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Adiponectin and Leptin Imbalance in Breast Cancer Patients with Metabolic Syndrome: A Case-Control Study Evaluating Diagnostic and Clinicopathological Associations

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ABSTRACT

Background: Breast cancer is prevalent among women globally and is linked to metabolic syndrome (MetS). Adipokines are implicated in tumor development by influencing metabolic and inflammatory processes. This study evaluated serum adiponectin and leptin levels in breast cancer patients with MetS and their association with clinicopathological tumor characteristics.

Methods: A case-control study was conducted in 150 women aged 35 to 70 years. Cases included 75 newly diagnosed breast cancer patients with MetS, and controls were 75 individuals with MetS matched for age and body mass index (BMI). Serum adiponectin and leptin levels were analyzed by direct enzyme-linked immunosorbent assay, and the data were analyzed using multivariate analysis, analysis of variance (ANOVA) or Kruskal-Wallis tests, and receiver operating characteristic (ROC) curve analysis as appropriate.

Results: Serum adiponectin levels were significantly lower (mean [SD], 7.32 [2.54] ng/mL vs 8.67 [3.78] ng/mL) and leptin levels were significantly higher (2127.79 [244.05] pg/mL vs 1567.21 [452.06] pg/mL) in cases than in controls. In the case group, adiponectin and leptin showed significant variation across BMI and Breast Imaging Reporting and Data System (BI-RADS) categories. Leptin levels were significantly associated with modified Bloom-Richardson score and estrogen receptor (ER) and progesterone receptor (PR) status and remained independently associated with breast cancer in multivariate analysis (adjusted OR = 1.005; 95% CI, 1.002–1.009; $P = 0.005$). ROC analysis demonstrated the superior diagnostic value of leptin (AUC = 0.847; 95% CI, 0.785–0.909; sensitivity, 78.7%; specificity, 81.3%) over adiponectin.

Conclusion: The marked adipokine imbalance, depicted as low levels of adiponectin and high leptin levels, suggests their potential as adjunctive biomarkers for identifying the risk of breast cancer in women with MetS.

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INTRODUCTION

Breast cancer is the most common cancer and fifth leading cause of cancer-related deaths in women, with 2.3 million new cases diagnosed worldwide in 2020, according to GLOBOCAN

data.[1,2] In India, breast and cervical cancers were the 2 most common cancers, contributing 39.4% of total cancer incidence in 2020.[3] The World Health Organization reports that breast cancer accounts for a large proportion of all newly diagnosed cancer cases in women worldwide and remains a major public health concern despite advancements in screening and treatment. The rising incidence of breast cancer has been linked, in part, to the increased prevalence of lifestyle-related risk factors such as obesity, sedentary lifestyle, and metabolic disorders.[4]

The diagnostic criteria for metabolic syndrome (MetS) encompass abdominal obesity, hypertension, hyperglycemia, dyslipidemia (elevated triglycerides and decreased high-density lipoprotein (HDL) cholesterol), and insulin resistance. The International Diabetes Federation and the National Cholesterol Education Program-Adult Treatment Panel (NCEP-ATP III) state that MetS is diagnosed when a person satisfies at least 3 of the following criteria: blood pressure ≥ 130/85 mm Hg, triglycerides ≥ 150 mg/dL, HDL < 50 mg/dL (in women), waist circumference > 88 cm (in women), and fasting glucose ≥ 100 mg/dL.[5] It is becoming well acknowledged that this condition plays a significant role in the development of cancer, especially breast cancer.[6] Women with MetS have a higher risk of breast cancer with poor clinical outcomes, according to epidemiological research. The underlying mechanisms that connect MetS with breast cancer include dysregulation of adipokines, insulin resistance, altered lipid metabolism, and chronic low-grade inflammation.[7]

Adipose tissue is an endocrine organ involved in the secretion of a variety of bioactive molecules, termed adipokines. Adiponectin and leptin have opposite biological functions and a potential role in cancer development. Adiponectin is an adipokine known for its insulin-sensitizing and anti-inflammatory properties, which are decreased in individuals with obesity and MetS. Adiponectin has been shown to have antiproliferative and proapoptotic effects in experimental studies and may inhibit tumor growth by activating metabolic pathways such as AMP-activated protein kinase (AMPK) and peroxisome proliferator-activated receptor signaling.[8]

In contrast, leptin is an adipokine with proinflammatory properties and is generally increased in the circulation of obese individuals. Leptin has been shown to stimulate tumor cell proliferation, angiogenesis, and metastasis through the activation of several oncogenic signaling pathways, including the Janus kinase-signal transducer and activator of transcription (JAK-STAT), mitogen-activated protein kinase (MAPK), and phosphatidylinositol-3-kinase (PI3K)-Akt pathways. High levels of leptin have been linked to a higher risk of breast cancer and more aggressive tumor characteristics.[9]

Recent evidence suggests that the imbalance between adiponectin and leptin plays an important role in linking obesity and MetS with breast cancer pathogenesis. A reduced adiponectin-to-leptin ratio (ALR) has been proposed as a marker of adipose tissue dysfunction and metabolic inflammation. Also, altered adipokine levels may influence tumor progression, receptor expression, and molecular subtypes of breast cancer.[10,11]

Despite growing evidence supporting the role of adipokines in breast cancer biology, data assessing their association with breast cancer in patients with MetS remain limited and inconsistent. This gap is particularly apparent in the Indian population, which has a higher prevalence of MetS and a scarcity of population-specific evidence. Furthermore, the relationship between adipokine levels and tumor characteristics such as receptor status, stage, grade, and molecular subtype is not yet fully understood.

The present study, therefore, had 2 primary objectives: (1) to evaluate serum adiponectin and leptin levels in breast cancer patients with MetS, and (2) to compare these levels with those of MetS subjects without breast cancer. The study also aimed to explore the association between adipokine levels and tumor characteristics in breast cancer patients.

METHODS

Study design and setting

A hospital-based case-control study was conducted at St. Ann's General and Cancer Hospital, a tertiary care hospital in Telangana, India, over an 18-month period from March 2024 to September 2025. The study was approved by the institutional ethics committee (reference No. SAIEC/PhD DISS/2023/01) and conducted in accordance with the principles of the Declaration of Helsinki.[12] Written informed consent was obtained from all participants prior to enrollment.

Sample size

The sample size was calculated using the formula for the comparison of mean serum leptin and adiponectin levels between 2 independent groups: $n = 2 \times (Z_{1-\alpha/2} + Z_{1-\beta})^2 \times \sigma^2 / d^2$. Where $Z_{1-\alpha/2}$ is 1.96 (for $\alpha = 0.05$), $Z_{1-\beta}$ is 0.84 for 80% power, the standard deviation (σ) values for the case and control groups were derived from a previous study conducted in the Indian population, and $d = 1.45$ represents the clinically significant difference between the 2 groups.[11] Based on these assumptions, a total sample size of 150 participants (75 cases and 75 controls) was determined.

Study participants

Women aged 35 to 70 years with MetS were eligible for inclusion.

Case definition

Cases comprised 75 newly diagnosed breast cancer patients with MetS. Breast cancer diagnosis was confirmed by histopathological examination and supported by clinical and radiological findings.

Control definition

Controls comprised 75 women with MetS attending the same hospital for routine health examinations and with no evidence of breast cancer, as confirmed by clinical breast examination and mammogram. Controls were frequency-matched to cases for age (± 5 years) and BMI (± 2).

Inclusion criteria

The study included female participants between 35 and 70 years of age who had a newly diagnosed, histologically confirmed breast cancer prior to the initiation of any treatment. Eligible participants were also required to have metabolic syndrome (MetS) as defined according to the National Cholesterol Education Program Adult Treatment Panel III (NCEP-ATP III) diagnostic criteria.

Exclusion criteria

Participants were excluded if they were pregnant, had severe liver disease, autoimmune diseases, or other chronic inflammatory conditions, or were receiving hormonal therapy. Individuals with a history of any type of cancer, those who had previously received chemotherapy, and patients who were unwilling to participate in the study were also excluded.

Data collection and variables

Baseline demographic, clinical, anthropometric, reproductive, and lifestyle characteristics were collected using a structured data collection form. Data were collected on sociodemographic characteristics (age and gender), chief complaints, comorbidities, past medical and medication histories, family history, reproductive history (menstrual history, obstetric history, and menopausal status), and social history (alcohol intake, tobacco chewing, and smoking). Anthropometric measurements included height (cm), weight (kg), and waist circumference (cm), and vital signs recorded comprised systolic and diastolic blood pressure. We recorded clinical parameters including blood sugar, lipid profile (triglycerides, HDL), histopathological findings, receptor status (ER, PR, human epidermal growth factor receptor 2 (HER2)), cancer subtype (luminal A, luminal B, triple-negative, HER2-enriched), and BI-RADS category.

Estimation of adipokines

Venous blood samples (5 mL) were obtained from each participant in both the case and control groups following a 12-hour overnight fast. Within 6 hours of collection, samples were centrifuged at 1000*g* for 20 minutes, and the resultant serum was aliquoted and stored at −20 °C until subsequent analysis of serum adiponectin and leptin concentrations. Serum adiponectin and leptin levels were measured using commercially available enzyme-linked immunosorbent assay (ELISA) kits for human adiponectin (detection range, 1.563–100 ng/mL, with a minimal detectable concentration of 0.938 ng/mL) and human leptin (detection range, 31.25–2000 pg/mL, with a minimal detectable concentration of 18.75 pg/mL), respectively. All case and control group samples were labeled, blinded, and assayed in the same analytical run per the manufacturer's instructions (FineTest; Wuhan Fine Biotech Co, Ltd). The ALR was calculated after standardizing adiponectin and leptin concentrations to the same unit (pg/mL) and was included as a marker of adipokine imbalance and adipose tissue dysfunction.

Bias

Several measures were taken to minimize potential bias. Cases and controls were recruited from the same institution during the same study period. Controls were matched to cases by age and BMI to minimize confounding. Standardized procedures were used for anthropometric measurements, blood collection, sample processing, and laboratory analyses. Blinding of laboratory personnel to case-control status was implemented to reduce measurement bias.

Statistical analysis

Data were analyzed using SPSS Statistics version 27.0.1 (IBM Corp).[13] Measures of central tendency (mean or median) were used to summarize the data, and standard deviation was employed to assess dispersion. The independent *t* test was used for comparisons between 2 groups, whereas ANOVA or the Kruskal-Wallis test was applied for comparisons among more than 2 groups. Multivariate logistic regression analysis was performed to assess the independent association of adiponectin and leptin with breast cancer after adjusting for potential confounders. ROC curves were constructed for adiponectin and leptin to determine AUC, sensitivity, specificity, and cutoff values. Odds ratios (ORs) with

95% CIs were reported. A 2-sided *P* value < 0.05 was considered statistically significant.

Table 1. Sociodemographic Characteristics of the Study Population

Demographics/ selected characteristics	Mean (SD) or No. (%) (case group, n = 75)	Mean (SD) or No. (%) (control group, n = 75)	*P* value
Age, y	49.97 (8.36)	50.43 (7.14)	0.72
BMI	28.87 (2.64)	28.94 (2.05)	0.85
Marital status			
Married	74 (98.7)	75 (100)	1.00
Unmarried	1 (1.3)	0 (0)	NA
Family history	15 (20.0)	0 (0)	NA
Social history			
Alcohol intake	0 (0)	0 (0)	NA
Tobacco chewing	20 (26.7)	6 (8.0)	0.003
Smoking	0 (0)	0 (0)	NA
Comorbidities			
Diabetes mellitus	56 (74.7)	61 (81.3)	0.33
Hypertension	48 (64.0)	30 (40.0)	0.003
Hypothyroidism	8 (10.7)	8 (10.7)	1.00
Dyslipidemia	19 (25.3)	15 (20.0)	0.44
Others	1 (1.3)	0 (0.0)	NA
Reproductive history			
Age at menarche, y	12.61 (1.09)	12.63 (1.22)	0.92
History of breastfeeding	70 (93.3)	73 (97.3)	0.25
Hysterectomy	11 (14.7)	1 (1.3)	0.003
Menopause	27 (36.0)	22 (29.3)	0.38
Metabolic syndrome components			
Systolic blood pressure, mm Hg	134.17 (4.28)	133.84 (3.85)	0.62
Diastolic blood pressure, mm Hg	90.93 (2.48)	89.40 (2.10)	< 0.001
Fasting blood sugar, mg/dL	140.79 (14.94)	131.01 (5.28)	< 0.001
HDL cholesterol, mg/dL	40.44 (2.94)	44.18 (3.24)	< 0.001
Triglycerides, mg/dL	170.72 (8.45)	157.72 (4.25)	< 0.001
Waist circumference, cm	98.47 (2.29)	96.57 (2.33)	< 0.001
Adipokine levels			
Adiponectin, ng/mL	7.32 (2.54)	8.67 (3.78)	0.011
Leptin, pg/mL	2127.79 (244.05)	1567.21 (452.06)	< 0.001
Adiponectin-to-leptin ratio (ALR)	3.44 (1.26)	5.53 (2.89)	< 0.001

BMI, body mass index (calculated as weight in kilograms divided by height in meters squared); HDL, high-density lipoprotein.
Data are presented as mean (SD) or No. (%). Continuous variables (age, BMI, age at menarche, systolic blood pressure, diastolic blood pressure, fasting blood sugar, HDL, triglycerides, waist circumference, adiponectin, and leptin) were compared using the independent-samples *t* test. ALR was calculated after unit standardization. Categorical variables (marital status, breastfeeding history, tobacco chewing, diabetes, hypertension, hypothyroidism, dyslipidemia, menopause, and hysterectomy) were compared using the χ^2 test as appropriate. A *P* value < 0.05 was considered statistically significant.

Additionally, there were no missing data for the variables included in the final analysis.

RESULTS

Table 1 summarizes the sociodemographic and baseline characteristics of the study participants. The mean age of participants was found to be similar in both groups, with the case group having a mean age of 49.97 (8.36) years, while the control group had a mean age of 50.43 (7.14) years. The BMI was also comparable between the groups, reported as 28.87 (2.64) for the case group and 28.94 (2.05) for the control group. Waist circumference was found to be 98.47 (2.29) cm in the case group. All study participants were married except 1 in the case group. None of the study participants were smokers or alcohol consumers. However, a significant family history of breast cancer was observed in the case group, affecting 15 cases (20.0%). The most prevalent comorbidities were diabetes and hypertension. Metabolic parameters—including systolic and diastolic blood pressure, fasting blood glucose, and triglycerides—were significantly higher in the case group compared with controls, whereas HDL levels were significantly lower. In terms of reproductive history, most study participants attained menarche at a mean age of 12 (1) years, and about 70 (93.3%) in the case group and 73 (97.3%) in the control group had breastfed their infants. Only 27 cases (36.0%) and 22 controls (29.3%) had attained menopause. The clinicopathological and histological characteristics of tumors in the case group are summarized in Table 2.

Table 2. Chief Complaints, Clinicopathological, and Histological Characteristics of the Case Group

Characteristics	No. (%) (cases, n = 75)
Location	
Right breast	35 (46.7)
Left breast	39 (52.0)
Both breasts	1 (1.3)
Onset of symptoms	
0-3 mo	35 (46.7)
4-6 mo	29 (38.7)
6-9 mo	10 (13.3)
> 9 mo	1 (1.3)
Lump description	
Swelling + palpable	22 (29.3)
Painful + palpable	11 (14.7)
Palpable	10 (13.3)
Swelling + nipple discharge	3 (4.0)
Swelling + skin changes	7 (9.3)
Axillary lymphadenopathy	15 (20.0)
Painful + tenderness	3 (4.0)
Ulceration	4 (5.3)
Quadrants	
Upper outer	40 (53.3)
Upper inner	16 (21.3)
Lower outer	5 (6.7)
Lower inner	3 (4.0)
Central	11 (14.7)
Histological subtype of tumor	
Infiltrating ductal carcinoma	73 (97.3)
Ductal carcinoma in situ	2 (2.7)
Modified Bloom-Richardson score	
3-5	1 (1.3)
6-7	35 (46.7)
> 8	39 (52.0)
Tumor size	
T1	23 (30.7)
T2	46 (61.3)
T3	4 (5.3)
T4	2 (2.7)
Nodal status	
N0	4 (5.3)
N1	59 (78.7)
N2	10 (13.3)
N3	2 (2.7)
Metastasis	
M0	66 (88.0)
M1	4 (5.3)
MX	5 (6.7)
Hormonal receptor status	
Positive estrogen receptor	48 (64.0)
Positive progesterone receptor	48 (64.0)
Positive HER2	20 (26.7)
Molecular subtype of tumor	
Luminal A	33 (44.0)
Luminal B	15 (20.0)
HER2	5 (6.7)
TNBC	22 (29.3)

HER2, human epidermal growth factor receptor 2; TNBC, triple-negative breast cancer.

Association of adipokine levels in case and control groups

An independent t test revealed a statistically significant difference ($t = -2.575$, $P = 0.011$) in the mean adiponectin concentration of the case group (7.32 [2.54] ng/mL) and the control group (8.67 [3.78] ng/mL). The mean leptin level was considerably higher among cases (2127.79 [244.05] pg/mL) compared with controls (1567.21 [452.06] pg/mL), and this difference had statistical significance ($P < 0.001$), as shown in Table 1 and Figure 1. Also, the ALR remained significantly lower in the breast cancer group compared with controls after unit standardization of adiponectin and leptin concentrations (both expressed in pg/mL), indicating a greater degree of adipokine imbalance among breast cancer patients with MetS (Table 1).

Association of adipokine levels with clinical characteristics of the case group

Various tumor characteristics of the case group interpreted by ANOVA are presented in Table 3. There was a significant association between the modified Bloom-Richardson score and leptin levels ($F = 9.489$, $P < 0.001$). Adiponectin concentrations were not significantly associated with ER, PR, or HER2 receptor status, but leptin concentrations were significantly associated with ER and PR status, though not with HER2 receptor status, among the case group.

Association of BI-RADS category and BMI with adipokine levels in case and control groups

Adiponectin levels showed a significant decreasing trend with increasing BI-RADS category (Kruskal-Wallis $H = 6.87$, $P = 0.009$), whereas leptin levels tended to increase with increasing BI-RADS category, with the highest levels observed in BI-RADS 5 lesions (Kruskal-Wallis $H = 5.12$, $P = 0.024$). These findings suggest an association between leptin and increasing radiological severity. In the control group, adiponectin and leptin levels were not significantly associated with the BI-RADS score categories, as shown in Table 4. ANOVA indicated that the variation in adiponectin and leptin levels among the different BMI categories was statistically significant ($F = 3.12$, $P = 0.049$ and $F = 5.84$, $P = 0.004$, respectively) in the case group. However, in the control group, no statistically significant difference was observed, as shown in Table 4.

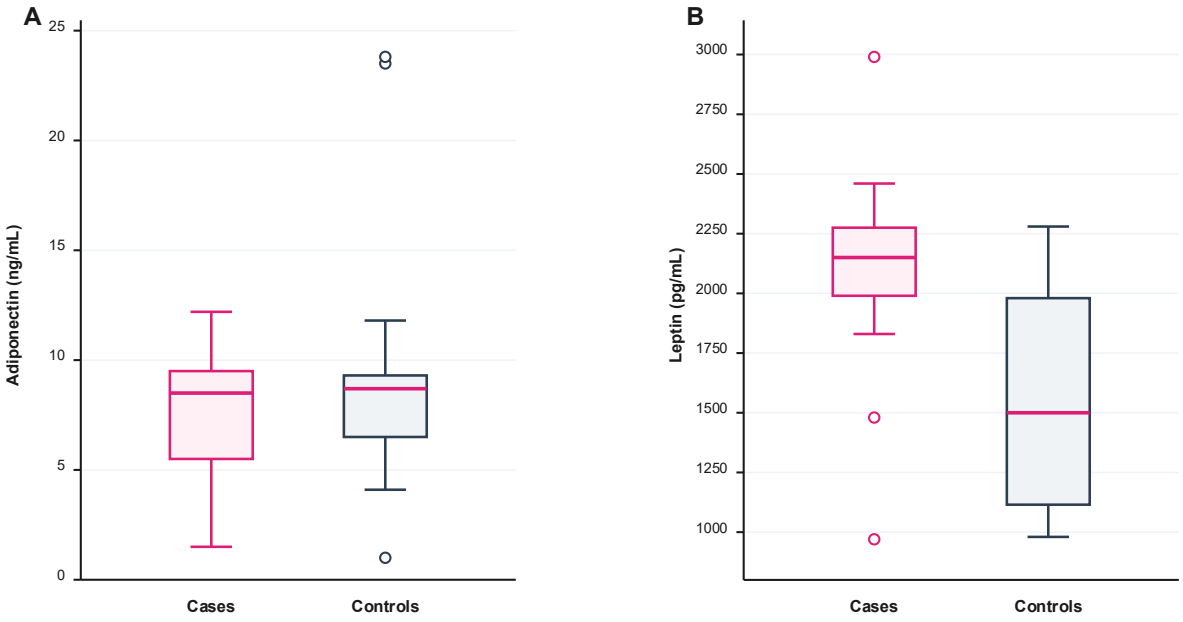

Figure 1. A, Serum adiponectin and B, leptin levels in case and control groups.

Table 3. Association of Adipokine Levels with Clinical Characteristics of the Case Group

S. no.	Variables of case group (n = 75)	Adiponectin (ng/mL) *F* statistic	Adiponectin (ng/mL) *P* value	Leptin (pg/mL) *F* statistic	Leptin (pg/mL) *P* value
1	Onset of symptoms	0.735	0.535	0.914	0.439
2	Lump description	0.675	0.612	0.739	0.569
3	Side involvement	0.213	0.809	1.445	0.243
4	Quadrants	0.190	0.664	1.043	0.310
5	Modified Bloom-Richardson score	0.022	0.978	9.489	< 0.001
6	ER status (Positive/Negative)	1.180	0.305	4.690	< 0.001
7	PR status (Positive/Negative)	1.068	0.281	3.020	0.034
8	HER2 (Positive/Negative)	0.162	0.689	0.995	0.322
9	TNM Staging				
	Tumor size	1.529	0.215	0.029	0.993
	Nodal status	1.735	0.168	0.364	0.779
	Metastasis	0.627	0.537	2.994	0.056
10	Molecular subtypes	0.374	0.772	0.791	0.503
11	Histological subtypes	0.387	0.700	0.050	0.960

ER, estrogen receptor; HER2, human epidermal growth factor receptor 2; PR, progesterone receptor.
P values were calculated using ANOVA. The classification of the above variables includes onset of symptoms: 0–3 months, 4–6 months, 7–9 months, > 9 months; lump description: palpable, painful, tenderness, skin changes, nipple discharge, axillary lymphadenopathy, and ulceration; side involvement: right, left, both; quadrants: upper outer, upper inner, lower outer, lower inner, central; tumor size: T1, T2, T3, T4; nodal status: N0, N1, N2, N3; metastasis: M0, M1, MX; molecular subtypes: luminal A, luminal B, HER2, triple-negative breast cancer; histological subtypes: infiltrating ductal carcinoma, ductal carcinoma in situ. A *P* value < 0.05 was considered statistically significant.

Association of adiponectin and leptin with breast cancer risk: multivariate logistic regression analysis

Multivariate logistic regression analysis was performed after adjusting for clinically relevant covariates and significant baseline differences, including hypertension, tobacco chewing, hysterectomy status, diastolic blood pressure, fasting blood glucose, HDL cholesterol, and triglycerides. After adjustment, serum leptin remained independently associated with breast cancer (adjusted OR = 1.005; 95% CI, 1.002–1.009; $P = 0.005$), whereas adiponectin was not independently associated with breast cancer (adjusted OR = 1.02; 95% CI, 0.73–1.43; $P = 0.914$). These findings suggest that leptin may be a more robust biomarker of breast cancer risk than adiponectin in the presence of MetS-related factors, as shown in Table 5.

Table 4. Association of BI-RADS Category and BMI with Adipokine Levels in the Case and Control Groups

Group	BI-RADS category	Adiponectin, ng/mL, mean (SD)	Adiponectin *P* value	Leptin, pg/mL, mean (SD)	Leptin *P* value
Cases (n = 75)	3	8.31 (1.11)	0.009	2129.58 (203.55)	0.024
	4A + 4B + 4C	7.07 (2.70)		2163.99 (190.00)	
	5	6.10 (3.00)		2173.30 (248.84)	
Controls (n = 75)	1	8.16 (2.47)	0.266	1601.97 (459.96)	0.707
	2	9.07 (4.64)		1518.00 (434.00)	
Group	BMI category	Adiponectin, ng/mL, mean (SD)	Adiponectin *P* value	Leptin, pg/mL, mean (SD)	Leptin *P* value
Cases (n = 75)	Overweight	7.44 (0.11)	0.049	2019.08 (27.52)	0.004
	Obese Class I	7.24 (2.54)		2120.85 (277.68)	
	Obese Class II	5.98 (2.60)		2327.05 (130.03)	
Controls (n = 75)	Overweight	8.13 (3.11)	0.918	1532.36 (350.12)	0.985
	Obese Class I	8.58 (3.79)		1569.37 (452.70)	
	Obese Class II	8.83 (3.82)		1565.87 (460.08)	

BI-RADS, Breast Imaging Reporting and Data System; BMI, body mass index.
A P value < 0.05 calculated via ANOVA was considered statistically significant for BMI; Kruskal-Wallis test $P < 0.05$ was considered significant for BI-RADS score.

ROC analysis of adiponectin and leptin in case and control groups

As depicted in Figure 2, the ROC curve analysis demonstrated the sensitivity and specificity of these biomarkers at different threshold values. At a cutoff value of ≥ 9.298, adiponectin, with an area under the curve (AUC) of 0.405 (95% CI, 0.314–0.497), showed low sensitivity (29.3%) but moderate specificity (76.0%). Leptin demonstrated a superior diagnostic performance, with an AUC of 0.847 (95% CI, 0.785–0.909) and a standard error of 0.032. At a cutoff value of ≥ 1977.760, sensitivity and specificity were 78.7% and 81.3%, respectively, and the Youden index was 0.600, indicating a good discriminatory performance. In contrast, adiponectin demonstrated poor diagnostic utility with a cutoff value of ≥ 9.298, a sensitivity of 29.3%, a specificity of 76.0%, and a Youden index of 0.053, as shown in Table 6.

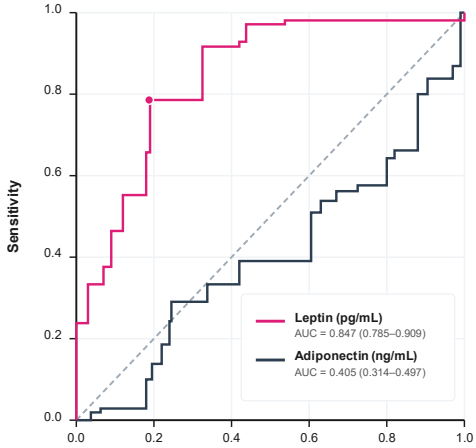

Figure 2. ROC curve of adiponectin and leptin in the case and control groups. ROC indicates receiver operating characteristic; AUC, area under the curve; CI, confidence interval. Leptin demonstrated good diagnostic ability, whereas adiponectin showed poor diagnostic performance.

Table 5. Multivariable Logistic Regression Analysis of Factors Associated with Breast Cancer

Variable	Adjusted OR	95% CI	*P* value
Adiponectin	1.02	0.73–1.43	0.914
Leptin	1.005	1.002–1.009	0.005
Hypertension	0.76	0.11–5.33	0.785
Tobacco chewing	2.99	0.21–41.70	0.416
Hysterectomy	0.001	0.000–4.823	0.112
Diastolic blood pressure	1.82	1.11–2.99	0.018
Fasting blood sugar	1.15	1.02–1.30	0.020
HDL cholesterol	0.58	0.42–0.82	0.002
Triglycerides	1.33	1.15–1.53	< 0.001

CI, confidence interval; HDL, high-density lipoprotein; OR, odds ratio.
Variables entered into the model included adiponectin, leptin, hypertension, tobacco chewing, hysterectomy status, diastolic blood pressure, fasting blood sugar, HDL cholesterol, and triglycerides. A *P* value < 0.05 was considered statistically significant.

These results imply that leptin demonstrates superiority in differentiating individuals with breast cancer from healthy controls, whereas adiponectin appears to possess relatively limited diagnostic utility within the context of this study.

Table 6. Area Under the Curve, Optimal Cutoff Values, and Diagnostic Indices of Adiponectin and Leptin

Adipokine	AUC (95% CI)	Cutoff	Sensitivity, %	Specificity, %	LR+	LR−	Youden index
Adiponectin	0.405 (0.314–0.497)	≥ 9.298	29.3	76.0	1.22	0.93	0.053
Leptin	0.847 (0.785–0.909)	≥ 1977.760	78.7	81.3	4.21	0.26	0.600

AUC, area under the curve; CI, confidence interval; LR+, positive likelihood ratio; LR−, negative likelihood ratio.

DISCUSSION

The present study revealed that the case and control groups had no statistically significant differences in baseline characteristics like age, BMI, age at menarche, past medical history (diabetes mellitus, dyslipidemia), breastfeeding history, menopause status, systolic blood pressure, and marital status ($P > 0.05$). Regarding metabolic parameters, the cases demonstrated significantly higher diastolic blood pressure, fasting blood glucose, triglyceride levels, and waist circumference, along with significantly lower HDL cholesterol levels compared with the controls ($P < 0.001$). Overall, these findings suggest that the case group exhibited a more adverse MetS profile and altered adipokine levels compared with the control group.

In terms of adipokines, serum adiponectin levels were significantly lower in cases compared with controls ($P = 0.011$), whereas serum leptin levels were significantly higher among cases ($P < 0.001$). Also, the breast cancer patients with MetS had significantly lower ALR levels when compared with controls, after unit standardization of adiponectin and leptin concentrations. The ALR is still considered a surrogate marker of adipose tissue dysfunction and metabolic inflammation, and the above finding suggests a greater adipokine imbalance in women with breast cancer. This substantiates the previous evidence on the reflection of reduced ALR in the proinflammatory and protumor metabolic milieu. The imbalance between these adipokines may better represent metabolic dysregulation associated with breast cancer than either marker alone, since leptin promotes tumor progression, whereas adiponectin exerts anti-inflammatory and antiproliferative effects.[11]

No strong associations were observed between adipokine levels and tumor size, nodal status, metastasis, tumor grade, or HER2 subtype. However, leptin was significantly associated with the modified Bloom-Richardson score ($P < 0.001$) and with molecular subtypes, including ER and PR status ($P < 0.001$ for each). Adiponectin and leptin showed significant variation across BMI and BI-RADS categories in the case group. Furthermore, multivariable logistic regression analysis showed an independent association of leptin with breast cancer after adjustment for clinically relevant confounders, whereas adiponectin showed no statistical significance. These findings suggest that leptin may

be a more robust biomarker candidate than adiponectin in the context of MetS-related breast cancer.

The mean age of breast cancer patients with MetS in the present study was 49.97 (8.36) years, which is comparable to controls and aligns with studies done in the Indian population.[14] Approximately 15 cases (20.0%) had a positive family history ($P < 0.001$), which is a nonmodifiable risk factor, indicating that genes such as the *BRCA1* and *BRCA2* genes have inherited mutations in the offspring.[15] Tobacco consumption, a modifiable risk factor, was significantly higher in the case group (26.7%) than in controls (8.0%). This is biologically plausible, as tobacco contains carcinogens—including polycyclic aromatic hydrocarbons and nitrosamines—that can induce oxidative stress, hormonal alterations, and DNA damage, thereby promoting breast carcinogenesis.[16]

Adiponectin exerts antitumor effects through several mechanisms, including activation of AMPK and inhibition of PI3K-Akt and MAPK pathways, reduction of aromatase activity and estrogen synthesis, and anti-inflammatory and antiangiogenic effects.[17] The present study complies with the literature, as serum adiponectin levels were reduced in the case group[11,18–23] and serum leptin levels were increased in this group.[11,20,21,23–25] Leptin is recognized as a protumor adipokine with multiple oncogenic effects, including activation of JAK-STAT3, PI3K-Akt, and MAPK signaling, promotion of angiogenesis via VEGF, stimulation of aromatase activity, and cross talk with estrogen receptor signaling.[26]

In the present study, none of the tumor characteristics were associated with adiponectin levels, but the modified Bloom-Richardson score and ER and PR status were found to be significantly associated with leptin levels, which complies with the literature.[26,27] Recent studies describe the leptin-estrogen axis, where leptin enhances estrogen signaling and promotes ER-positive tumor growth.[27]

The present study demonstrated a significant association between higher BI-RADS categories and an unfavorable adipokine profile characterized by decreased adiponectin ($P = 0.009$) and increased leptin ($P = 0.024$) levels in the case group. These findings support the hypothesis that adipokine imbalance contributes to breast tumor biology and radiological severity.[20]

Adipokine levels were strongly associated with increased BMI in the case group (adiponectin and BMI, $P = 0.049$; leptin and BMI, $P = 0.004$) compared with controls, which implies that obesity-associated adipokine imbalance may play a crucial role in breast cancer progression.[21] This finding aligns with the previous studies reported by Danthala *et al.*,[11] Homaee *et al.*,[19] and Assiri *et al.*[22]

With respect to adipokines and MetS parameters, the current study demonstrated significant correlations. Adiponectin showed protective associations with glycemic control, triglycerides, HDL, blood pressure, and central obesity, whereas leptin demonstrated adverse correlations with the same parameters. These findings are consistent with recent studies indicating that adipokine imbalance plays a key role in the pathogenesis of insulin resistance, dyslipidemia, hypertension, and obesity.[22,27–30] Thus, adiponectin and leptin may serve as important diagnostic biomarkers linking obesity to MetS and cardiovascular risk in breast cancer.

Only a few studies have reported the diagnostic utility of adipokines using ROC analysis. The present study demonstrated that leptin (AUC = 0.847; sensitivity, 78.7%; specificity, 81.3%) had more diagnostic value than adiponectin (AUC = 0.405; sensitivity, 29.3%; specificity, 76.0%) in newly diagnosed breast cancer cases. Kwiatkowska *et al.* conducted ROC analysis of pre- and posttreatment serum levels of adiponectin and leptin in luminal A and B invasive breast cancer patients and proposed that these adipokines could serve as prognostic noninvasive biomarkers, though further validation in larger cohorts is warranted.[31]

Limitations and future recommendations

The main limitation of the study includes a lack of generalizability of its findings to other populations or health care settings, as this was a single-center study conducted in a tertiary care hospital setting. The case-control design limits causal inferences and may overestimate the biomarker performance in ROC analysis. Although age and BMI were matched, residual confounding due to hypertension, tobacco chewing, hysterectomy history, and metabolic parameters was not completely excluded. Additionally, the study did not evaluate other inflammatory biomarkers such as CRP, IL-6, and TNF-α, along with other adipokines including visfatin, resistin, and omentin. Future studies aimed at assessing the diagnostic utility of combined biomarker approaches or multivariable prediction models incorporating clinicopathological and metabolic variables in diverse populations are warranted. Lifestyle interventions targeting obesity, insulin resistance, and MetS should be explored for their potential role in modulating adipokine levels and reducing breast cancer risk.

CONCLUSION

The study strengthens the concept that metabolic dysregulation and adipokine imbalance contribute

significantly to breast cancer pathogenesis. Adipokines may serve as potential adjunctive biomarkers for early detection and risk stratification and could represent promising therapeutic targets in the future. As leptin demonstrated a promising diagnostic performance in the present study, further external validation in a larger population is warranted.

ETHICAL CONSIDERATIONS

This study was approved by the St. Ann's Institutional Ethics Committee (SAIEC), Kazipet (reference No. SAIEC/PhD DISS/2023/01).

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DATA AVAILABILITY

The current study datasets are available upon request to the corresponding author with no restriction.

CONFLICT OF INTERESTS

Authors do not have any conflicts of interest to declare.

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AI DISCLOSURE

No AI tool was used in preparation of this manuscript.

AUTHOR CONTRIBUTION

DE: Conceptualization, Formal analysis, Investigation, Methodology, Project administration, Resources, Supervision, Visualization, Writing – original draft, Writing – review & editing. VRN: Conceptualization, Formal analysis, Investigation, Methodology, Project administration, Resources, Supervision, Visualization, Writing – original draft, Writing – review & editing. SSA: Conceptualization, Formal analysis, Investigation, Methodology, Resources, Supervision, Visualization, Writing – original draft, Writing – review & editing. BD: Conceptualization, Formal analysis, Investigation, Methodology, Project administration, Resources, Supervision, Visualization, Writing – original draft, Writing – review & editing. PRB: Conceptualization, Formal analysis, Investigation, Methodology, Resources, Visualization, Writing – original draft, Writing – review & editing. SRM: Conceptualization, Formal analysis, Investigation, Methodology, Project administration, Resources, Supervision, Visualization, Writing – original draft, Writing – review & editing.

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