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Original article

Correlation of serum leptin and resistin levels with the metabolic risk factors of pre- and postmenopausal women in South India



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ABSTRACT

Background: Menopausal status is related to weight gain and abnormal lipid and glucose metabolism leading to metabolic syndrome (METS) susceptibility.

Purpose: To determine circulating serum leptin and resistin levels and to correlate these levels in relation to the metabolic factors in pre- and postmenopausal women.

Methods: A cross-sectional study was carried out on 34 individuals who were postmenopausal and 31 individuals who had regular menstruation among south Indian rural women. Anthropometric indices, blood pressure, fasting blood sugar (FBS), fasting lipid profile, fasting leptin, and fasting resistin levels were measured.

Results: In a total of 65 women, the mean age of the premenopausal group was 38.65 ± 6.21 years and that of the postmenopausal group was 55.32 ± 6.32 years. The fasting serum leptin level was increased considerably in postmenopausal women when compared to premenopausal women ($p = 0.018$). Resistin had no significant relationship with metabolic factors except body mass index (BMI) in both of the groups. Triglycerides (TG) and FBS were lower in the premenopausal group when compared to the postmenopausal group ($p < 0.001$). Leptin was well correlated with BMI in premenopausal women ($r^2 = 0.7120$, $p < 0.0001$) as well as postmenopausal women ($r^2 = 0.2470$, $p = 0.0028$). Leptin also had a significant correlation with FBS in both pre- ($r^2 = 0.1373$, $p = 0.0402$) and post-menopausal women ($r^2 = 0.2141$, $p = 0.0401$). Systolic blood pressure (SBP) was positively associated with leptin levels in postmenopausal women ($p < 0.001$).

Conclusion: Leptin was found to have significant association with metabolic factors when compared to resistin in pre- and postmenopausal women and there is no doubt that association of BMI and FBS elevates the level of leptin in both categories.

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1. Introduction

Metabolic syndrome (METS) is a cluster of risk factors known to promote or increase the risk of cardiovascular mortality and morbidity [1,2]. The prevalence of this syndrome and its components increases with age and after the onset of the menopause; hence more postmenopausal women are likely to experience the syndrome closely related with the hormonal changes taking place during the climacteric [3]. The change-over from pre- to post-menopause is associated with the development of many features of the METS, including (1) increased central body fat; (2) a transferal towards a more atherogenic lipid profile, with increased low density lipoprotein (LDL) and triglyceride (TG) levels, reduced high density lipoprotein (HDL), and small, dense LDL particles; and (3) increased glucose and insulin levels. The development of these risk factors may be a direct result of ovarian failure or, alternatively, an indirect result of the metabolic consequences of central fat redistribution with estrogen deficiency. It is unclear whether the transition to menopause increases cardiovascular risk in all women or only those who develop features of the METS [3,4]. The risk for cardiovascular events, type 2 diabetes mellitus, and decreased quality of life increases directly in relation to body mass index (BMI) [5,6]. It is difficult to determine a certain age for menopause because the menopause age differs in different societies. According to the literature, the mean menopause age has a wide range of 39–59 years [7]. The mean age of menopause ranges in Indian women from 40.32 years to 48.84 years [8,9].

The concept of markers has been introduced in the last few decades. A marker is a measurable variable found in an available biological sample or detected by tissue imaging. A marker might reflect underlying disease pathophysiology, predict future events, and assess the response to treatment. They serve as sensitive detectors of early target organ damage [10,11]. Leptin has a variety of important central and peripheral actions to regulate energy balance and metabolism, fertility, and bone metabolism that are mediated by specific cell surface leptin receptors [12]. One of the main advances in the field of metabolic control of body weight and obesity treatment was identification of the fact that leptin plays an important role in controlling body weight, signaling to the central nervous system (CNS) the amount of body fat. Indeed, leptin levels are positively correlated to indices of body fat, namely total fat mass, percent body fat, and BMI. Normally menstruating women show higher leptin levels than postmenopausal women, thus suggesting a stimulatory effect of estrogen and/or progesterone and an inhibitory action of androgens on plasma leptin concentrations [13]. Resistin belongs to a family of cysteine-rich secreted polypeptides produced by monocytes/macrophages [14]. It is also regarded as a novel adipokine that has been suggested to play a role in the development of insulin resistance and obesity. Resistin has been reported to play a pivotal role in the progression of METS. Reports have suggested that obesity is characterized by inflammation—paralleling the condition with other diseases. Some studies established that leptin and resistin could be a major link between obesity and inflammation in cardiovascular diseases (CVD) [15,16], but the influence of menopause

on leptin and resistin levels is still poorly understood. Indian women seem to have a peculiar body phenotype, characterized by increased waist circumference (WC), increased waist/hip ratio, excessive body fat mass, increased plasma insulin levels and insulin resistance, as well as an atherogenic dyslipidemia, with low levels of HDL cholesterol and increased TG levels [17]. In addition, unique genetic markers could potentially make Indians more susceptible to cardiometabolic risks [18]. Cardiovascular risk is poorly managed in Indian rural women, especially during the menopausal transition when susceptibility to cardiovascular events increases. Hence this study was undertaken particularly in the Indian rural female population to estimate the metabolic risk factors and to evaluate the correlation of leptin and resistin levels with BMI, blood sugar, and lipid profiles in pre- and postmenopausal women.

2. Methods

2.1. Study design

A cross-sectional study was conducted along with the Department of Community Medicine, SRM Medical College Hospital and Research Centre, SRM University, Kattankulathur, India from June 2012 to November 2012.

2.2. Study population

The participants in this study were 65 adult females, aged 25–70 years from rural areas in and around Kattankulathur. None of the participants were taking any medication nor had any evidence of metabolic diseases aside from modest obesity. All participants provided written informed consent for the procedures of this study. Postmenopausal women who had at least a 1-year history of cessation of menses were included. All participants gave informed consent. The study was approved by an institutional ethics committee of SRM Medical College Hospital and Research Centre and the procedures followed were in accordance with the applied guidelines.

2.3. Samples and measurements

2.3.1. Physical examination

A questionnaire was completed at each health center by trained interviewers. Demographic information was achieved by a questionnaire. Height and body weight were measured without shoes and with the study participants wearing light clothes. Height was measured to the nearest 0.1 cm and weight was measured to the nearest 0.1 kg. Measurements were carried out using portable calibrated electronic weighing scales and inflexible measuring bars. BMI was calculated as weight/height^2 (kg/m^2). Individuals were classified into (1) normal, (2) overweight, or (3) obese, based on the definition of obesity for the population in India. Constant tension tape was used to measure the WC at the midpoint between the inferior costal margin and the highest point of the hip bone across the midaxillary line, with arms relaxed at the sides. The waist/hip ratio was calculated as an index of central obesity. Blood

pressure was measured using a mercury-free liquid crystal display (LCD) sphygmomanometer (Diamond, BPDG 234 LCD Super Deluxe, 34, Electronic Co-op Estate, Pune-Satara Road, Pune 411009, Maharashtra, India); two readings were taken at 10-minute intervals after participants had been seated for at least 10 minutes. The two readings were averaged. Systolic blood pressure (SBP) \geq 140 mmHg and diastolic blood pressure (DBP) \geq 90 mmHg were considered high.

2.4. Biochemical measurements

Blood samples of 6 mL were obtained in the morning (9:00 AM–11:00 AM) by venous puncture after overnight fasting (at least 12 hours fasting), 2 mL of blood were transferred into a sodium ethylenediaminetetraacetic acid (EDTA) vacutainer, and then the plasma was separated by centrifugation for glucose estimation. The remaining samples were transferred to plain tubes and allowed to clot at room temperature for 45 minutes before centrifugation to separate the serum. Centrifugation was done using a Centrifuge 5430R (Eppendorf). The samples were then aliquoted into Eppendorf tubes and stored at -20°C until analysis. Plasma glucose and serum total cholesterol (TC), TG, HDL, and LDL levels were determined through a fully automated clinical chemistry analyzer (EM 360; Transasia, ERBA Diagnostics [Transasia Bio-Medicals Ltd. Flat No. 3/5, 1st Floor, Raghupriya Apartments, 3, Krishnama Rd, Nungambakkam, Chennai-600034]) using ERBA diagnostics kits (ERBA Diagnostics Mannheim GmbH). Serum leptin and resistin concentrations were measured by an enzymatically amplified “two step” sandwich-type immunoassay using Human Leptin Quantikine enzyme-linked immunosorbent assay (ELISA) Kit (catalog no. DLP00; R&D Systems, Inc. 614 McKinley Place NE Minneapolis, MN 55413, USA) and Human Resistin Quantikine ELISA Kit (catalog no. DRSN00; R&D), respectively.

2.5. Statistical analysis

Statistical analysis was performed using GraphPad prism version 5.01 for Windows (GraphPad Software, Inc., 2236 Avenida de la Playa La Jolla, CA 92037, USA). Continuous variables are expressed as mean \pm standard deviation (SD). Leptin and resistin concentrations were logarithmically transformed to correct their skewed distribution. An independent t test was used to compare continuous variables between pre- and postmenopausal women. Logistic regression analysis was performed to assess the independent correlations between different components of metabolic risk factors and log-transformed leptin and resistin. For all statistical assessments, a *p* value <0.05 was considered statistically significant.

3. Results

Baseline and metabolic characteristics for the participants included in the cross-sectional analyses are summarized in Table 1. In a total of 65 study participants, the mean age of the premenopausal group was 38.65 ± 6.21 years and that of the postmenopausal group was 55.32 ± 6.32 years ($p > 0.05$). The

Table 1 – Baseline characteristics and leptin and resistin levels of pre- and postmenopausal women.

Variable	Premenopausal women	Postmenopausal women	<i>p</i>
Age (y)	38.65 \pm 6.21	55.32 \pm 6.32	ns
Height (m)	150.32 \pm 6.34	150.97 \pm 5.80	ns
Weight (kg)	55.81 \pm 8.54	56.51 \pm 8.98	ns
BMI (kg/m ²)	24.81 \pm 3.58	25.45 \pm 3.78	ns
Waist (cm)	98.04 \pm 8.26	98.81 \pm 8.13	ns
Hip (cm)	110.51 \pm 9.25	112.96 \pm 10.04	ns
Waist/hip ratio	0.72 \pm 0.18	0.79 \pm 0.21	ns
SBP (mm Hg)	125.84 \pm 12.57	138.12 \pm 17.65*	<i>p</i> < 0.001
DBP (mm Hg)	77.52 \pm 9.11	79.76 \pm 12.58	ns
TC (mg/dL)	171.68 \pm 40.78	179.95 \pm 34.50	ns
TG (mg/dL)	179.8 \pm 56.5	251.50 \pm 296.20*	<i>p</i> < 0.001
HDL (mg/dL)	39.71 \pm 8.30	40.00 \pm 6.97	ns
LDL (mg/dL)	109.42 \pm 26.39	121.97 \pm 27.88*	<i>p</i> < 0.001
Blood sugar (mg/dL)	131.13 \pm 51.54	131.29 \pm 44.00	ns
Leptin (ng/mL)	11.72 \pm 3.90	18.56 \pm 3.63*	<i>p</i> = 0.018
Resistin (ng/mL)	2.34 \pm 1.21	3.35 \pm 1.66	ns
TC/HDL ratio	4.56 \pm 1.32	4.42 \pm 2.45	ns
HDL/LDL ratio	0.35 \pm 0.14	0.35 \pm 0.32	ns
TG/HDL ratio	3.75 \pm 2.15	5.51 \pm 2.34	ns

Values are expressed as mean \pm standard deviation.

ns = nonsignificant ($p > 0.05$).

* $p < 0.001$ is significant.

BMI = body mass index; DBP = diastolic blood pressure; HDL = high density lipoprotein; LDL = low density lipoprotein; SBP = systolic blood pressure; TC = total cholesterol; TG = triglycerides.

BMI for the pre- and postmenopausal groups were 24.81 ± 3.58 kg/m² and 25.45 ± 3.78 kg/m², respectively ($p > 0.05$). SBP showed statistical significance between the two groups ($p < 0.001$). When we compared both the groups regarding height, weight, waist/hip ratio, TC, HDL, LDL, TC/HDL ratio, HDL/LDL ratio, TG/HDL ratio, and resistin, no difference was observed statistically. TG and blood sugar levels were lower in the premenopausal group when compared to the postmenopausal group ($p < 0.001$). The fasting serum leptin level was increased significantly in postmenopausal women when compared to premenopausal women ($p = 0.018$) (Table 1).

Leptin was well correlated with BMI in premenopausal women ($r^2 = 0.7120$, $p < 0.0001$) (Fig. 1A) as well as in postmenopausal women ($r^2 = 0.2470$, $p = 0.0028$) (Fig. 1B). Resistin also significantly related with the BMI in premenopausal ($r^2 = 0.4256$, $p < 0.0001$) (Fig. 2A) and postmenopausal women ($r^2 = 0.3645$, $p = 0.0002$) (Fig. 2B). All the baseline parameters were compared with the normal weight (BMI 18.5–24.9 kg/m²) and overweight (BMI 24.9–29.9 kg/m²) in both pre- and postmenopausal women (Table 2). A significant difference in serum leptin and TG level was noted in both normal and overweight groups at the pre- and postmenopausal stage ($p < 0.001$). A positive difference in fasting blood sugar (FBS) was evident in postmenopausal normal weight and overweight women ($p < 0.001$); the remaining parameters did not show significant difference as related to BMI.

Fasting serum lipid profiles were correlated with leptin and resistin in both pre- and postmenopausal women (Fig. 3); there was a rise in leptin and resistin levels in association with respected lipid profiles in pre- and postmenopausal women ($p > 0.05$). Leptin had positive correlation with FBS in both pre-

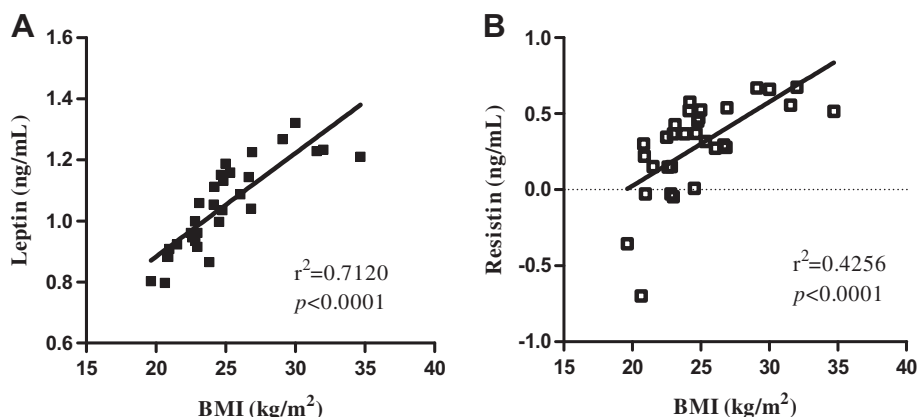


Fig. 1 – The relationship between body mass index (BMI) and (A) serum leptin and (B) serum resistin levels in premenopausal women.

($r^2 = 0.1373$, $p = 0.0402$) and postmenopausal women ($r^2 = 0.2141$, $p = 0.0401$) but resistin had no significant difference in association with blood sugar between the groups ($r^2 = 0.0521$, $p = 0.2165$ versus $r^2 = 0.5923$, $p = 0.1655$, respectively) (Fig. 4).

Leptin and resistin circulating levels were correlated with SBP and DBP in pre- and postmenopausal women (Table 3). SBP was significantly associated with the leptin levels in postmenopausal women ($p < 0.001$), but statistically there was no correlation in blood pressure with resistin levels in both pre- and postmenopausal women ($p > 0.05$).

4. Discussion

METS is a metabolic disorder that includes cardiovascular risk factors that are more prevalent in postmenopausal women. Several METS women patients carry on with their lives without any diagnostic symptoms until a health disorder related to METS appears. This study reports for the first time the relationship between leptin and resistin and metabolic factors in adult Indian rural women. Based on the estimation of biomarkers, there was a significant correlation between

leptin and associated metabolic risk factors such as BMI, FBS, and blood pressure rather than resistin. The relationship between leptin level and BMI is an important indicator of obesity in both groups but WCs and hip measurements were not correlated with leptin. In our study, we found that there was no significant independent effect of aging on serum leptin and resistin, nor did we confirm the observation of Moller et al [19] that aging alters the relationship between leptin levels and fat content (Fig. 5).

Our study showed a nonsignificant difference in the mean values of BMI estimated for the two groups. Previous studies [20,21] reported that premenopausal women demonstrated higher leptin production than postmenopausal women but our data did not support these observations; instead, our study indicated that leptin level was significantly increased in relation to body weight but not related to the climacteric. Our research findings suggest that menopausal status does not have a significant impact on resistin production. However, a similar comparison made in another study found that menopausal status does not have a significant impact on leptin production [22]. Because the present study showed that the significant lowering of leptin impacts long-term weight control, the idea of utilizing leptin as a prime

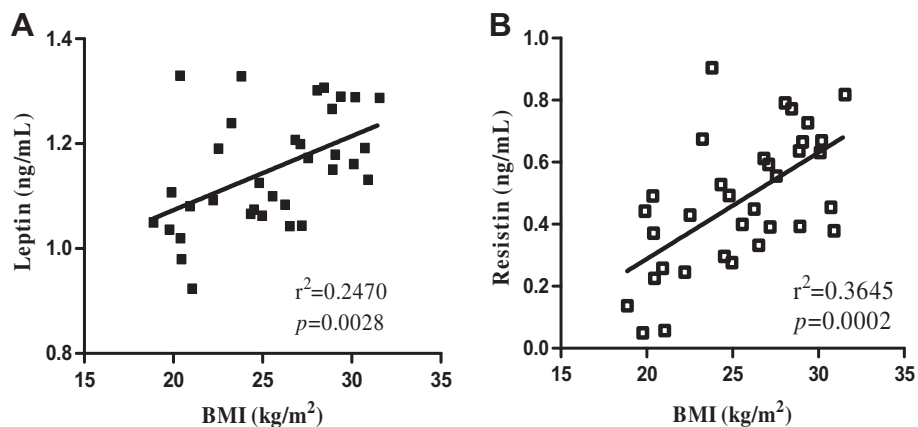


Fig. 2 – The relationship between body mass index (BMI) and (A) serum leptin and (B) serum resistin levels in postmenopausal women.

Table 2 – Correlation between normal and overweight with association of different variables in both pre- and postmenopausal women.

Variable	Premenopausal women			Postmenopausal women		
	Normal weight	Overweight	p	Normal weight	Overweight	p
Age (y)	38.0 ± 7.01	40.0 ± 4.03	ns	54.81 ± 4.72	55.78 ± 7.57	ns
SBP (mm/Hg)	120.29 ± 12.25	128.2 ± 12.08	ns	132.31 ± 12.99	138.72 ± 21.21	ns
DBP (mm/Hg)	75.29 ± 8.80	82.20 ± 8.30	ns	81.44 ± 8.71	78.28 ± 15.34	ns
TC (mg/dL)	174.52 ± 42.88	167.7 ± 37.4	ns	174.63 ± 31.09	184.50 ± 37.54	ns
TG (mg/dL)	169.6 ± 48.5	201.3 ± 68.2*	p < 0.001	183.0 ± 77.4	256.4 ± 195.8*	p < 0.001
HDL (mg/dL)	41.81 ± 8.86	35.30 ± 4.81	ns	40.25 ± 7.09	39.78 ± 7.06	ns
LDL (mg/dL)	108.38 ± 28.59	111.60 ± 22.31	ns	118.38 ± 27.17	125.17 ± 28.89	ns
Blood sugar (mg/dL)	114.38 ± 19.90	166.3 ± 77.1	ns	124.1 ± 48.8	132.0 ± 40.29*	p < 0.001
Leptin (ng/mL)	9.77 ± 2.56	15.81 ± 2.98*	p < 0.001	13.22 ± 3.80	18.75 ± 3.11*	p < 0.001
Resistin (ng/mL)	1.92 ± 1.0	3.21 ± 1.19	ns	2.68 ± 1.71	3.95 ± 1.40	ns
TC/HDL ratio	4.24 ± 0.9	5.61 ± 1.03	ns	4.38 ± 1.11	4.74 ± 1.65	ns
HDL/LDL ratio	0.3 ± 0.08	0.3 ± 0.1	ns	0.33 ± 0.99	0.34 ± 0.86	ns
TG/HDL ratio	3.04 ± 2.74	3.5 ± 2.3	ns	2.0 ± 1.02	3.8 ± 2.83	ns

Values are expressed as mean ± standard deviation.

ns = nonsignificant.

* p < 0.001 is significant.

BMI = body mass index; DBP = diastolic blood pressure; HDL = high density lipoprotein; LDL = low density lipoprotein; SBP = systolic blood pressure; TC = total cholesterol; TG = triglycerides.

biomarker for obesity might be considered in both female groups. Pantsulaia et al [23] reported that differences between pre- and postmenopausal women were nonsignificant statistically in association with serum resistin levels. In our study, we tried to determine if there was any correlation between serum leptin concentration and serum LDL concentration in addition to other serum biochemical parameters, but no significant correlation was found between serum leptin concentration and serum lipid profile in our study groups and this reflects the findings of an earlier study [24]. Serum leptin levels had no positive correlation with blood pressure, HDL, and FBS in the female population [25]. Our

cross-sectional study also predicts that resistin level was negatively associated with lipid profiles in both female study groups. Specifically, we found no independent associations between resistin and markers of obesity.

Comparison of TG levels between the two groups showed a highly significant difference. The postmenopausal group had considerably higher TG levels than the premenopausal group. These findings were coincident with that of other researchers who found TG levels to be higher in the postmenopausal than the premenopausal group [13], but certain studies have reported no effect [26,27]. Many studies address the relation of menopause with blood pressure. Bengtsson et al [28] showed that there is a little reduction in SBP after the menopause. Some other studies showed that blood pressure is not changed with menopause status, but our rural population study reported that there is a significant increase in SBP at the

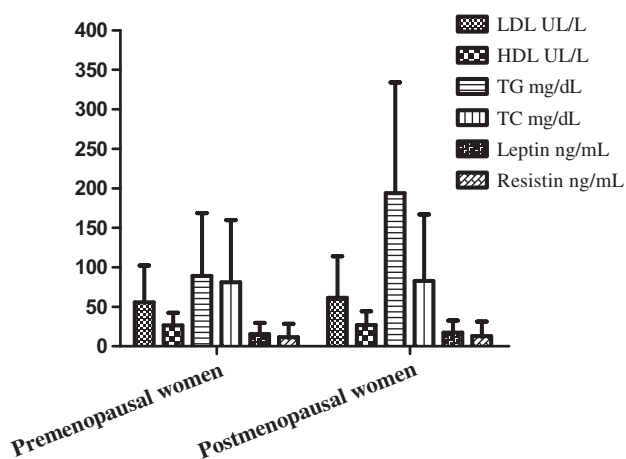


Fig. 3 – The relationship between serum leptin and resistin levels and lipid profiles in pre- and postmenopausal women. HDL = high density lipoprotein; LDL = low density lipoprotein; TC = total cholesterol; TG = triglycerides.

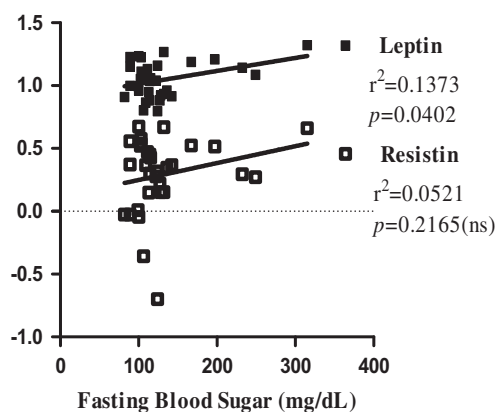


Fig. 4 – The correlation between circulating levels of serum leptin and resistin and fasting blood sugar in premenopausal women.

Table 3 – The relationship between circulating leptin and resistin levels and blood pressure.

Biomarkers	Premenopausal women		Postmenopausal women	
	SBP > 140 mmHg	DBP > 90 mmHg	SBP > 140 mmHg	DBP > 90 mmHg
Leptin (ng/mL)	15.57 ± 4.60	13.17 ± 3.95	23.03 ± 6.64*	16.13 ± 3.70
Resistin (ng/mL)	2.80 ± 1.61	2.39 ± 1.62	4.48 ± 2.07	3.53 ± 2.06

Values are expressed as mean ± standard deviation.

* $p < 0.001$, significant; $p > 0.05$, nonsignificant.

DBP = diastolic blood pressure; SBP = systolic blood pressure.

postmenopausal stage, which might be due to increased BMI and lipid profiles [29]. It has been shown that there is an elevation in SBP among postmenopausal women without any significant change in DBP. This may suggest that SBP is one of the risk factors for CVD among postmenopausal women with METS.

Our results showed a significant increase in FBS in the postmenopausal group, particularly in the overweight population. A rise in blood sugar is one of the most important risk factors for METS. There are some limitations of this study that should be considered. Only those women residing in rural areas were studied and the results of this study may not reflect the overall pre- and postmenopausal women of the general population in India. The mean age range of the premenopausal women group was very close to the postmenopausal group.

In conclusion, our study demonstrated that leptin was found to have significant association with metabolic factors rather than resistin in pre- and postmenopausal women. The serum concentration of leptin was secreted by adipocytes and correlated positively with the BMI in both groups. Overall, leptin contributes to the development of diabetes and obesity in both categories. Higher levels of leptin might predict the increased risk of developing type II diabetes, impaired glucose metabolism, and CVD. Even though estrogen plays an important role in menopause transition, body weight is directly proportional to leptin levels. Further longitudinal and cross-sectional studies with larger numbers of participants are required to confirm the relationship among the markers, metabolic factors, and menopausal status.

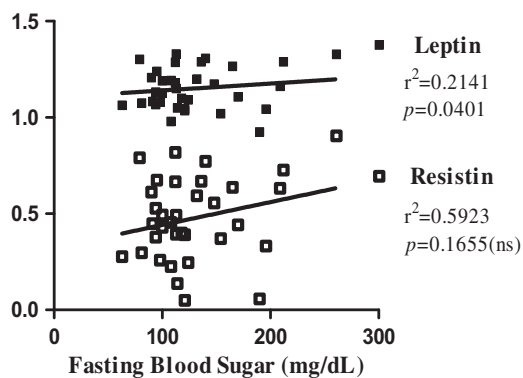


Fig. 5 – The correlation between circulating levels of serum leptin and resistin and fasting blood sugar in postmenopausal women.

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