Original Article

Cardiometabolic Risk in Pre- and Post-Menopausal Women with Special Reference to Insulin Resistance: A Cross-Sectional Study

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ABSTRACT

Background: Reduced levels of estrogen have been associated with metabolic alterations and increased insulin resistance (IR) in postmenopausal women, thus predisposing them to cardiometabolic risks. The aim of this study was to assess alterations in parameters of cardiometabolic risk in apparently healthy pre- and post-menopausal women and to study the effect of IR on these metabolic parameters. **Methods:** A cross-sectional study was conducted on randomly selected apparently healthy women (n = 262). These women were categorized as premenopausal (n = 184) and postmenopausal (n = 78). Anthropometric measurements, blood pressure, lipid profile, fasting glucose, and insulin concentrations were estimated on all the participants using standard protocols. Homeostatic model assessment of IR was computed to estimate the level of IR. **Results:** Most lipid parameters, blood pressure, waist circumference, and fat percentage were significantly higher ($P < 0.05$) in postmenopausal women than premenopausal women. On subcategorizing women with respect to IR (<3, >3), metabolic parameters (e.g., triglyceride − 104.7 ±53.2 mg/dl, Blood Sugar Level Fasting (BSLF) – 103.3 ± 40.1 mg/dl, and fasting serum insulin − 23 ± 12.3 mIU/L) were also higher ($P < 0.001$) in premenopausal women having IR >3. Significantly higher low-density lipoprotein (132.7 ± 38.7 mg/dl vs. 114.4 ± 25 mg/dl) and total cholesterol (211.3 ± 40.5 vs. 184.8 ± 29.4 mg/dl) were observed in postmenopausal women with IR >3 ($P < 0.05$) along with higher BSLF (126.6±54.3 mg/dl**) and fasting insulin levels (22.3 ± 12.1 mIU/L) ($P < 0.001$). **Conclusion:** This study reveals that IR may predispose women to increased cardiometabolic risk. Urgent attention needs to be focused toward metabolic health of women.

KEYWORDS: *Cardiometabolic parameters, homeostatic model assessment of insulin resistance, insulin resistance, postmenopausal, premenopausal*

INTRODUCTION

Menopausal age of Caucasian women is reported between 48 and 55 years, usually occurs earlier in Indian women, the average age being between 40 and 49 years.[1] Recent studies across the world have thrown light on the increased cardiometabolic risks in postmenopausal women as compared to their corresponding premenopausal counterparts.[2,3] Postmenopausal women may be predisposed to increased cardiovascular risks, possibly due to depletion in the ovarian follicles followed by subsequent reduction in estradiol concentrations.[3-5]

In addition, deranged lipid profiles with alterations in low-density lipoprotein cholesterol (LDL-C), high-density lipoprotein-cholesterol (HDL-C), triglycerides (TGs), total cholesterol (TC), and reduced glucose tolerance have also been previously reported in this group of women. On the other hand, as compared to postmenopausal phase of the women, secretion

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of estradiol in premenopausal women may offer a cardioprotective effect.[5]

Insensitivity of the target tissues in the human body to the action of pancreatic insulin is regarded as insulin resistance (IR).[6,7] In premenopausal women, increase in weight or abdominal obesity can result in IR. Insulin insensitivity often observed in postmenopausal women may be because of the changes in her hormonal status and fat redistribution coupled with reduced adiponectin secretion.[6]

However, in case of normal insulin sensitivity, metabolic parameters seen in postmenopausal need to be further examined. Furthermore, Indian studies on IR among premenopausal women affecting their metabolic status are scant. Hence, the objectives of the current study were (1) to assess the alterations in parameters of cardiometabolic risk as judged by anthropometric (body mass index, waist circumference), biochemical (lipid profile, IR), and body composition parameters in apparently healthy pre- and post-menopausal women and (2) to study the association of IR with the above parameters in pre- and post-menopausal women.

METHODS

A cross-sectional study was conducted on a population of women belonging to upper- and middle-socioeconomic status in the city of Pune, India, from the year 2015 to 2016. Women from housing societies, residential areas, schools, and corporate offices were approached. Of the 354 women who were approached, a total of 262 apparently healthy women (74%) agreed to be a part of this study. Based on standard deviation of homeostasis model assessment (HOMA)-IR levels from previous studies,[8] sample size of 262 was sufficient to detect the differences in HOMA-IR levels at 15% margin of error and two-sided 5% level of significance so as to achieve a power of the study to be at 0.8. Written informed consent was obtained from the participants preceding the commencement of the study. The research protocol was approved by the Institutional Ethics Committee.

Data on age and menopausal status were collected using a validated questionnaire. Anthropometric measurements, blood pressure, lipid profile, fasting glucose (FG), and serum insulin (SI) concentrations were assessed to compare these parameters between the two groups of women.

Apparently healthy women from the age group of 20 to 60 were considered for the study and were screened by using a validated questionnaire to identify preexisting comorbidities. Participants previously diagnosed with comorbidities such as hypertension, diabetes mellitus, hypothyroidism, and cardiovascular disease and who were on any medications for the same were excluded from the study.

Standard anthropometric measurements of weight, height, waist circumference, and body fat percentage were assessed in the study group. Weight was measured using an electronic scale (Tanita, SC240 MA, India) to the nearest 0.1 kg with the study patients in light clothing and no shoes. Standing height was determined using a portable stadiometer (Seca 213) to the nearest 1 mm. Waist circumference was assessed by using a stretch-resistant measuring tape (SECA) to the closest 0.1 cm with the participant standing erect; measurements were made from between the lower margin of least palpable rib and highest of the iliac crest at the end of normal expiration. Blood pressure was measured using a sphygmomanometer after the patient was seated and was allowed to rest. Body fat percentage was estimated using Bioelectrical Impedance Analysis (SC240 MA, Tanita, India).

Venous blood was drawn under aseptic conditions post 12-h fasting and was transferred into a sterile vacationer (BD, Franklin Lakes, NJ, USA). A complete lipid profile test including TC, TGs, and HDL-C were performed enzymatically. The Friedewald equation was used to obtain the LDL-C concentrations. FG was measured by using the hexokinase method. Fasting insulin was evaluated by enzyme-linked immunosorbent assay (DRG diagnostics, Germany; intra-assay coefficient of variance [CV] 2.6%, interassay CV 2.9%).

HOMA IR (mg/dl) was computed by using the formula:[9]

$$HOMA\ IR\ (mg/dl) = \frac{Fasting\ glucose\ (mg/dl) \times fasting\ insulin\ (mIU/L)}{405}$$

There is varying literature on cutoff point for detecting IR through HOMA-IR in women. A few studies suggest values ranging from 1.5 to 3.5.[10,11] As HOMA-IR cutoffs are dependent of differences in ethnicity, age, and other cofactors, median value of 3 was considered for categorizing women as per IR into groups.

Descriptive statistics of all the cardiometabolic parameters (mean and standard deviation) were computed for women from both the groups. Normality of the data was evaluated using the Kolmogorov–Smirnov test. Pre- and post-menopausal women were compared using nonparametric tests for nonnormal variables (Mann–Whitney test) and independent sample *t*-test on parameters which followed a normal distribution. The two groups were further stratified on the basis of HOMA IR in order to assess the effect of increased IR. The parameters were reanalyzed on the basis of these groups using the Mann–Whitney and *t*-test on the respective parameters.

To observe the percentage of women with abnormal cardiometabolic parameters, the percentage abnormal was calculated by using cross-tabulation analysis. Tests were conducted using the IBM Corp. Released 2012. IBM SPSS Statistics for Windows, Version 21.0. Armonk, NY: IBM Corp. and level of significance was considered at (two-tailed *P* value) *P* < 0.05 and *P* < 0.001, respectively.

RESULTS

Mean age of pre- and post-menopausal apparently healthy women was 36.2 ± 6.5 and 52.7 ± 7.1 years, respectively. Higher mean TC, TG, TG/HDL ratio, and LDL-C were observed in postmenopausal women in comparison with their premenopausal counterparts (*P* < 0.05). A similar trend was also seen for FG, systolic blood pressure, diastolic blood pressure, waist circumference, and fat percentage (fat%) [Table 1]. A percentage of women with abnormal parameters in both groups are in line with the above results [Figure 1]. However, the HDL-C levels of postmenopausal women were higher than in the premenopausal women. Furthermore, there were no differences in fasting insulin concentrations between the two groups [Table 1]. To study the impact of IR on cardiometabolic parameters, the two groups were further subclassified based on HOMA-IR (> and <3. It was observed that among premenopausal women with HOMA-IR >3, TG levels, TG/HDL ratio, FG, and SI levels were higher as compared to premenopausal women with HOMA-IR <3, indicating changes in their cardiometabolic parameters at younger age (*P* < 0.05) [Table 2]. Furthermore, the HDL-C levels

were significantly lower (*P* < 0.05) in premenopausal counterparts with HOMA IR >3 [Table 2]. Interestingly, among postmenopausal women with HOMA IR >3, TC and LDL-C levels were higher (*P* < 0.05) as compared to the group postmenopausal women with HOMA IR <3 [Table 2]. In addition, alterations in the TG/HDL ratio, FG, fasting insulin, waist circumference, and fat% were detected in the postmenopausal group with HOMA IR >3 when compared to their fellow counterparts [Table 2]. Increased IR affected the metabolic parameters in premenopausal as well as postmenopausal women [Figure 2].

DISCUSSION

The results of our cross-sectional study on pre- and post-menopausal apparently healthy women suggest that increased cardiometabolic risk was observed in
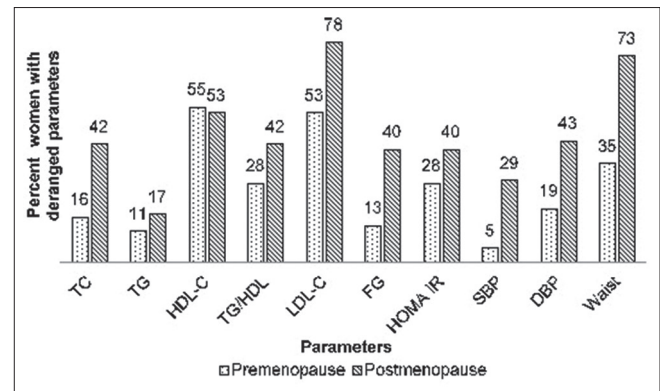

Figure 1: Deranged parameters in pre- and post-menopausal women

Table 1: Comparison of anthropometric and cardiometabolic parameters in pre- and post-menopausal women			
	Premenopausal (*n*=184)	**Postmenopausal (*n*=78)**	**Total (*n*=262)**
Age (years)	36.2±6.5	52.7±7.1**	41.1±10.1
Height (cm)	154.6±6	154.5±6	154.6±6
Weight (kg)	59.9±12	65±10.7**	61.4±11.8
BMI (kg/m²)	25.2±4.7	27.2±4.2**	25.8±4.6
Cholesterol (mg/dl)	169.3±30.6	195.3±36.4**	177.1±34.5
TG† (mg/dl)	85.9±45.8	111.2±61.2**	93.4±52
HDL-C† (mg/dl)	48.5±9.8	51.4±12.6	49.3±10.8
TG/HDL† ratio	1.9±1.3	2.3±1.5*	2.1±1.4
LDL-C (mg/dl)	103.7±26.7	121.7±32.2**	109.1±29.5
FG† (mg/dl)	93.4±23.1	106.5±38.7**	97.3±29.2
Fasting insulin† (mlU/L)	12.4±9.5	13.7±10.5	12.8±9.8
HOMA IR† (mg/dl)	2.9±2.7	3.7±3*	3.2±2.8
SBP† (mmHg)	115.3±12.9	127.1±14.1**	118.8±14.3
DBP† (mmHg)	78.1±10.1	83.8±13.2**	79.8±11.4
Waist (cm)	85.4±11	94±9.9**	88±11.4
Fat (%)	35.2±7.3	38.1±7.2**	36.1±7.4

*Level of significance (*P*<0.05), **Level of significance (*P*<0.001), †Represents skewed parameters. Values represent the mean±SD.
BMI: Body mass index, TG: Triglyceride, HDL-C: High-density lipoprotein-cholesterol, LDL-C: Low-density lipoprotein-cholesterol, HOMA-IR: Homeostatic model assessment of insulin resistance, SBP: Systolic blood pressure, DBP: Diastolic blood pressure, SD: Standard deviation, FG: Fasting glucose

Table 2: Comparison of anthropometric and cardiometabolic parameters in pre- and post-menopausal women with respect to homeostatic model assessment of insulin resistance

	Premenopausal		Postmenopausal	
	HOMA <3 (*n*=132)	HOMA >3 (*n*=52)	HOMA <3 (*n*=47)	HOMA >3 (*n*=31)
Cholesterol (mg/dl)	167.9±30.5	173±30.7	184.8±29.4	211.3±40.5*
TG (mg/dl)	78.5±40.3	104.7±53.2**	92.5±34.1	139.5±80.5*
HDL-C (mg/dl)	49.5±10.4	45.7±7.4*	51.9±13	50.7±12.1
TG/HDL ratio	1.7±1.1	2.4±1.5**	1.9±0.9	3.0±2*
LDL-C (mg/dl)	102.7±26	106.3±28.3	114.4±25	132.7 ± 38.7*
FG (mg/dl)	89.5±8.2	103.3±40.1*	93.2±11.5	126.6±54.3**
Fasting insulin (mlU/L)	8.2±2.4	23±12.3**	8.0±2.7	22.3±12.1**
SBP (mmHg)	114.7±13.6	116.9±10.9	124.8±13.6	130.7±14.5
DBP (mmHg)	78.5±10.8	77.1±7.9	84.5±15.4	82.7±8.6
Waist (cm)	84.6±11.1	87.4±10.8	91±8.5	98.5±10.2*
Fat (%)	35.0±7.5	35.8±6.8	36.5±7.8	40.7±5.1*

*Level of significance (*P*<0.05), **Level of significance (*P*<0.001). Values represent the mean±SD. BMI: Body mass index, TG: Triglyceride, HDL-C: High-density lipoprotein-cholesterol, LDL-C: Low-density lipoprotein-cholesterol, HOMA IR: Homeostatic model assessment of insulin resistance, SBP: Systolic blood pressure, DBP: Diastolic blood pressure, SD: Standard deviation, FG: Fasting glucose
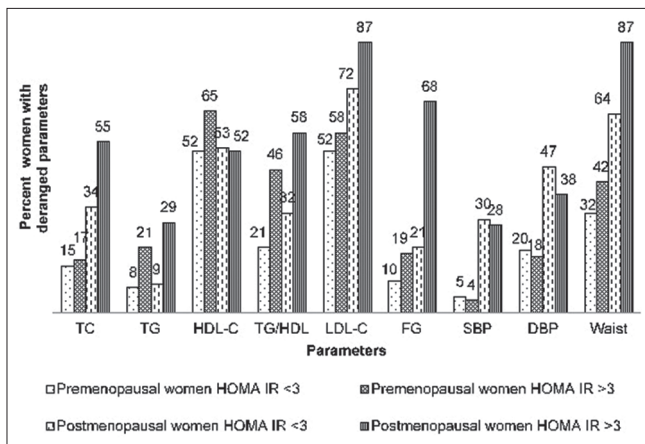

Figure 2: Deranged parameters in pre- and post-menopausal women with respect to homeostasis model assessment insulin resistance

postmenopausal women in comparison with their premenopausal counterparts. Further, women in both groups with higher IR (as indicated by HOMA-IR), had deranged metabolic parameters in comparison with women who had a lower HOMA-IR.

It was observed that lipid parameters, i.e., TC, LDL-C, TG, and TG/HDL ratio were higher in postmenopausal women when compared to premenopausal women. These results are in line with a similar study conducted on 47 premenopausal and 77 postmenopausal apparently healthy Indian women.[12] Moreover, the TC and LDL-C levels were observed to be higher only in the postmenopausal women with higher IR. This suggests that rise in TC and LDL-C, which are important cardiometabolic risk factors, are possibly not affected by IR but by loss of estrogen in postmenopausal women.

Estrogen is known to play a vital role in the regulation of the LDL-C receptors in the liver.[13] Reduced estrogen levels have been shown to increase plasma lipoprotein and hepatic TG lipase leading to accumulation of LDL-C fragments.[12,14] Thus, downregulation of estrogen could account for the perturbations in lipid profile parameters observed in postmenopausal women. In addition, increased central obesity in this group of women could affect the lipid parameters, further causing insulin insensitivity at the cellular level.[15,16] Together with the postmenopausal state, an increase in HOMA-IR in the postmenopausal women further increased cardiovascular risk.[17]

Our study also revealed alterations in metabolic parameters of premenopausal women who exhibited higher IR as compared to the ones with lower IR. Several studies have previously thrown light on the effect of increased IR in women affected with polycystic ovary syndrome and other comorbidities.[18-20] Furthermore, a recent study conducted on the middle-aged premenopausal women proposed that central obesity coupled with altered lipid profile were the main causative factors for the development of IR and metabolic syndrome in them.[21] However, the effect of IR on the metabolic health of apparently healthy premenopausal women is yet to be extensively studied. IR leads to excessive production of free fatty acids which are further metabolized in the liver.[8] Increment of TG and decline in HDL-C levels coupled with impaired vascular function could pose a potential threat to premenopausal women with IR.[8] Thus, our study suggests that premenopausal women exhibiting IR are at a higher risk of developing cardiometabolic abnormalities.

An interesting observation of our study was the increased HDL-C levels in postmenopausal women. Other studies on postmenopausal women have reported analogous patterns of rise in HDL levels.[22,23] It has recently been suggested

that this increase could be a protective mechanism of the human body to counter the effect of metabolic alterations following menopause.[22] However, additional studies on Indian women are required to support this theory.

The strength of our study is that we have assessed both pre- and post-menopausal women and while it is known that cardiometabolic perturbations are more likely in postmenopausal women, our study shows that the these are made worse by the presence of IR. Moreover, our study also demonstrates that IR in a premenopausal state leads to metabolic alterations. However, ours is a cross-sectional study, and thus, we cannot comment on the causality. We also have an unequal sample size in the two groups, but we have confirmed the results by performing an analysis on a subset. Further, we have not been able to carry out hormonal analysis on our participants.

CONCLUSION

Cardiometabolic risk is increased in postmenopausal women and higher IR poses a greater threat. IR in premenopausal women also raises their cardiovascular risk. Urgent attention needs to be focused on cardiac health of women, especially for women who are postmenopausal and those with increased IR. Longitudinal and cohort studies are required to confirm our results.

Conflicts of interest

There are no conflicts of interest.

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