTRODUCTION

In recent decades, the influence of globalization has played a pivotal role in the makeover of women's lifestyle with the considerable emergence of risk factors such as, central

adiposity, glycemic abnormality, cardiovascular disease (CVD), dyslipidemia, and hypertension.^[1-4] The prognosis

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Access this article online

Quick Response Code:



Website:
www.jmidlifehealth.org

DOI:
10.4103/0976-7800.98814

and case history of CVD are different in men and women. Among women, the risk of CVD accredited to metabolic syndrome (MS) shown to be particularly high, and it is estimated half of all cardiovascular events in women is related to MS.^[5] Despite the increase of MS and CVD incidence among women notably following menopause, the underlying effect of menopause on cardio metabolic risk factors remain ill-defined.

Menopause is a biological process characterized by cessation of the menstrual cycle in women with a decline in age approximately between 40 and 60 years but naturally observed at 51 years.^[6] The hormonal alterations during the menopausal transition contribute more to the changes in the distribution of body fat than general obesity, which has been demonstrated by increased abdominal fat deposition influenced by low estrogen and high androgen.^[7] It was reported that there are 49% increase in abdominal fat and 22% increment of the subcutaneous fat of women in the postmenopausal stage compared to premenopausal women suggesting that the ultimate change after menopause is associated with obesity linked traits such as a high proportion of the body fat mass and central adiposity.^[8] Obesity in turn is directly related to the development of a group of chronic noncommunicable diseases (NCDs), including insulin resistance, diabetes, and CVD^[9-12] This constitutes the first cause of mortality in menopausal women.^[12]

Predominantly, menopause is a phenomenon of aging in women. Aging is accompanied by physical inactivity and decrease in energy metabolism associated with the increase in food intake, which contributes to weight gain. Higher waist diameters and waist-to-hip ratios in older women in a couple of studies substantiate the effect of age on regional body composition of women.^[13,14] Altered body composition and fat distribution during the initial phase of post menopause have been attributed to age than menopause in a few studies. However, menopause-linked differences have not been entirely rooted out.^[15] Besides this, an obvious influence of aging has also been found on cardio metabolic risks aggravating in menopausal women.^[16] Even so, it is still a debate, whether this cardio metabolic aberration are because of the changing hormonal milieu with declining estrogen at menopausal transition, or it is just the consequence of aging and sedentary lifestyle causing general obesity.

It has been reported that the Asia-Pacific population is edging towards developing diabetes, CVD or hypertension at a lower BMI than the rest of ethnic populations due to the tendency of having a higher body-fat percentage and central adiposity without developing general obesity.^[17,18] As far as Asian Indians are concerned, very few studies

have been undertaken to identify the components of the MS following menopause. Moreover, it is evident that Indian women may be comparatively worse off than men with regard to the risk factors for CVD.^[19,20] For better comprehension of the condition, it would be useful to compare pre- and postmenopausal women. Therefore, this study aims to elucidate the interrelationships of age, menopause and related obesity and evaluate their independent effects on aggravation of cardio metabolic risk factors.

MATERIALS AND METHODS

Study design and sample characterization

The study was approved by Institutional Ethical Committee (IOE), Anthropological Survey of India, Kolkata. With prior informed consent, a total of 402 women aged between 30 and 75 years were enrolled in the cross-sectional study with subsequent medical camps in random sectors, in and around Mysore, Karnataka, India. However, only 316 women were included in the study following exclusion criteria, which were diseases influencing body weight like abnormal thyroid (15 cases) and diabetes (46 cases) or undergoing a diet plan or regular physical activity (3 cases). Most of them were classified as sedentary workers on enquiring about their occupation and day-to-day activities. Hysterectomized or ovariectomized women (20 cases) with malignancies (two cases) were excluded. None of the participants were under medication, which might have influenced their body weight (e.g., glucocorticoid, pioglitazone, lipid lowering agents, antidepressants or under infertility treatment). None of them ever used hormone therapy (HT) either. The subjects were grouped into two groups one those who are in transitional or climacteric phase that is the perimenopausal phase, which extends two years before the last menstruation and followed by one year of amenorrhea with menstruation irregularities and pre menopausal stage defined as women at climacteric age with certain physiological changes but still have a regular menstrual cycle. Another group of women with complete cessation of the menstrual cycle for more than a year but not because of surgical resection of the uterus or ovaries called to be on postmenopausal stage. Finally, 147 postmenopausal women and 169 pre menopausal women were accepted for the study.

Anthropometric measurements

A standardized questionnaire was administered that included a personal and family history of chronic disorders, gynecological anomalies, medication intake, physical activity, dietary information, alcoholism, and smoking status. Anthropometric measurements such as height, weight, waist (WC) and hip circumference (HC) were taken. Height was measured using Holtain Anthropometric rod

and weight was taken with lighter clothing, and no foot wears. Waist circumference (WC) was measured at the midpoint at the bottom of the rib cage and the top of the lateral border of the iliac crest during minimal respiration. The Omron fat monitor was used to measure total body-fat percentage, basal metabolic rate (BMR) and body mass index (BMI). BMI above 25 kg/m² was considered as obese^[17]. A standard mercury sphygmomanometer was used to record systolic (SBP) and diastolic blood pressures (DBP) in the first and fifth Korotkoff sounds.

Laboratory analysis

Venous blood (12 h fasting) was collected to assess glucose, high-density lipoprotein cholesterol (HDL), low density lipoprotein cholesterol (LDL), triglyceride, total cholesterol, glycated hemoglobin (HbA1c) using plasma with the help of automated biochemical analyzer EM360 Transasia, and ERBA kits. Postprandial plasma glucose (PGLU) was measured after 2 hours of administering 75 g of glucose to the subjects (WHO, OGTT).

Statistical analysis

All the analysis was done using SPSS 11.5. The independent *t*-test was used for describing the characteristic difference between the groups. Analysis of covariates (ANCOVA), adjusted for age and BMI, was used to evaluate the effect of menopausal status on physical and metabolic factors. Pearson's correlation coefficients were measured to assess the interrelationship between age, obesity traits and cardio metabolic risk factors in all the subjects. Multiple stepwise linear regression model analysis was applied to determine the independent effect of age, menopause, general obesity, and central obesity on each different cardio metabolic risk factors. The colinearity between different traits of general (BMI and total body-fat percentage) or central obesity (WHR or WC) was evaluated by tolerance values. If high colinearity existed between two variables defining same characteristic, only one among them was selected for stepwise regression.

RESULTS

The comparative statistics (*t*-test and ANCOVA) between the groups is given in Tables 1 and 2. Postmenopausal women were significantly of higher age, weight, fat percentage ($P < 0.001$), BMI and WHR ($P < 0.01$), and lower height and BMR ($P < 0.001$) than pre menopausal women. The levels of cardio metabolic risk factors were found to be elevated in postmenopausal women than premenopausal women except for lower HDL. After adjusting for BMI and age in the analysis of covariance, the mentioned menopause-associated differences in anthropometric and metabolic parameters was not consistent. Though WC showed a significant increase in

postmenopausal women after adjustment but HDL, fasting glucose, postprandial glucose, and CRP levels seized to show any significant difference. HbA1c did not differ with menopausal status.

Correlations between the physical and metabolic parameters have been shown in Table 3 with significant Pearson's coefficients discernibly marked. Age was found to be positively correlated with systolic blood pressure, fasting glucose, triglyceride, cholesterol, LDL levels and fat percentage ($P < 0.001$), weight ($P < 0.01$), BMI, postprandial glucose, HbA1c, and diastolic blood pressure ($P < 0.05$). Conversely, it is negatively correlated with height, HC ($P < 0.01$), and BMR ($P < 0.001$). Significant correlations were also established between BMI, diastolic BP, triglyceride, cholesterol, LDL cholesterol, and HbA1c levels. Only fat percentage was found to be significantly associated with CRP positively and with HDL inversely. Although WC showed correlations with each of the metabolic factors except CRP and HDL but WHR showed mild association with triglyceride levels only. Strong correlations were observed between HC and levels of HbA1c and LDL. BMR showed significant correlations with HbA1c, LDL and diastolic blood pressure.

The colinearity was tested between the independent variables, such as age, BMI, fat percentage, WHR or WC, and menopausal status. For the total subjects, the levels of tolerance between independent variables were, age = 0.289, menopausal status = 0.293, fat percentage = 0.692, WC = 0.720. Since low colinearity was observed between the variables to say; age, menopausal status, fat percentage and WC, they were finally considered as independent variables for multiple stepwise regression analysis for each of the cardiometabolic risk factors. Table 4, shows the multiple stepwise regression standardized coefficient and R² value for the accepted model for each dependent variable.

Menopausal status was found to be an independent factor for fasting and postprandial glucose, blood pressure, triglyceride, cholesterol, and LDL. WC was a significant predictor of almost all cardio metabolic risk factors except for diastolic BP and CRP. Total fat percentage showed its positive independent effect on glycated hemoglobin A1c, diastolic blood pressure, and CRP but negative effect on HDL levels. However, age was observed to have independent effect only on HbA1c to some level.

DISCUSSION

This study hypothesized that menopause induced obesity is a major determinant of abnormal metabolic profiles in menopausal women. Thus, this study aimed at clarifying the controversial idea of whether the age or menopausal

Table 1: Comparison of anthropometric factors between pre- and postmenopausal women

	Premenopausal women *n = 169	Postmenopausal women *n = 147	P value [†]	P value [‡]
Age (years)	35.07 ± 3.78	56.67 ± 9.36	<0.001	–
Height (m)	1.53 ± 0.05	1.50 ± 0.06	<0.001	0.034
Weight (kg)	54.28 ± 12.74	60.38 ± 11.51	<0.001	0.035
Waist circumference (cm)	78.21 ± 12.73	78.66 ± 10.64	0.901	<0.001
Hip circumference (cm)	97.61 ± 11.41	92.17 ± 11.19	<0.001	0.042
Body mass index (kg/m ²)	23.86 ± 5.29	25.46 ± 4.61	0.005	–
Waist-hip ratio	0.81 ± 0.12	0.85 ± 0.10	0.002	0.002
Fat percentage	34.21 ± 5.83	36.73 ± 7.81	0.001	0.019
Basal metabolic rate	1274.70 ± 192.16	1089.79 ± 253.01	<0.001	0.001

*Means ± SD, [†]independent t-test, [‡]ANCOVA, adjusted for age and BMI

Table 2: Comparison of metabolic factors between pre- and postmenopausal women

	Premenopausal women *n = 169	Postmenopausal women *n = 147	P value [†]	P value [‡]
Fasting glucose (mg/dl)	87.17 ± 13.94	96.65 ± 24.96	<0.001	0.069
Postprandial glucose (mg/dl)	108.71 ± 26.41	117.28 ± 34.45	0.015	0.062
Glycated hemoglobin A1c (%)	5.50 ± 1.28	5.83 ± 2.02	0.092	0.675
Systolic blood pressure (mmHg)	113.88 ± 16.89	126.48 ± 21.0	<0.001	0.008
Diastolic blood pressure (mmHg)	77.02 ± 11.74	80.84 ± 12.44	0.006	0.023
Triglyceride (mg/dl)	106.13 ± 61.09	137.46 ± 72.20	<0.001	0.007
Total cholesterol (mg/dl)	166.52 ± 35.73	186.97 ± 39.11	<0.001	0.014
HDL cholesterol (mg/dl)	48.34 ± 8.7	45.78 ± 10.92	0.023	0.326
LDL cholesterol (mg/dl)	82.88 ± 21.85	92.81 ± 23.53	<0.001	0.020
C-reactive protein (mg/l)	1.09 ± 0.74	1.35 ± 1.09	0.016	0.054

*Means ± SD, [†]independent t-test, [‡]ANCOVA, adjusted for age and BMI

Table 3: Pearson correlation coefficients between anthropometric and cardiometabolic risk factors of 316 women

	Age	Systolic BP	Diastolic BP	HbA1c	Postprandial glucose	Fasting glucose	Triglyceride	Cholesterol	HDL	LDL	CRP
Age	1	0.314 [‡]	0.134 [*]	0.125 [*]	0.117 [*]	0.211 [‡]	0.183 [‡]	0.232 [‡]	-0.100	0.187 [‡]	0.109
Height	-0.235 [†]	-0.150 [†]	0.000	-0.064	-0.036	0.049	-0.036	-0.145 [†]	0.013	-0.128 [*]	-0.023
Weight	0.204 [†]	0.042	0.184 [†]	0.124 [*]	0.052	0.063	0.106	0.104	-0.024	0.182 [‡]	0.056
BMI	0.122 [*]	0.104	0.204 [‡]	0.162 [†]	0.086	0.061	0.129 [*]	0.170 [†]	-0.031	0.248 [‡]	0.065
W.C.	0.023	0.182 [†]	0.172 [†]	0.223 [‡]	0.142 [*]	0.183 [†]	0.198 [‡]	0.221 [‡]	-0.033	0.287 [‡]	0.072
H.C.	-0.180 [†]	0.057	0.126 [*]	0.199 [‡]	0.080	0.078	0.054	0.140 [*]	0.026	0.196 [‡]	0.021
WHR	0.099	0.098	0.038	0.026	0.085	0.100	0.127 [*]	0.047	-0.061	0.084	0.059
Fat percentage	0.196 [‡]	0.187 [†]	0.206 [‡]	0.003	0.083	0.115 [*]	0.145 [†]	0.206 [‡]	-0.159 [†]	0.230 [‡]	0.239 [‡]
BMR	-0.338 [‡]	-0.006	0.128 [*]	0.144 [*]	0.058	0.052	0.069	0.044	0.037	0.126 [*]	-0.032

Correlation coefficients, (^{*}P≤0.05, [†]P≤0.01, [‡]P≤0.001)

Table 4: Effects of age, menopausal status and measures of obesity on cardiometabolic risk factors

Cardio metabolic risk factors	**R ²	Age	Menopausal status ^{††}	Fat percentage	Waist circumference
Fasting glucose (mg/dl)	0.088		0.234 [‡]		0.185 [‡]
Postprandial glucose (mg/dl)	0.040		0.141 [*]		0.143 [†]
Glycated hemoglobin A1c (%)	0.097	0.173 [†]		0.208 [‡]	0.334 [‡]
Systolic blood pressure (mmHg)	0.134		0.318 [‡]		0.184 [‡]
Diastolic blood pressure (mmHg)	0.057		0.123 [*]	0.184 [‡]	
Cholesterol (mg/dl)	0.120		0.266 [‡]		0.223 [‡]
Triglyceride (mg/dl)	0.092		0.231 [†]		0.199 [‡]
HDL-C cholesterol (mg/dl)	0.025			-0.159 [†]	
LDL-C cholesterol (mg/dl)	0.129		0.216 [‡]		0.288 [‡]
C-reactive protein (mg/l)	0.057			0.239 [‡]	

**Multiple stepwise standardized regression coefficients; (^{*}P≤0.05, [†]P≤0.01, [‡]P≤0.001), ^{††}Menopausal status, premenopause = 0, postmenopause = 1

transition is the leading and independent cause for cardiometabolic risk factors aberration. Most of the studies on the prevalence of MS among Indian women and women across the world have shown a higher percentage of MS in postmenopausal women consistently based on comparative statements on metabolic components between pre and post menopausal groups.^[21-25] In a study in eastern India, revealed significant differences in lipid metabolism, plasma glucose and blood pressure between the subjects who differed primarily in their menopausal state independent of age and BMI.^[24] The studies on French, North Taiwanese and Chinese women, showed invariably similar results.^[16,26,27] In our study population, a significant rise in LDL, cholesterol, triglyceride and blood pressure was observed in postmenopausal women after adjusting for covariates age and BMI. However, HDL levels remained unchanged as in Chinese, in contrast to the studies suggesting a rise or fall.^[2,3,16,27-31] Circulating CRP level is elevated in, metabolically abnormal Type 2 diabetes, used as a marker for CVD, obesity and diagnosis of MS.^[32] In addition, CRP level is an important correlate of use of HT among postmenopausal women.^[7] However, we did not find a significant difference between the groups after adjusting for the confounders, may be because of the elimination of women under HT and relatively small sample size in our study. The significant differences in variables that was observed in our study prior to confounder optimization could not be followed post adjustments, might be due to colinearity in the variables.

Customarily, with other reports, we ascertained increase in the body fat mass and central obesity with menopause, independent of age and BMI. Furthermore, lower BMR at menopause indicative of decreased energy expenditure and relatively more physical inactivity, ultimately grounds for the afore mentioned increments.^[16,33-37] Therefore, the result seemed to support the distinctive effect of menopause on changes in physical characteristic and total body composition of post-menopausal women.

Previous studies have confirmed the remarkable role of intra abdominal fat mass and central obesity in worsening of CVD risk indices after menopause.^[16,38-40] Thus, a strong and significant association of the WC with almost every metabolic risk factor and correlation of total body-fat percentage with the major components such as glucose, triglyceride, HDL, CRP, and blood pressure in this study reflects the decisive role of central adiposity and fat composition for metabolic anomalies after menopause.

Studies contributing to causal attributes for high prevalence of metabolic risk factors after menopause are few and found contradicting to each other. Gohle *et al.*,^[41] demonstrated an increase in the incidence of CVD with postmenopausal phase and Framingham Cohort showed

that the women with surgical or early menopause are also at higher risk. Contrastingly in a cross-sectional study in Brazil aging was reported as the primary factor for the increase in MS at menopause.^[42,43] However, Chang *et al.*, reported independent effects of age as well as menopause to mediate worsened CVD risk factors in postmenopausal women. A recent study on Iranian women demonstrated menopausal status as a predictor of MS independent of age.^[44] In our study, although age showed a significant correlation with measures of general obesity (fat percentage and BMI) and many of the metabolic risk factors but failed to show its independent effect on them except for HbA1c in regression models. Also no significant association was observed between age and central obesity measures (WC and WHR). Whereas the WC, have not only shown stronger correlations with almost all risk variables but also found to have its independent effect on components of the cardio metabolic risk factors. Besides, menopausal status and body-fat percentage showed a remarkable predicting effect. Collectively, it can be suggested that age may be one of the factors for obesity in menopausal women but may not be an independent cause for metabolic abnormalities. However, central fat accumulation during menopausal transverse can be accredited for alterations in risk variables.

The conflicts in the past studies encompassing menopause-related differences, and their predicting factors are explained by improper methods for measuring risk variables, inclusion and exclusion criteria for study subjects and confounding factor's influences. Thus, we have tried to circumvent the devastating effect of these facets to obtain a convincing result. Though very few studies have been reciprocated in an Asian Indian population with a similar object, but are accountable for suggesting that menopause plays a vital role to alter body composition and post-menopausal women are more prevalent to MS, thus are at higher risk for cardiovascular problems.^[21,22,24,45] As per the author's knowledge, this study is the first attempt to predict the probable causes for menopause-related differences in a woman's physiology in Indian subcontinent. But the results are not evocative of generalizing to the Asian Indian population owing to the socioeconomic and regional diversity. Also woman's lifestyle pertaining to quantum of regular physical activity and nutrition plays an inevitable role in life, after menopause. Thus, the lack of elaborated measures for afore said factors can be a limitation in the present study.

CONCLUSION

The postmenopausal women are at higher risk of developing MS and associated disorders than premenopausal women. The hormonal transition at menopause leads to augmentation in general and central obesity which in turn independently

causes abnormalities in metabolic risk variables. Though aging could not show a convincing independent influence but relative physical inactivity and falling BMR with age after menopause may be accountable for menopausal obesity. Thus, it can be documented that menopausal status and related central obesity is the major predictor above the age, for metabolic risks in menopausal women of Karnataka South India. Finally, the rest of the variances of the risk variables may be ascribed to the genetic entities in menopausal women.

ACKNOWLEDGMENTS

This work is a part of the Anthropological Survey of India, project Entitled "People of India: Bio cultural adaptations"; we express our gratitude to the Director, Anthropological Survey of India, Ministry of Culture, Government of India, Kolkata for supporting the project. We are thankful to all subjects Mysore, Karnataka who voluntarily participated in this study and provided blood samples. We are also thankful to Lions Club Mysore, Dr. Vikas Modi and Dr. Ramakrishna of Amritakripa Hospital, Rupanagar, Mysore and paramedical staff for organizing medical camps and extending their valuable help during the collection of samples. Thanks are due to our colleagues Ms. Lakshmi, Mr. Abrar Alam, Ms. Pratiksha Bhat, and Dr. Pushpa Jogihalli for their sincere involvement at various levels in this project. Authors would also like to thank the officials of Anthropological Survey of India for providing technical and administrative support.

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How to cite this article: Dasgupta S, Salman M, Lokesh S, Xaviour D, Saheb SY, Ravi Prasad BV, *et al.* Menopause versus aging: The predictor of obesity and metabolic aberrations among menopausal women of Karnataka, South India. *J Mid-life Health* 2012;3:24-30.

Source of Support: Anthropological Survey of India, Kolkata, Ministry of Culture, Government of India., **Conflict of Interest:** None declared.

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