Relationship between serum leptin concentration and insulin resistance syndrome in patients with type 2 diabetes mellitus

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Introduction
Type 2 diabetes mellitus is known for its morbidity and mortality worldwide. It has been demonstrated in recent studies that abnormal levels of adipocytokines may contribute to insulin resistance and type 2 diabetes.

Objective
The aim of the present study was to assess the relationship between serum leptin levels and insulin resistance syndrome in type 2 diabetic patients.

Patients and methods
A total of 80 individuals were enrolled into this study, and were divided into two groups –20 healthy persons comprised the control group and 60 patients with type 2 diabetes mellitus comprised the disease group. The disease group was further divided into those with evidence of metabolic syndrome (30 patients) and those without (30 patients). Parameters such as age, sex, and anthropometric measures and biochemical indicators such as fasting and postprandial blood sugar, HbA1c, lipid profile, leptin, and fasting insulin were determined.

Results
Higher leptin and insulin levels were observed in patients with metabolic syndrome ($P < 0.001$).

Conclusion
High serum leptin is a good indicator and can act as a minimally invasive marker for early detection of insulin resistance syndrome.

Keywords:
insulin resistance syndrome, leptin concentration, type 2 diabetes mellitus

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Introduction

Insulin resistance syndrome refers to the cluster of abnormalities and related physical outcomes that occur more commonly in insulin-resistant individuals. Given tissue differences in insulin dependence and sensitivity, manifestations of insulin resistance syndrome are likely to reflect the composite effects of excess insulin and variable resistance to its actions [1]. Metabolic syndrome confers upon an individual a substantial increase in cardiovascular disease (CVD) risk – approximately twice as high as those without the syndrome. Compared with those without metabolic syndrome, those with it are at an increased risk of mortality from CVD, coronary heart disease, stroke, vascular dysfunction, and all-cause mortality [2]. In addition to CVD and type 2 diabetes, individuals with metabolic syndrome are seemingly more susceptible to other conditions including polycystic ovary syndrome, fatty liver, cholesterol gallstones, asthma, sleep disturbances, and some forms of cancer such as breast, pancreatic, colorectal, and prostate [3]. Although the pathogenesis of metabolic syndrome and its components is not well understood, central obesity and insulin resistance are recognized as causative factors [4].

Several different organizations have outlined diagnostic criteria for metabolic syndrome, which include values for obesity (waist circumference or BMI), triglyceride (TG) levels, high-density lipoprotein (HDL) levels, hypertension, hyperglycemia, and sometimes urine albumin or albumin and creatinine ratio. Regardless of which criteria are used, the primary concern is early detection of potential CVD complications and early intervention [5].

Leptin is an adipokine, which under normal physiological conditions functions to reduce appetite, increase energy expenditure, increase sympathetic activity, facilitate glucose utilization, and improve insulin sensitivity [6]. It is expressed in levels proportionate to adipose mass, and although it is mainly produced mostly by adipocytes, it is also produced by vascular smooth muscle cells, cardiomyocytes, and placenta in pregnant women. The functional leptin receptor is in

the hypothalamus where it functions to increase energy expenditure and reduce appetite. The receptor is also found in other organs such as the heart, liver, kidneys, and pancreas; it is also present in the smooth muscle and endothelium of heart, brain vasculature, and myometrium [7].

Obesity is associated with high levels of leptin; chronic overexpression of leptin reduces leptin receptors, and thus diminishes signaling and impairs responsiveness to exogenous leptin, which suggests that obese humans are resistant to this adipocyte hormone [8].

In addition, it has been suggested that leptin levels predict metabolic syndrome development independent of obesity [9]. Besides its effect on appetite and metabolism, leptin acts in the hypothalamus to increase blood pressure through activation of the sympathetic nervous system [10]. High circulating levels of leptin are reported to explain much of the increase in the renal sympathetic tone observed in obese individuals [11]. Leptin also affects vascular structure by promoting hypertension, angiogenesis, and atherosclerosis [7].

The aims of our study were to assess the relationship between serum leptin levels and metabolic syndrome in type 2 diabetic patients and to asses Leptin's role as a biomarker for metabolic syndrome.

Patients and methods

Patient recruitment

This study was conducted at the internal medicine department and outpatient clinics in Assiut University Hospitals, from October 2011 to June 2013. A total of 60 patients diagnosed with type 2 diabetes mellitus (T2DM) were selected and divided into two groups. The first group included 30 patients (20 males and 10 females) with evidence of metabolic syndrome (based on WHO criteria). The second group included 30 patients with T2DM (10 males and 20 females), but none of them had evidence of metabolic syndrome. Totally, 20 healthy persons (11 males and nine females) were selected as controls. All participants had no other diseases such as liver cell failure, renal failure, respiratory failure, or cardiac failure.

The study was approved by the Ethics Committee of the Faculty of Medicine, Assiut University. All patients were informed about the method and the possible complications of the procedure, and a written consent was obtained.

All participants (patients and controls) were subjected to thorough history taking and complete clinical examination, routine investigations (fasting and postprandial plasma glucose, lipids profile, complete blood count, and liver and kidney function tests), and anthropometric studies. Specific investigations included determination of fasting serum insulin by Immulite System (Siemens Healthineers, Erlangen, Germany) and serum leptin concentrations.

WHO criteria for metabolic syndrome [12].

Insulin resistance	IGT, IFG, type 2 DM, or lowered insulin sensitivity, measured under hyperinsulinemic euglycemic conditions, glucose uptake below the lowest quartile for background population under investigation, plus any two of the following:
Body weight	Men: waist-to-hip ratio >0.90
	Women: waist-to-hip ratio >0.85
	And/or BMI >30 kg/m^2
Lipids	TGs ≥150 mg/dl and/or HDL-C <35 mg/dl in men or <39 mg/dl in women
Blood Pressure	≥140 systolic and 90 diastolic
Glucose	IGT, IFG, or type 2 DM
Others	Microalbuminuria: urinary excretion rate of >20 mg/min or albumin: createnine ratio of >30 mg/g

Biochemical methods

Serum leptin concentrations were measured using a sandwich ELISA test kit (Chemiluminescent Immunoassay Kit for Leptin; Abnova Company (Abnova, Taipei, Taiwan)), and serum insulin concentrations were measured by an Insulin (Human) Chemiluminesce Kit (USCN Life Science Inc.(Wuhan, China)).

Serum concentrations of glucose, total cholesterol (TC), triacylglycerols, HDL-cholesterol, low-density lipoprotein-cholesterol, and uric acid were measured on ILAB-600 Biochemical Analyzer (Instrumentation Laboratory, Lexington, Massachusetts, USA) using BioVendor sets. All samples were processed and examined according to the principles of good laboratory practice and under permanent intralaboratory and external quality control.

Anthropometric assessments included measurement of weight and height. Body weight was measured to the nearest 0.1 kg. Height of the participants without shoes was determined using a measuring tape, and subsequently BMI was calculated by dividing weight (kg) by height squared (m^2). In this study, individuals with BMI more than 25 kg/m^2 were considered as obese. Patients who had TC levels of more than 200 mg/dl, TG more than 150 mg/dl, HDL-C levels less than 40 mg/dl in males and less than 50 mg/dl in females, and low-density lipoprotein-cholesterol levels more than 100 mg/dl were considered to be dyslipidemic.

Statistical analysis

Data analysis

Data were analyzed using statistical package for social sciences software package version 20 (IBM SPSS, Chicago, Illinois, USA). The data are expressed as mean ± SD for continuous variables. Categorical variables are expressed as frequencies and percentages, and the comparison between these variables was carried out using χ^2-test. Numerical variables between three groups were analyzed by one-way analysis of variance test.

Significance of results

The results were considered nonsignificant if *P* greater than 0.05, significant if *P* 0.05 or less, and highly significant if *P* less than 0.01.

Results

From October 2011 to June 2013, 60 patients with T2DM meeting inclusion criteria and 20 healthy persons as controls were enrolled into our study.

Group I comprised 20 males and 10 females aged 24–55 (44.6 ± 6) years. Group II comprised 10 males and 20 females aged 33–53 (42.8 ± 6) years. Totally, 20 healthy persons (11 males and nine females) aged 24–55 (41.9 ± 7) years represented the control group (group III) as depicted in Fig. 1.

The calculated BMI was found to be 22.6 ± 3 in the control group, 21.3 ± 2 in group II, and 34.1 ± 4 in group I. Table 1 and Fig. 2 show these characteristics.

Table 2 and Figs. 3–5 show the mean levels of fasting blood sugar (FBS), postprandial blood sugar (PPBS), and glycated hemoglobin (HbA1c) of the studied groups, respectively.

Lipid profiles including serum cholesterol (mg/dl) and serum TG (mg/dl) of the studied groups are presented in Table 3 and Fig. 6.

Table 4 and Fig. 7 demonstrate the mean serum levels of leptin and insulin in the studied groups.

Table 5 shows the correlation between serum leptin and other parameters measured in the present study.

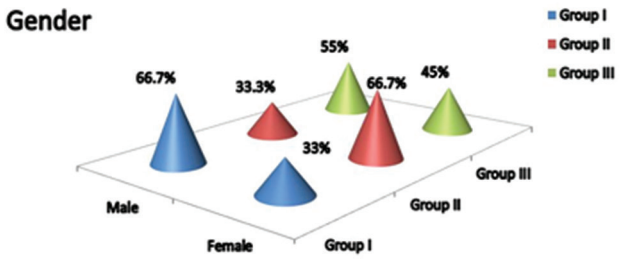
Table 1 and Fig. 2 show the mean age of the studied groups with no statistically significant difference between the groups ($P > 0.05$). Table 1 and Fig. 1 show the sex distribution of the studied groups with no statistically significant difference between the groups ($P > 0.05$). Finally, Table 1 and reveal that BMI was significantly higher in group I compared with group II and when compared with the group III ($P < 0.001$).

Table 2 and Figs. 3–5 show the mean levels of FBS, PPBS, and HbA1c of the studied groups, respectively. The mean serum levels of these parameters were significantly higher in group I when compared with group II and when compared with the group III ($P < 0.001$).

Table 3 and Fig. 6 illustrate the mean serum levels of TC and TG of the studied groups. There were significant differences in these parameters of group I when compared with group II ($P < 0.05$) and highly significant differences in group I when compared with group III ($P < 0.001$).

Table 4 and Figs. 7 show the mean serum levels of leptin and insulin; the mean serum levels of these

Figure 1



Sex distribution among the studied groups.

Table 1 Demographic data of all the groups included in the study

	Group I (*N*=30)	Group II (*N*=30)	*t*-Test	*P*	Group III (*N*=20)	Tests	*P*
Age (years)							
Mean±SD	44.6±6.8	42.8±6.2	1.08[a]	>0.5 (NS)	41.9±7.3	1.12[b]	>0.5 (NS)
Range	24-55	33-53			24-55		
Sex							
Male	20 (66.7)	10 (33.3)			11 (55.0)	0.32[c]	>0.5 (NS)
Female	10 (33.3)	20 (66.7)			9 (45.0)		
BMI							
Mean±SD	34.1±4.6	21.3±2.9	12.8[a]	<0.001[++]	22.6±3.25	130[b]	<0.001[++]
Range	26-41	15-26			19-32		

N=80. ANOVA, analysis of variance; S, significant. [a]Paired *t*-test. [b]*F*-test (ANOVA). [c]χ^2 -Test. [++]*P*<0.001, statistically highly significant.

Table 2 Comparison of fasting blood sugar (mg/dl), postprandial blood sugar, and glycated hemoglobin (mg/dl) between the studied groups

	Group I	Group II	*t*-Test	*P*	Group III	*F* (ANOVA)	*P*
FBG							
Mean±SD	168.7±30.8	126.6±12.3	8.6	<0.001*	90.6±13.4	88.8	<0.001*
Range	120-220	90-1115			70-110		
PPBS							
Mean±SD	318±63.8	212.9±14.5	8.8	<0.001*	110.9±8.1	118.4	<0.001*
Range	200-405	180-235			93-122		
HbA1c							
Mean±SD	10±1.05	7.79±1.26	7.5	<0.001*	4.9±0.45	145.9	<0.001*
Range	8-11.5	6.2-11			4.1-5.9		

N=80. ANOVA, analysis of variance; FBS, fasting blood sugar; HbA1c, glycated hemoglobin; PPBS, postprandial blood sugar. **P*<0.001, statistically highly significant.

Table 3 The lipid profiles including serum cholesterol (mg/dl) and serum triglycerides (mg/dl) of the studied groups

	Group I	Group II	*t*-Test	*P*	Group III	*F*-test (ANOVA)	*P*
TC							
Mean±SD	260.7±65.4	232.8±34.5	2.07	<0.05*	188.2±33.7	13.35	<0.001**
Range	180-370	190-300			155-310		
TG							
Mean±SD	228±63.8	199.9±37.3	2.08	<0.05*	143.2±39.9	17.7	<0.001**
Range	160-390	149-310			90-20		

N=80. ANOVA, analysis of variance; TC, total cholesterol; TG, triglycerides. **P*≤0.05, statistically significant. ***P*<0.001, statistically highly significant.

Table 4 Comparison between serum leptin (ng/ml) and serum insulin (μIU/ml) of the studied groups

	Group I	Group II	*t*-Test*	*P*	Group III	*F*-test (ANOVA)	*P*
Leptin							
Mean±SD	9.4±1.9	7.7±1.55	3.6	<0.001***	5.24±2.01	31.19	<0.001***
Range	7-14	4-10			2.3-8.2		
Insulin							
Mean±SD	116±38.5	13.27±4.8	14.5	<0.001***	7.2±1.72	182.6	<0.001***
Range	30-180	6-21			5.1-11.5		
Median	96.5	10.8			3.8		

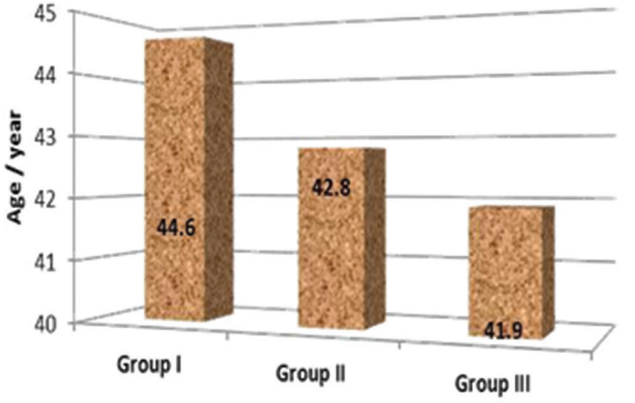
N=80. ANOVA, analysis of variance. ****P*<0.001, statistically highly significant.

Table 5 Correlation between serum leptin and other parameters

	r	*P*	Significance
Age	0.21	>0.05	NS
BMI	0.52	<0.001**	HS
FBS	0.65	<0.001**	HS
PPBS	0.37	<0.001**	HS
HbA1c	0.64	<0.001**	HS
TC	0.41	<0.001**	HS
TG	0.45	<0.001**	HS
Insulin	0.51	<0.001	HS

N=80. FBS, fasting blood sugar; HS, highly significant; HbA1c, glycated hemoglobin; PPBS, postprandial blood sugar; TC, total cholesterol; TG, triacylglycerols. ***P*<0.001, there are no significant differences with regard to age and highly statistically significant differences with regard to BMI, FBS, PPBS, HbA1c, total cholesterol, triglyceride, and serum insulin.

Figure 2



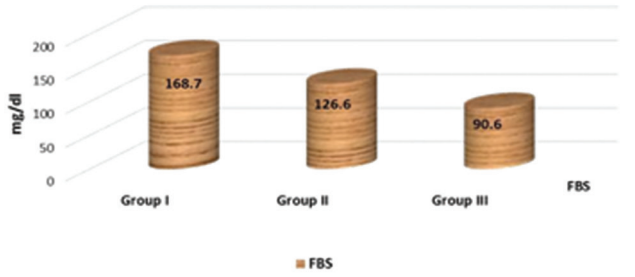
The mean age of the studied groups.

parameters were significantly higher in group I versus group II and group I versus group III ($P < 0.001$).

Discussion

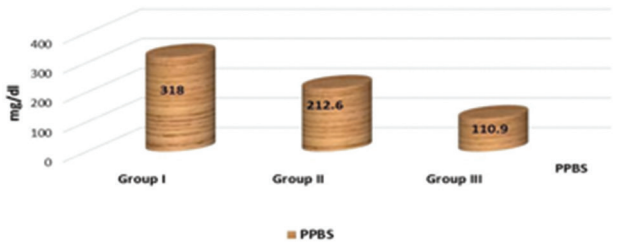
Insulin resistance is a common pathological state in type 2 diabetes in which target cells fail to respond to the physiological effects of insulin occurring in peripheral organs and leading to abnormalities in glucose, lipid, and protein metabolism. In fact, insulin resistance is present in the majority of patients with impaired glucose tolerance or T2DM, and it is also

Figure 3



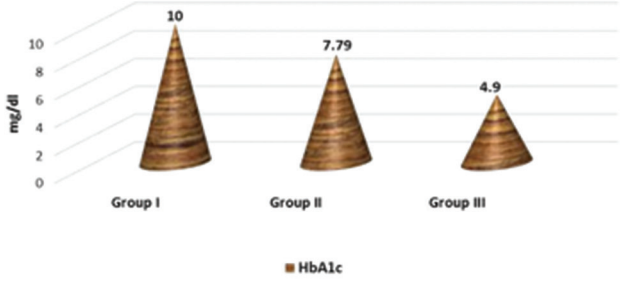
The mean fasting blood sugar among the studied groups. FBS, fasting blood sugar.

Figure 4



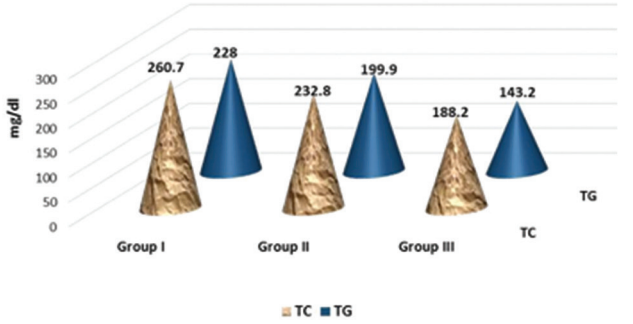
The mean postprandial blood sugar among the studied groups. PPBS, postprandial blood sugar.

Figure 5



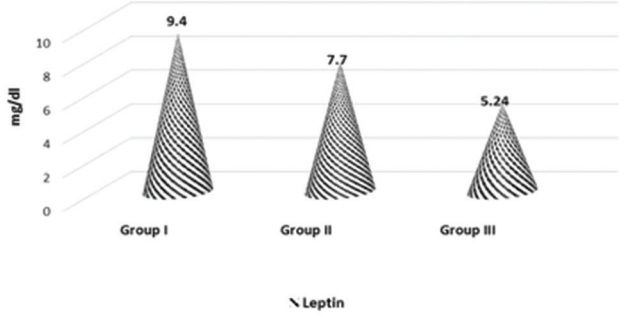
The mean glycated hemoglobin among the studied groups. HbA1c, glycated hemoglobin.

Figure 6



The mean serum total cholesterol and triacylglycerols among the studied groups. TC, total cholesterol; TG, triacylglycerols.

Figure 7



The mean serum leptin among the studied groups.

found in up to 25% of the general, apparently healthy population [13].

Insulin resistance is more strongly linked to intra-abdominal fat than to fat in other depots. Adipose tissue besides being a source of energy for the body is now well recognized as an endocrine organ, playing an important role in modulating insulin activity, inflammation, and vascular thrombosis. Regulated by multiple hormonal signals and nuclear hormone receptors, adipose tissue secretes numerous factors (adipokines) known to markedly influence lipid and glucose/insulin metabolism, oxidative stress, and cardiovascular integrity [14].

Leptin is an adipokine, which under normal physiological conditions functions to reduce appetite, increase energy expenditure, increase sympathetic activity, facilitate glucose utilization, and improve insulin sensitivity [4]. It is expressed in levels proportionate to adipose mass, and although it is produced mostly by adipocytes, it is also produced by vascular smooth muscle cells, cardiomyocytes, and placenta in pregnant women. The functional leptin receptor is in the hypothalamus where it functions to increase energy expenditure and reduce appetite. The receptor is also found in other organs such as the heart, liver, kidneys, and pancreas; it is also present in the smooth muscle and endothelium of heart, brain vasculature, and myometrium [7].

Leptin concentrations have been shown to correlate with insulin concentration and the degree of insulin sensitivity, and a role for leptin has been proposed in the etiology of insulin resistance and noninsulin-dependent diabetes mellitus [15].

The results obtained from our study showed no statistically significant difference ($P > 0.05$) regarding the age and sex of participants. However, there was a significantly higher difference in BMI of group I when compared with group II and group III ($P < 0.001$).

FBS levels were found to be 168.7 ± 3 and 126.6 ± 1 mg/dl in groups I and II, respectively, as compared with 90.6 ± 1 mg/dl in normal, healthy controls. PPBS levels were 318 ± 6 in group I, 212.9 ± 1 in group II, and 110.9 ± 8 in the control group. The mean serum levels of these parameters were significantly higher in group I when compared with group II and with group III ($P < 0.001$). The levels of HbA1c were also observed to be statistically highly significant ($P < 0.001$) in patients with metabolic syndrome (10 ± 1%) when compared with patients without metabolic syndrome (7.7 ± 1%) and with healthy controls (4.9%).

In addition, serum cholesterol and TG levels were observed to be significantly high in patients with metabolic syndrome when compared with patients without metabolic syndrome and with healthy controls ($P < 0.001$). In addition, there was a statistically significant difference between these parameters when group I was compared with group II ($P < 0.05$).

Moreover, the mean serum levels of leptin and insulin were significantly high ($P < 0.001$) in group I (9.4 ± 2 for leptin and 116 ± 9 for insulin) versus group II (7.7 ± 1 for leptin and 13.2 ± 4 for insulin) and healthy controls (5.2 ± 2 for leptin and 7.2 ± 1 for insulin).

Correlations between serum leptin and other parameters measured in this study showed no significant differences regarding age of participants, but highly significant differences with regard to BMI, FBS, PPBS, HbA1c, TC, TG, and serum insulin were found ($P < 0.001$).

In fact, the most important finding of this study was the positive relationship between serum leptin and serum insulin – that is, serum leptin level increases with increase in serum insulin ($r = 0.51$, $P < 0.001$). Therefore, in insulin resistance syndrome, where there is a hyperinsulinemic state, we predict that there are high serum leptin levels. In other words, high serum leptin may be a good indicator of the insulin resistance syndrome.

In our study, there were significant findings with regard to serum leptin and serum insulin. Serum leptin showed a significant difference between the studied groups ($P < 0.001$). In addition, serum insulin showed the same result ($P < 0.001$). Serum leptin measured in the studied groups showed a positive relationship with body fat, represented by BMI ($r = 0.52$, $P < 0.001$), and showed a positive relationship with fasting blood glucose and postprandial blood glucose ($r = 0.65$, $P < 0.001$ and $r = 0.37$, $P < 0.001$, respectively). Our findings also showed a positive relationship between serum leptin and TC ($r = 0.41$, $P < 0.001$) and TG ($r = 0.45$, $P < 0.001$).

The positive relationships between serum leptin and insulin with BMI signify that body fat or obesity plays a role in the development of both hyperleptinemia and hyperinsulinemia presented by insulin resistance syndrome.

The results of various studies are positively correlated to circulating leptin concentrations and obesity, despite the antiobesity actions of leptin [16,17]. Serum leptin levels were observed to be higher in the obese group and positively correlated with body fatness and obesity [18]. This is also in agreement with Adil Omar who found that leptin concentrations were high in both the obese group and the diabetic obese group and showed a direct positive relationship with BMI and waist circumference [19].

Zuo *et al.* [20] in their population-based study in China reported that leptin was independently associated with all measures of adiposity; however, there was a sex difference in the association of various levels of adiposity measures with leptin, where in men BMI had the strongest association with leptin, whereas in women the strongest association was with triceps skinfold.

Martins Mdo *et al.* [21] concluded that elevated serum leptin, particularly in obese individuals, should be taken as a warning sign of energy imbalance, poor diet, hyperinsulinemia, insulin resistance, or changes in other metabolic risk factors that are strongly associated with CVD and T2DM.

Moreover, our study showed that serum leptin levels were statistically significantly raised in patients with metabolic syndrome who were obese (group I), were also high in nonobese T2DM patients (group II), but normal or low in healthy controls. Our study is supported by the findings of a previous study, which observed that elevated leptin levels could confound an association with diabetes. The study concluded that leptin may play a role in the pathophysiology of diabetes, possibly by suppressing insulin secretion [22]. Goya *et al.* [23] conducted a prospective study in 2007. The study found that increased levels of serum leptin and low adiponectin were associated with increased risk of type 2 diabetes [23].

This was also similar to the study by Anil and colleagues in India who showed an association between increased serum leptin levels and T2DM patients. They concluded that higher leptin levels may be considered as an additional risk factor in patients of T2DM with high BMI (obesity) and dyslipidemia [24].

Our data are also in agreement with the data of Javad and Doudi who concluded that hyperleptinemia is a good predictor of insulin resistance syndrome [25].

In addition, Radka *et al.* [26] reported a significant role of serum leptin in determining insulin resistance syndrome.

Maghbooli *et al.* [27] examined the association between plasma leptin concentrations and insulin resistance in patients with diabetes mellitus, and found that elevated leptin concentrations were positively associated with insulin levels, BMI, and Homeostatic model assessment (HOMA). The same results were obtained by Baban *et al.* [28].

A study from China proved the positive relationship between leptin and insulin resistance syndrome (metabolic syndrome), as well as the important finding that hyperleptinemia could be a new component of metabolic syndrome [29].

Lee *et al.* [30] found that leptin was elevated in postmenopausal women with metabolic syndrome.

In a study on adolescents, Huang *et al.* [31] concluded that plasma leptin levels in adolescents could be a predictor for the development of metabolic syndrome disorders and CVDs.

Similar findings of elevated leptin associated with metabolic syndrome, independent of BMI, were found in a Korean population. In this study by Yun *et al.* [32], serum leptin levels increased as the components of metabolic syndrome increased, regardless of obese and nonobese weight status, implying that reduction in leptin levels may be protective, regardless of weight loss.

Moreover, it has been demonstrated by different studies that hyperleptinemia is an independent risk factor for progression of insulin resistance in type 2 diabetes [33].

On the other hand, a study from India concluded that leptin, although an obesity marker, is not significantly correlated with insulin resistance alone, which may point toward the multifactor causation of insulin resistance in T2DM. In other words, complex interactions between adipocytokines are proposed to be involved in the causation of insulin resistance, and any single molecule alone (including leptin) may have insignificant associations with the level of insulin resistance [34].

Piyali and colleagues are in agreement with Ko who reported that the leptin/adiponectin ratio is a more effective parameter of insulin resistance than adiponectin or leptin alone [35].

Yoshinaga *et al.* [36] found that leptin was the most sensitive marker for predicting metabolic syndrome (and cardiovascular risk) in elementary school children.

Moreover, Lee *et al.* [30] found a positive correlation with leptin and abdominal obesity (one of the components of metabolic syndrome), as well as with a number of components of metabolic syndrome.

Contrary to this, Martins *et al.* [37], found a direct, positive association between leptin and obesity, hyperinsulinemia, and insulin resistance, but was only weakly related to other components of metabolic syndrome.

Although there is some dissension in the literature about whether leptin is associated with metabolic syndrome independent of BMI, the general consensus is that it is elevated in metabolic syndrome in children, the elderly, females, and males, and therefore can serve as an effective biomarker on a screening panel for metabolic syndrome [4].

The main limitations of our study are, first, the use of BMI as a measure of fat mass – although BMI is a good measure for overweight, one needs to be aware of its limitation as an indirect measure of fat mass; and second, the long-term effect of antidiabetic treatment on leptin levels was not assessed.

Conclusion

The following conclusions were made:

- Positive relationship between serum leptin and insulin resistance syndrome in which serum leptin can play a major predictive role of insulin resistance syndrome
- Hyperleptinemia could be a new component of insulin resistance syndrome
- Leptin can be used as a useful biomarker for diagnosis and early identification of metabolic syndrome.

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Nil.

Conflicts of interest

There are no conflicts of interest.

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