Original Article

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Serum Leptin-adiponectin Ratio in Patients With and Without Metabolic Syndrome: A Cross-sectional Study

Biochemistry Section

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ABSTRACT

Introduction: Metabolic Syndrome (MetS) is one of the most significant global public health concerns. Leptin, adiponectin, and the Leptin-adiponectin (LA) ratio have been shown to be informative biomarkers for obesity, Type 2 Diabetes Mellitus (T2DM), and Cardiovascular Diseases (CVD). Many contributing factors, such as Insulin Resistance (IR), adipose tissue dysfunction, chronic inflammation, and genetic factors, are proposed to be the aetiological factors of MetS. Leptin and adiponectin have opposite effects on IR, so the combined use of these adipokines may serve as a better biomarker in MetS.

Aim: To determine serum leptin levels, adiponectin levels, and the LA ratio in patients with and without MetS.

Materials and Methods: This cross-sectional study was conducted in the Department of Biochemistry and Medicine at the Regional Institute of Medical Sciences (RIMS), Imphal, Manipur, India, from January 2021 to October 2022. The study included 50 diagnosed cases of MetS and 50 individuals without MetS. Leptin, adiponectin, and parameters of MetS {Body Mass Index (BMI), weight, Waist Circumference (WC), skinfold thickness, High-density Lipoprotein (HDL), Triglycerides (TG), and Blood Pressure (BP)} were assessed in the study. The data were statistically analysed using Independent Sample t-test and Pearson's correlation test.

Results: There were 23 males and 27 females in the study group. The mean age was found to be 61.10±12.52 years in cases and 57.08±10.67 years in controls. Leptin levels were significantly higher in cases (26.58±14.6 ng/mL) compared to controls (12.99±8.59 ng/mL). However, adiponectin levels were significantly decreased in cases (7.16±4.19 µg/mL) compared to controls (12.18±9.4 µg/mL). The LA ratio was found to be higher in cases (5.38±4.71 ng/µg) than in the controls (1.84±1.99 ng/µg). Multiple linear regression analysis demonstrated that the LA ratio was strongly associated with MetS among Leptin, Adiponectin, and the LA ratio ($p<0.05$).

Conclusion: Metabolic syndrome was strongly associated with an increased LA ratio, leptin, and decreased adiponectin levels. The LA ratio can better discriminate the risk of MetS than leptin and adiponectin alone and may be used as a sensitive clinical surrogate biomarker of MetS.

Keywords: Adipose tissue, Blood pressure, Diabetes mellitus, Insulin resistance, Obesity

INTRODUCTION

The MetS is a complex disorder and is considered a worldwide epidemic [1]. MetS is defined by a cluster of interconnected factors that directly increase the risk of Coronary Heart Disease (CHD), other forms of Atherosclerotic CVDs (ASCVD), and T2DM. Its main components are dyslipidemia, elevation of arterial BP, dysregulated glucose homeostasis, abdominal obesity and IR [1].

According to the International Diabetes Federation (IDF) definition, an individual is deemed to have MetS if he or she has central obesity (WC ≥90 cm for South and East Asian men and ≥80 cm for South and East Asian women, with ethnicity-specific values assumed if BMI is >30 kg/m^2), plus any two of the following four factors: 1) raised TG (≥150 mg/dL) or specific treatment for this lipid abnormality; 2) reduced HDL cholesterol (<40 mg/dL in males, <50 mg/dL in females) or specific treatment for this lipid abnormality; 3) raised BP (BP ≥130/85 mmHg) or treatment of previously identified hypertension; and 4) raised fasting plasma glucose (≥100 mg/dL) or previously diagnosed T2DM [2].

The aetiopathogenetic mechanisms of MetS are complex and could not be fully explained. Many contributing factors and mechanisms have been proposed, including IR, adipose tissue dysfunction, chronic inflammation, oxidative stress, circadian disruption, microbiota, genetic factors, maternal programming, etc., [3]. Two adipokines, adiponectin and leptin, secreted from adipose tissue, are found to be strongly associated with cardiometabolic disorders [4]. Various studies [5-7] have demonstrated that leptin, adiponectin, and the LA ratio could be informative biomarkers for obesity, MetS, T2DM, and ASCVD. In recent years, the LA ratio has been suggested to deserve further consideration and could be used as a possible component of MetS [8].

Leptin, the product of the obese (ob) gene, is a 16 kDa polypeptide of 146 amino acid residues, a non glycosylated polypeptide. It acts via its receptor, lep-R, to regulate appetite, energy balance, body mass, and metabolism by inhibiting the synthesis and release of Neuropeptide Y (NPY) in the arcuate nucleus [9]. Adiponectin is a 30-kDa glycoprotein of 244 amino acid residues. Adiponectin regulates glucose and lipid homeostasis by promoting a strong insulin-sensitising effect, fatty acid oxidation, mitochondrial biogenesis, and mediating anti-oxidative and anti-inflammatory effects [10].

Although leptin or adiponectin were separately associated with the risk of MetS, T2DM, and Coronary Artery Disease (CAD), in a study by Kumar R et al., it was found that the serum leptin levels were higher in obese patients than in the controls [11]. Similar studies found that the association of T2DM risk with the LA ratio was stronger than with leptin or adiponectin alone [12-15]. However, it is still hard to draw a definite conclusion about the causal relationship due to inconsistent findings.

Therefore, the present study was conducted to estimate the levels of serum leptin and adiponectin in patients with and without MetS and to determine the serum leptin-adiponectin ratio in patients with and without MetS.

MATERIALS AND METHODS

This cross-sectional study was conducted in the Department of Biochemistry and Medicine at the Regional Institute of Medical Sciences, Imphal, Manipur, India from January 2021 to October 2022. The study was approved by the Research Ethics Board, RIMS, Imphal (Ref. No. A/206/REB-Comm(SP)/RIMS/2015/680/22/2020).

Inclusion criteria: In the present study, individuals aged 30 years and above, irrespective of diagnosed cases of MetS, who gave written consent to participate in the study voluntarily, were included. Age-matched individuals without MetS were also included as controls.

Exclusion criteria: Patients with T1DM, chronic kidney disease, a history of CVD, liver disorders (such as primary dyslipidemia, hepatitis B and C, alcoholic liver disease, carcinoma), patients with immune deficiency (malignancy, renal failure, connective tissue disease, liver cirrhosis, congestive heart failure), pregnant women, patients on steroid therapy, and patients on Assisted Reproductive Treatment for Human Immunodeficiency Virus/Acquired Immunodeficiency Syndrome (AIDS/HIV) were excluded from the study.

Sample size calculation: The sample size was calculated using the following formula, using the value of the serum adiponectin to leptin ratio (A/L ratio) as a biomarker:

$$n=\frac{(u+v)^2\ (s1^2+s2^2)}{(m_1-m_2)}$$

where, n=sample size, u=1.64 (Taking power as 95%), v=2.53 (Confidence level of 98%), s1=Standard deviation of A/L ratio in patients without MetS, s2=Standard deviation of A/L ratio in patients with MetS, m1=Mean of A/L ratio in patients without MetS, m2=Mean of A/L ratio in patients with MetS.

Taking m1=1.01, s1=1.24 for A/L ratio among healthy subjects, and m2=0.26, s2=0.24 for A/L ratio among MetS patients from a study conducted by Fruhbeck G et al., [13],

$$n=\frac{(1.64+2.53)^2\ (1.24^2+0.24)^2}{(1.01-0.26)^2}$$

n=49.37~50.

In the present study, 50 participants were included in each group, i.e., 50 patients with MetS and 50 patients without MetS, making a total of 100 participants in the study.

Study Procedure

Eligible participants with MetS were recruited consecutively from the Medicine Outpatient Department (OPD) and wards of RIMS, Imphal. When one patient with MetS was recruited, one eligible participant without MetS was also recruited conveniently from the patient party or OPD attendees. Eligible participants with MetS or without MetS were identified using IDF (2006) criteria [2]. This criteria requires the presence of WC ≥90 cm in men or ≥80 cm in women (for the Asian population) plus any two or more of the following four risk factors:

1. Serum TG ≥150 mg/dL.
2. Serum HDL <40 mg/dL in men, <50 mg/dL in women.
3. BP ≥130/85 mmHg or treatment of previously diagnosed hypertension.
4. Fasting plasma glucose ≥100 mg/dL or previously diagnosed diabetes mellitus.

Standardised protocols were used to measure body weight, height, WC, BMI, and BP.

Overnight fasting venous blood of about 6 mL was collected from the anterior cubital vein under aseptic precautions from the patients with and without MetS. About 2 mL of blood was collected in a fluoride vial for blood glucose estimation, and the remaining blood sample was collected in a sterile vial and allowed to centrifuge at 3000 rpm for 10 minutes to obtain serum, which was used for the estimation of leptin, adiponectin, TG, and HDL.

Serum leptin was measured by the Sandwich Enzyme-linked Immunoassay (ELISA) method using the LEPTIN ELISA kit [16] from DBC-Diagnostics Biochem Canada Inc., with a range of 3.7-11.1 ng/mL in women and 2.0-5.6 ng/mL in men, having a sensitivity of 0.50 ng/mL. Serum adiponectin was measured by the Sandwich ELISA method using the Adiponectin ELISA kit [17] from Mediagnost, Germany, with a mean of 10.2 µg/mL in females and 6.8 µg/mL in males, having a sensitivity of <0.27 ng/mL.

Fasting Blood Glucose (FBG) was determined after enzymatic oxidation in the presence of glucose oxidase with a cut-off range of 60-100 mg% using the Randox Glucose kit [18]. Serum TG was estimated by the Enzymatic colorimetric test by Human Gessellschaft fur Biochemica und Diagnostica mbH [19], with a cut-off range of 36-150 mg%. Serum HDL cholesterol was estimated using the Human Gessellschaft fur Biochemica und Diagnostica mbH HDL kit [20], with a cut-off range of >40 mg%.

STATISTICAL ANALYSIS

The data were analysed using IBM SPSS version 21 for Windows. Descriptive statistics such as mean, Standard Deviation (SD) and proportion were used to summarise the findings. Continuous data such as age, weight, height, BMI, waist circumference, serum leptin, serum adiponectin, and LA ratio were expressed as mean and standard deviation. The independent sample t-test was used to compare the levels of leptin, adiponectin, and LA ratio in cases and controls. Pearson's correlation analysis was used to find correlations between dependent variables. A p-value <0.05 was considered statistically significant.

RESULTS

All the study participants were 30 years of age and above, with a minimum age of 30 years and a maximum age of 80 years. The mean age of the patients was 61.10±12.52 years, with 44% being male and 56% being female. The maximum number of MetS cases was seen in the age group 61-70 years (34%). In this study, females outnumbered males among the cases, but the difference in the number of males and females is statistically insignificant [Table/Fig-1].

Parameters	Control (N=50) N(%)	Cases (N=50) N(%)	p-value
Age (years)			
30-40	9 (18)	7 (14)	0.07
41-50	10 (20)	9 (18)	
51-60	16 (32)	10 (20)	
61-70	10 (20)	17 (34)	
71-80	5 (10)	7 (14)	
Gender			
Male	21	23	0.426
Female	29	27	

[Table/Fig-1]: Distribution of cases and controls by demographic parameters.

In the present study, the mean weight, BMI, WC, pulse rate, SBP, DBP, and skinfold thickness were significantly higher in cases compared to controls, with a p-value <0.01. However, there was no significant difference in the mean (±SD) levels of age and height between controls and cases, with p-values of 0.07 and 0.202, respectively [Table/Fig-2].

[Table/Fig-3] shows a comparison of the mean levels of metabolic parameters between males and females among cases using an independent sample t-test. The height was significantly higher in males compared to females, but BMI was found to be significantly increased in females compared to males (p-value <0.05).

The mean (±SD) levels of the leptin-to-adiponectin ratio (LA ratio), FBG, and Triacylglycerol (TG) levels were significantly increased in cases when compared to controls, and the levels of adiponectin and HDL cholesterol were lower in cases than controls (p<0.01).

However, Haemoglobin (Hb) levels did not show any significant difference between controls and cases (p=0.197) [Table/Fig-4].

Parameters	Control (N=50) Mean±SD	Cases (N=50) Mean±SD	p-value
Age (years)	57.08±10.67	61.10±12.52	0.07
Height (cm)	161.33±6.69	159.65±6.18	0.202
Weight (kg)	53.21±5.40	74.21±8.66	<0.01
BMI (kg/m^2)	20.42±1.82	29.14±3.20	<0.01
WC (cm)	75.23±4.90	91.81±5.0	<0.01
Pulse (per min)	75.58±5.68	79.312±7.52	<0.01
Systolic BP (SBP) (mmHg)	112.83±9.19	138.65±11.99	<0.01
Diastolic BP (DBP) (mmHg)	75.00±5.04	89.63±8.74	<0.01
SFT (mm)	5.27±0.94	8.69±2.41	<0.01

[Table/Fig-2]: Distribution of cases and controls by clinical and metabolic parameters.

Parameters	Female (N=27) Mean±SD	Male (N=23) Mean±SD	p-value
Age (years)	64.08±12.30	57.59±12.11	0.05
Height (cm)	155.77±4.32	164.23±4.76	<0.01
Weight (kg)	73.31±10.51	75.27±5.86	0.44
BMI (kg/m^2)	30.16±3.74	29.93±1.86	0.01
WHR	1.09±0.09	1.10±0.04	0.86
Pulse (per min)	80.46±8.38	77.95±6.28	0.25
Systolic BP (SBP) (mmHg)	136.62±12.77	141.05±10.80	0.20
Diastolic BP (DBP) (mmHg)	88.92±10.28	90.45±6.62	0.55
SFT (mm)	9.12±2.96	8.18±1.44	0.18

[Table/Fig-3]: Distribution of clinical and metabolic parameters between male and female among the cases.

Variables	Control (N=50) Mean±SD	Cases (N=50) Mean±SD	p-value
Leptin (ng/mL)	12.99±8.59	26.58±14.6	<0.01
Adiponectin (µg/mL)	12.18±9.4	7.16±4.19	<0.01
LA Ratio (ng/µg)	1.84±1.99	5.38±4.71	<0.01
FBG (mg%)	94.33±10.16	194.06±66.2	<0.01
HDL (mg%)	47.42±4.91	26.54±7.91	<0.01
TG (mg%)	125.75±35.07	198.56±88.68	<0.01
Hb (g/dL)	13.94±11.98	11.66±1.7	0.197

[Table/Fig-4]: Distribution of cases and controls by different biochemical parameters.

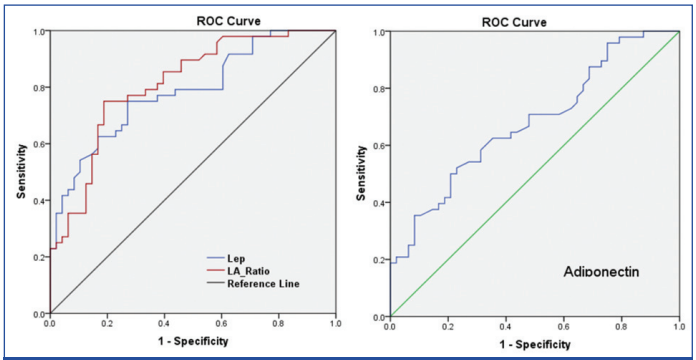
The serum adiponectin levels show a significant positive correlation with HDL. It also shows a statistically significant negative correlation with serum leptin, TG, weight, BMI, WC, BPs, and Solitary Fibrous Tumour (SFT). It is also seen that serum leptin level has a significant positive correlation with FBG, weight, BMI, WC, BP (both SBP and DBP), and SFT, whereas no significant correlation with TG levels. Leptin shows a significant negative correlation with HDL. The LA ratio showed a significant positive correlation with weight, BMI, WC, SFT, and BP (SBP and DBP) using Pearson's correlation analysis, but its correlation with HDL level was found to be negatively significant [Table/Fig-5].

As shown in [Table/Fig-6,7], the LA ratio has the highest Area Under Curve (AUC) value of 0.811 for the diagnosis of MetS by using the study-specific cut-off value 2.65 (sensitivity=0.750, specificity=0.813). Similarly, leptin has an AUC value of 0.785 for the diagnosis of MetS by using the study-specific cut-off value 16.05 (sensitivity=0.750, specificity=0.729). Adiponectin has the least power for the diagnosis of MetS with an AUC value of 0.679 by using the study-specific cut-off value 8.4 (sensitivity 0.521, specificity 0.771).

[Table/Fig-8] showed a multiple linear regression analysis for the prediction of leptin, adiponectin, and LA ratio by the components of

Parameters	Adiponectin		Leptin		LA ratio	
	r-value	p-value	r-value	p-value	r-value	p-value
FBG (mg%)	-0.197	0.055	0.290	<0.01	0.167	0.104
TG (mg%)	-0.216	0.034	0.154	0.135	0.136	0.185
HDL (mg%)	0.363	<0.01	-0.269	<0.01	-0.363	<0.01
Weight (kg)	-0.250	0.014	0.410	<0.01	0.355	<0.01
BMI (kg/m^2)	-0.230	0.024	0.451	<0.01	0.351	<0.01
WC (cm)	-0.282	<0.01	0.419	<0.01	0.359	<0.01
Systolic BP (SBP) (mmHg)	-0.269	<0.01	0.402	<0.01	0.477	<0.01
Diastolic BP (DBP) (mmHg)	-0.243	0.017	0.375	<0.01	0.462	<0.01
SFT (mm) Leptin	-0.235 -0.254	0.021 0.012	0.481	<0.01	0.368	<0.01

[Table/Fig-5]: Pearson's correlation of adiponectin, leptin and LA ratio with parameters of Metabolic Syndrome (MetS).
Correlation is significant at the 0.01 level (2-tailed)



[Table/Fig-6]: Receiver Operating Characteristic (ROC) curve of leptin, adiponectin and leptin-adiponectin ratio.

Variables	AUC	SE	PPV	NPV	Sig
LA Ratio	0.811	0.044	80.0	76.5	<0.001
Leptin	0.785	0.046	73.5	74.5	<0.001
Adiponectin	0.679	0.054	61.7	69.4	0.006

[Table/Fig-7]: Area under the ROC curve.
SE: Standard error; PPV: Positive predictive value; NPV: Negative predictive value

MetS such as BMI, WC, WHR, SFT, BP (SBP and DBP), FBG, TG, and HDL. These variables can significantly predict LA ratio, F=4.333, p<0.001, R2=0.338. This regression analysis also demonstrated that LA ratio levels could be predicted better by these variables than Leptin (F=3.94, p<0.001, R2=0.316) and adiponectin (F=1.89, p=0.057, R2=0.182) alone levels after adjustment for age. The 'R' value for the prediction of leptin and LA ratio were 0.563 and 0.581, respectively, indicating a good level of prediction with p-values of both <0.001, whereas the model did not show a good level of prediction for adiponectin (R=0. 427, p=0.06). The general form of the equation to predict the LA ratio from the components of MetS will be as follows: Predicted LA ratio=0.85-(0.21×BMI)-(0.44×WC)+(0.59×WHR) +(0.34×SFT)+(0.24×sys BP)+(0.13×dias BP)-(0.33×FBG)-(0.09×TG)-(0.32×HDL). Similarly, the predicted value of leptin and adiponectin can be calculated from their respective general form of the equation.

DISCUSSION

Over the last few years, there has been increasing evidence of an association between MetS and adipokines. The present study adds some additional information on the association between leptin, adiponectin, and the LA ratio with MetS.

Blood pressure showed a significant negative correlation with adiponectin levels, whereas it showed a positive correlation with leptin and LA ratio levels, which is consistent with the findings of Senarathne R et al., [21]. The mean level of SFT among cases was significantly higher than among controls and among those with MetS, which is consistent with the study done by Vasan SK

Model	Model summary			Analysis of Variance (ANOVA)			
	R	R^2	SE	Mean square regression	Mean square residual	F	Sig
Leptin	0.563	0.316	12.01	567.56	144.25	3.94	<0.001
Adiponectin	0.427	0.182	7.33	101.58	53.70	1.89	0.06
LA ratio	0.581	0.338	3.53	51.66	11.92	4.33	<0.001
MetS components	Leptin		Adiponectin		LA ratio		
	β	Sig	β	Sig	β	Sig	
BMI (kg/m^2)	-0.027	0.908	0.292	0.259	-0.214	0.357	
WC (cm)	-0.208	0.425	0.021	0.940	-0.435	0.091	
WHR	0.562	0.024	-0.171	0.527	0.593	0.016	
SFT (mm)	0.484	0.006	-0.217	0.250	0.341	0.046	
Systolic BP (SBP) (mmHg)	0.103	0.599	-0.095	0.659	0.239	0.218	
Diastolic BP (DBP) (mmHg)	-0.090	0.627	0.025	0.902	0.132	0.472	
FBG (mg%)	-0.030	0.830	0.158	0.304	-0.333	0.017	
TG (mg%)	-0.052	0.669	0.003	0.982	-0.092	0.437	
HDL (mg%)	0.229	0.198	0.477	0.015	-0.315	0.073	

[Table/Fig-8]: Multiple linear regression analysis of leptin, adiponectin and LA ratio as dependent variable with components of Metabolic Syndrome (MetS).
β=Coefficient of regression

et al., [22]. There were significant differences in the mean levels of HDL and TG between controls and cases. There was a positive correlation between TG and other MetS components, while a negative correlation existed between HDL and adiponectin, which is consistent with the study done by Tao LX et al., [23].

Leptin strongly correlates negatively with adiponectin and HDL, which is statistically significant and consistent with the findings of Diwan AG et al., [24]. Leptin strongly correlates positively with BMI, weight, WC, SFT, FBG, TG, and BP, which were statistically significant, and negatively with adiponectin and HDL in a study by Chen VC et al., [25]. Furthermore, in other studies by Gupta V et al., Esfanjani AT et al., [26], and Targońska SB et al., [27,28], the L:A ratio was significantly positively correlated with the same metabolic parameters of this study and negatively correlated with HDL. These correlations may be due to the important role of leptin in the long-term regulation of body weight by maintaining a balance between the body's food intake and energy expenditure [29].

Higher leptin levels, in conjunction with obesity and weight gain, are likely involved in the subsequent development of diabetes [30]. Higher levels of leptin and the leptin-adiponectin ratio have been found to be associated with increased weight gain in studies by Zurita-Cruz JN et al., Lee KW and Shin D, Mohammed SW and Nasser BD [6,31,32]. Adiponectin was lower in obese subjects with Type 2 diabetes. In contrast, leptin and the leptin/adiponectin (L/A) ratio were higher. Linear regression analysis showed that adiponectin was negatively associated with metabolic parameters, whereas leptin and the L/A ratio were positively associated [14]. In a study by LiG et al., [33], an increased L/A ratio in paediatric cases of Metabolic Syndrome (MetS) was found to be a better diagnostic marker for MetS than leptin or adiponectin alone, similar to a study by Albarracína MLG and Torresb AYF [15]. Adiponectin is involved in the regulation of glucose levels as well as fatty acid breakdown through its insulin-sensitising and anti-inflammatory effects [34]. In the present study, serum adiponectin levels were significantly lower in MetS, with no significant gender difference observed. Adiponectin showed a significant positive correlation with HDL and a negative correlation with leptin, TG, weight, BMI, WC, SFT, and BP. Adiponectin levels were decreased in MetS since insulin lowered the adiponectin levels in patients with T2DM, but it did not change the levels in healthy subjects. Insulin receptor dysfunction is associated with increased circulating adiponectin. Insulin directly suppresses adiponectin secretion from the adipose tissue [11,12,35].

Leptin and adiponectin have opposing effects on subclinical inflammation. Leptin upregulates cytokines and is considered a proinflammatory cytokine. In contrast, adiponectin downregulates the expression of many proinflammatory immune mediators and exerts anti-inflammatory properties [36]. The present study revealed that the LA ratio levels were significantly higher among MetS subjects as compared to control subjects. The LA ratio shows a strong positive correlation with leptin levels, weight, BMI, WC, SFT, and BP.

The ROC curve analysis was performed to assess the predictive value of leptin, adiponectin, and the LA ratio for diagnosing MetS. The LA ratio exhibited the highest AUC value of 0.811 for diagnosing MetS using the study-specific cut-off value of 2.65 (sensitivity=0.750, specificity=0.813), indicating that the LA ratio provides the best predictive value among the three variables. This finding is consistent with the study conducted by Yosaee S et al., [37]. The LA ratio reflects the combined effect of both leptin and adiponectin, as well as the imbalance of leptin-adiponectin in the development of MetS. These findings were comparable to the study conducted by Adejumo EN et al., [7].

Limitation(s)

The study was conducted on a limited study population; hence, the results should be extrapolated to a larger study population. Another limitation is that the study was done on already diagnosed cases of MetS; therefore, a longer study duration would be better to study the relationship of adiponectin and leptin with respect to MetS.

CONCLUSION(S)

Higher leptin levels and LA ratio were significantly associated with an increased incidence of MetS, whereas lower adiponectin levels were associated with an increased incidence of MetS. The leptin-adiponectin ratio had a better ability to discriminate the risk of MetS than leptin and adiponectin alone. Leptin, adiponectin, and LA ratio can be potential useful biomarkers for the early detection of MetS. Since the LA ratio had the best predictive value for the detection of MetS, continuous monitoring of the LA ratio may be helpful for early detection before the development of MetS co-morbidities and could be used as a sensitive clinical surrogate biomarker of MetS. However, further studies will be required to confirm these study findings.

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