Observational Study

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Association of serum leptin and insulin levels among type 2 diabetes mellitus patients

A case–control study

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Abstract

Secretion of insulin is compromised in type 2 diabetes (T2DM) individuals and inadequate to accommodate for insulin resistance (IR) in peripheral tissue. Hyperleptinemia reflects leptin resistance, which is a key factor in the production of IR in T2DM patients, making leptin a potential biomarker for evaluating IR levels. The objective of the study was to assess the association of serum leptin and insulin levels among T2DM patients. This case-control research was carried out on T2DM patients. A total of 73 patients diagnosed with T2DM (the case group) and 40 healthy participants (control; group 3) were enrolled according to the American Diabetes Association (ADA) criteria. In the case group, T2DM patients were enrolled with metabolic syndrome (group 1, n = 38) or without metabolic syndrome (group 2, n = 35) according to the WHO criteria. Metabolic profiles of T2DM patients with or without metabolic syndrome were evaluated, and compare these two groups with healthy controls. The subjects of all groups were age- and gender-matched. Body mass index (BMI, $P < .01$), fasting ($P = .0133$) and postprandial ($P < .01$) blood sugar levels, % glycated hemoglobin (HbA1c, $P < .01$), and lipid profile ($P < .01$) were found significantly different and higher in group 1 as compared to groups 2 and 3. Serum leptin and insulin levels were found higher and significant in patients with metabolic syndrome ($P < .01$ for both). The values of serum leptin levels were 10.01 ± 2.7 ng/mL, 6.9 ± 2.4 ng/mL, and 4.11 ± 1.8 ng/mL, and those of serum insulin 120 ± 40.7 μIU/mL, 20.43 ± 5.2 μIU/mL, and 11.4 ± 2.5 μIU/mL in groups 1, 2, and 3, respectively. There was a positive linear correlation between BMI, blood sugar, HbA1c, serum cholesterol (TC), and triglycerides (TG) with serum insulin and leptin levels in the case group. An extremely significant correlation ($R = 0.74$, $P < .001$) was found in BMI and serum leptin level in the case group. Serum leptin and insulin levels have a positive association, with serum leptin being a significant predictor of IR syndrome (Evidence Level: 5; Technical Efficacy: Stage 3).

Abbreviations: ADA = American Diabetes Association, BMI = body mass index, CBC = complete blood count, CVD = cardiovascular diseases, FBS = fasting blood sugar, HbA1c = glycated hemoglobin, HDL-C = high-density lipoprotein cholesterol, IR = insulin resistance, KFT = kidney functioning tests, LDL-C = low-density lipoprotein-cholesterol, LFT = liver functioning test, PPBS = postprandial blood sugar, T2DM = type 2 diabetes, TC = serum cholesterol, TG = triglyceride, WC = waist circumference, WHO = World Health Organization, χ^2-test = Chi-square test.

Keywords: adipocytokines, blood sugar level, diabetes mellitus, inflammation, insulin resistance, metabolic syndrome, serum cholesterol, serum leptin

1. Introduction

In the last century, diabetes mellitus is reported a rising epidemic.[1] Diabetes is a common chronic disease.[2] Type 2 diabetes (T2DM) was first recognized as a component of metabolic syndrome in 1988.[3] Hyperglycemia, insulin resistance (IR), and insulin deficiency are the hallmarks of T2DM (non-insulin-dependent diabetes).[4] T2DM is caused by a combination of genetic, environmental, and behavioral risk factors.[5]

Diabetes is becoming more common and prevalent across the world.[6] Diabetes affects more than 250 million people worldwide, with the figure projected to rise to 400 million by 2030.[5] Diabetes is a metabolic condition marked by a recurrent rise in blood sugar levels (hyperglycemia) caused by insulin secretion, IR, or both.[3] Diabetes is classified into two groups generally, firstly type 1 diabetes, which affects 5 to 10% of people with diabetes, is an autoimmune condition that destroys pancreatic cells, resulting in an absolute insulin deficiency, and secondly, T2DM, which affects more than 90% of people with diabetes is affected by the composite of IR and relative, but not total insulin deficiency.[7] As a result, the secretion of insulin is compromised in these individuals and inadequate to accommodate IR in peripheral tissue.[8]

Adipocyte-derived hormone leptin is also known as adipocytokine because it plays a part in adipose tissue inflammation.[9] It performs a wide range of functions, the most important of

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The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

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which is to maintain energy balance.[10] This is accomplished by lowering appetite or energy consumption while rising energy expenditure. As a result, it is appropriately referred to as the satiety hormone.[11] Leptin has recently been discovered to mediate insulin secretion and peripheral tissue sensitivity.[12] Hyperleptinemia, which reflects leptin resistance, is a key factor in the production of IR in T2DM patients, making leptin a potential biomarker for evaluating IR levels.[13] Furthermore, it has been proposed that leptin levels are independent of obesity; predict the development of metabolic syndrome.[14] In addition to its impact on appetite and obesity, leptin activates the sympathetic nervous system in the hypothalamus, which increases blood pressure.[15] High levels of circulating leptin are believed to be responsible for the increase in renal sympathetic tone seen in overweight people.[16] Leptin causes hypertension, angiogenesis, and atherosclerosis,[17] both can be used as a biomarker for metabolic syndrome diagnosis and early detection.[18]

Although the pathogenesis of metabolic syndrome and its components is unclear, central obesity and IR have been identified as causative factors.[19] Obesity (waist circumference (WC) or body mass index (BMI)), triglyceride (TG) levels, hypertension, hyperglycemia, and urinary albumin or albumin and creatinine ratio are all diagnostic criteria for metabolic syndrome, according to many different organizations.[3] There are too many different organizations, and the primary concern regardless of the parameters used is early identification of possible cardiovascular disease (CVD) problems and early intervention.

Leptin is an inflammatory adipocytokine that involved metabolic processes. Not only leptin, but also other cytokines, such as cardiothrophin-1,[20] omentin,[21] and neuregulin[22] are associated with T2DM and IR. Additionally, diabetic microvascular complications have close relationship with adipocytokines including omentin,[23] urinary kidney injury molecule,[24] and neuregulin.[25] Therefore, studying the association of leptin and IR in T2DM is rational.

The aim of this present study was the evaluation of the correlation between serum leptin and serum insulin levels in T2DM patients with metabolic syndrome.

2. Materials and Methods

2.1. Statement of ethics

The study protocols were approved by the Tianjin TEDA hospital Ethical Committee (IEC reference no. 15124TEDAhec1 dated 11 January 2019). The study follows the law of China and the V2008 Declaration of Helsinki. All methods were carried out in accordance with STROBE guidelines and regulations. Written informed consent was obtained from all subjects to participate in the study.

2.2. Inclusion criteria

Patients diagnosed with T2DM (the case group) were enrolled according to the American Diabetes Association (ADA) criteria.[26] In all cases, participants were split into 2 groups. In group 1, T2DM patients with metabolic syndrome enrolled according to the World Health Organization (WHO) criteria.[27] In group 2, T2DM patients were included without metabolic syndrome and in group 3 total of 40 healthy participants (male and females) were selected for control.

2.3. Exclusion criteria

Those participants were excluded who had any other diseases such as renal failure, liver cell failure, respiratory failure, or cardiac failure.

All participants were enrolled after taking to complete clinical examination, routine investigations such as fasting and postprandial plasma glucose test, lipid profile, complete blood count (CBC), liver functioning test (LFT), kidney functioning tests (KFT), and anthropometric assessments. The blood sample was taken for leptin and insulin assessment.

2.4. Anthropometric assessments

Anthropometric assessments included the measurement of weight and height. The weight was taken down to the nearest 0.1 kg. A measuring tape was used to determine the height.

2.4.1. BMI. BMI was calculated by dividing weight in kg by height squared (m^2).

2.4.2. Obese. BMI of more than 25 kg/m^2 was considered obese.

2.4.3. Dyslipidemia. Patients who had serum cholesterol (TC) levels of more than 200 mg/dL, TG more than 150 mg/dL, high-density lipoprotein cholesterol (HDL-C) levels less than 40 mg/dL in males and less than 50 mg/dL in females, and low-density lipoprotein-cholesterol (LDL-C) levels more than 100 mg/dL were dyslipidemia.

2.5. Biochemical assessments

Serum leptin concentrations were measured using a sandwich ELISA kit (Thermo Fisher Scientific Inc., Waltham, MA) and serum insulin concentrations were measured by an insulin kit (Thermo Fisher Scientific Inc., Waltham, MA) according to the previously described method.[18]

2.6. Statistical analysis

For continuous data, normality was analyzed using the Kolmogorov Smirnov test. For comparison of categorical variables, the Chi-square test (χ^2-test) was used. Comparison of non-normal continuously distributed variables the Mann Whitney *U*-test (2 groups) or Kruskal Wallis test (3 groups or more) was used for statistical analysis. The Dunn's multiple comparisons test was applied on multiple comparisons between groups for post hoc analysis. Statistical analysis was carried out using the statistical package for social science, version 22 (SPSS-22, IBM, Chicago, IL, USA). A P-value < .05 has been considered significant. Pearson's correlation was developed between serum leptin and other baseline and biochemical parameters.

3. Results

3.1. Study population

This case-control study was done between 15 January 2019 and 17 March 2017 in the Tianjin TEDA Hospital, Tianjin, China. A total of 73 patients diagnosed with T2DM (the case group) were enrolled according to the American Diabetes Association (ADA) criteria and seven patients with T2DM excluded who had any other diseases. In all cases, participants were split into 2 groups. In group 1, T2DM patients with metabolic syndrome enrolled according to the WHO criteria. In group 2, T2DM patients were included without metabolic syndrome and in group 3 total of 40 healthy participants (male and females; between 24 and 53 age groups) were selected (the control group). A flow chart for the study population is presented in Fig. 1.

3.2. Baseline characteristics of groups

The general characteristics of groups are summarized in Table 1. The age of groups 1, 2, and 3 ranged from 24 to 54, 26

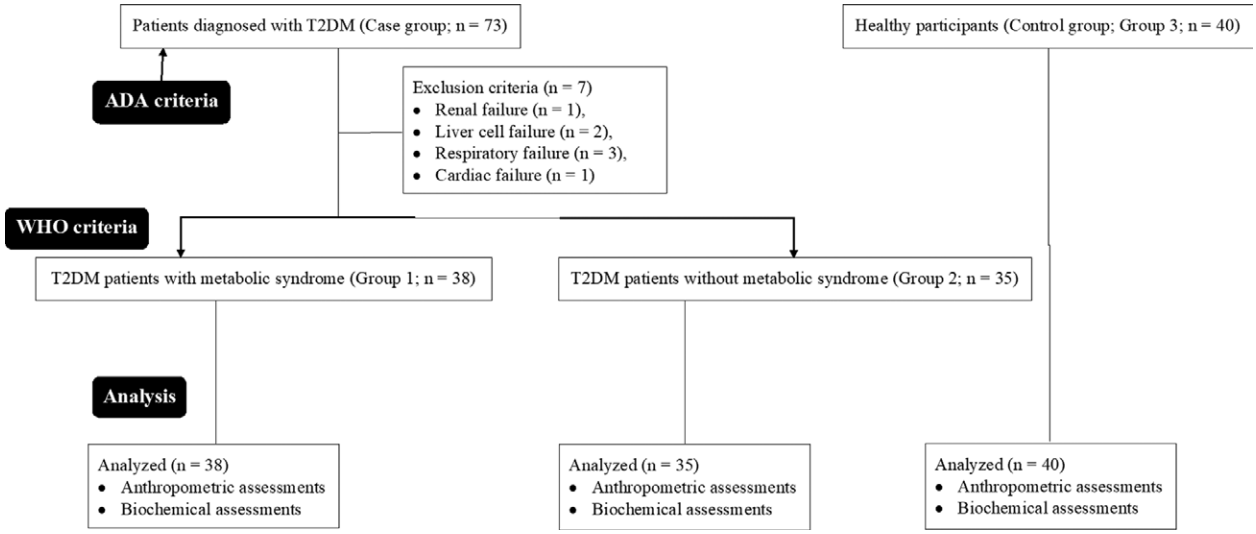

Figure 1. Flow diagram of the study. ADA = American Diabetes Association, T2DM = type 2 diabetes, WHO = World Health Organization.

Table 1

General baseline characteristics of subjects.

	Group				
	Case group (T2DM patients)		Control group		
Variable	Group 1	Group 2	Group 3		
Characteristics	T2DM patients with metabolic syndrome	T2DM patients without metabolic syndrome	Healthy participants	Comparison	
Numbers of persons	38	35	40	χ^2-Value	*P*-value
Age (years)					
Minimum	24	26	25	N/A	.2164 (Kruskal Wallis test)
Maximum	54	51	53		
Mean ± SD	43 ± 7.15	40.2 ± 7.06	41.8 ± 6.19		
Gender					
Male	22(58)	16(46)	23(58)	1.397	.4974 (χ^2-test)
Female	16(42)	19(54)	17(42)		
BMI (kg/ m^2)					
Minimum	23	22	22	N/A	<.0001 (Kruskal Wallis test)
Maximum	38	30	29		
Mean ± SD	31.32 ± 4.02	26.71 ± 1.99	26.05 ± 1.65		

BMI = body mass index, N/A = not applicable, T2DM = type 2 diabetes.

Categorical data are presented as frequency (percentage) and non-normal continuously distributed variables are presented as mean ± standard deviation (SD).

For categorical data, the Chi-square test (χ^2-test) was used to compare the groups. Kruskal Wallis test followed by the Dunn's multiple comparisons post hoc test was applied non-normal continuously distributed variables.

A *P*-value less than .05 was considered significant.

to 51, and 25 to 53 years, respectively by a mean of 43 ± 7.15; 40.2 ± 7.06, and 41.8 ± 6.19 years, respectively. Comparing the mean age of the groups, the analysis showed similar ($P = .2164$, Kruskal Wallis test) age between all groups, that is, did not differ significantly. In other words, the subjects of all groups were age-matched. Further, the gender was found similar ($P = .4974$, χ^2-test) between the selected three groups, that is, also not differed significantly. However, BMI was found significantly ($P < .01$, Kruskal Wallis test/Dunn's multiple comparisons test) different and higher in group 1 as compared to groups 2 and 3. The Kruskal Wallis test following the Dunn's multiple comparisons test also shows homogeneity for BMI between group 2 and group 3 ($P > .05$, Kruskal Wallis test/ Dunn's multiple comparisons test). BMI distribution of participants is reported in Figure 2.

3.3. Biochemical parameter

The biochemical parameter levels of the groups are summarized in Table 2. Comparing the mean biochemical parameter levels of the three groups, a post hoc test showed a significant difference in fasting blood sugar (FBS) level between group 1 and group 3 ($P < .01$, Kruskal Wallis test/Dunn's multiple comparisons test), postprandial blood sugar (PPBS) level between group 1 and group 2 ($P < .01$, Kruskal Wallis test/Dunn's multiple comparisons test), between group 1 and group 3 ($P < .01$, Kruskal Wallis test/Dunn's multiple comparisons test), and between group 2 and group 3 ($P < .01$, Kruskal Wallis test/Dunn's multiple comparisons test). Also, for glycated hemoglobin (HbA1c) levels a significant difference was reported between group 1 and group 2 ($P < .01$, Kruskal Wallis test/Dunn's multiple comparisons

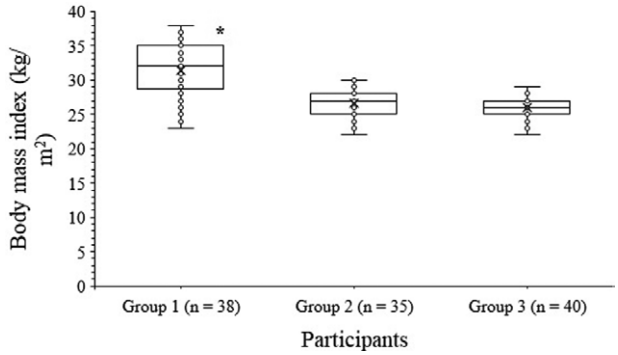

Figure 2. Distribution of body mass index in studied groups. *Higher in group 1 as compared to groups 2 and 3.

test), between group 1 and group 3 ($P < .01$, Kruskal Wallis test/Dunn's multiple comparisons test), and between group 2 and group 3 ($P < .01$, Kruskal Wallis test/Dunn's multiple comparisons test). The mean lipid profiles including TC and TG were found significantly different in all groups and higher in group 1 as compared to the other groups ($P < .01$ for both, Kruskal Wallis test/Dunn's multiple comparisons test).

3.4. Distribution of serum leptin and insulin

Serum leptin level was reported higher in group 1 compared to group 2 (10.16 ± 2.59 ng/mL versus 7.49 ± 1.52 ng/mL, $P < .01$, Kruskal Wallis test/Dunn's multiple comparisons test) and compared to group 3 (10.16 ± 2.59 ng/mL versus 4.73 ± 1.62 ng/mL, $P < .01$, Kruskal Wallis test/Dunn's multiple comparisons test). Also, serum leptin level was reported higher in group 2 compared to group 3 ($P < .01$, Kruskal Wallis test/Dunn's multiple comparisons test, Fig. 3). Serum insulin level was reported higher in group 1 compared to group 2 (125.29 ± 2.59 µIU/mL versus 21.74 ± 8.14 µIU/mL, $P < .01$, Kruskal Wallis test/Dunn's multiple comparisons test) and compared to group 3 (125.29 ± 2.59 µIU/mL versus 10.15 ± 2.61 µIU/mL, $P < .01$, Kruskal Wallis test/Dunn's multiple comparisons test, Fig. 4). In other words, type 2 diabetes may be related to serum leptin and serum insulin.

3.5. Correlation between serum leptin and other baseline and biochemical parameters

There was a positive linear correlation between the selected parameters (BMI, FBS, PPBS, HbA1c, TC, TG, and insulin) and serum leptin levels in case groups (groups 1 and 2; Table 3). An extremely significant correlation ($R = 0.74$, $P < .001$, Pearson's correlation) were found in BMI and serum leptin level in the case group. Its large value indicates a strong relationship between BMI and serum leptin. The correlation between age and serum leptin level was found to be null ($P > .05$, Pearson's correlation).

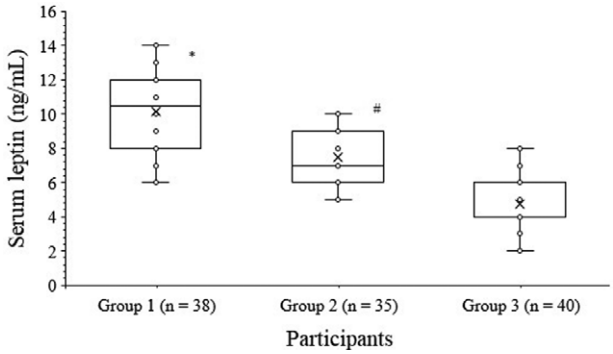

Figure 3. Distribution of serum leptin in studied groups. *Higher in group 1 as compared to groups 2 and 3. #Higher in group 2 as compared to group 3.

Table 2

Biochemical parameter.

Parameters	Group 1	Group 2	Group 3	
Characteristics	**T2DM patients with metabolic syndrome**	**T2DM patients without metabolic syndrome**	**Healthy participants**	**Comparison**
Numbers of persons	**38**	**35**	**40**	***P*-value**
Fasting blood sugar (mg/dL)				
Minimum	108	82	65	.0133
Maximum	211	112	100	
Mean ± SD	155.40 ± 27.10	103.70 ± 20.80	77.10 ± 8.60	
Postprandial blood sugar (mg/dL)				
Minimum	210	170	85	<.0001
Maximum	390	225	119	
Mean ± SD	287.98 ± 58.79	193.89 ± 18.49	108.30 ± 12.10	
% Glycated hemoglobin				
Minimum	7	6	4	<.0001
Maximum	11	11	7	
Mean ± SD	8.95 ± 1.42	6.87 ± 1.06	4.28 ± 1.06	
Serum cholesterol (mg/dL)				
Minimum	190	200	150	<.0001
Maximum	360	280	300	
Mean ± SD	250.68 ± 59.39	212.28 ± 38.78	177.49 ± 28.11	
Triglyceride (mg/dL)				
Minimum	145	140	90	<.0001
Maximum	380	300	220	
Mean ± SD	221.85 ± 71.19	181.28 ± 41.58	134.69 ± 36.22	

Data are presented as mean ± standard deviation (SD).

Kruskal Wallis test followed by the Dunn's multiple comparisons post hoc test was applied between groups.

A *P*-value less than .05 was considered significant.

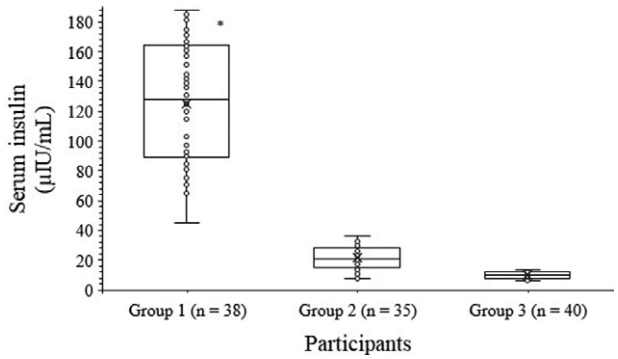

Figure 4. Distribution of serum insulin in studied groups. *Higher in group 1 as compared to groups 2 and 3.

Table 3

Correlation (*r*) between serum leptin and other parameters in case group.

Parameters	Value of *r*	*P*
Age (years)	0.31	.5
Body mass index (kg/m^2)	0.74	.003*
Fasting blood sugar (mg/dL)	0.68	.002*
Postprandial blood sugar (mg/dL)	0.41	.02*
% Glycated hemoglobin	0.69	.001*
Serum cholesterol (mg/dL)	0.46	.02*
Triglycerides (mg/dL)	0.51	.002*
Insulin (μIU/mL)	0.54	.003*

*Significant $P < .05$.

4. Discussion

Our present study showed statistically insignificant differences ($P > .05$) in the age and sex of participants. However, there were significantly higher differences in BMI, FBS, PPBS, serum leptin level, and serum insulin levels in group 1 when compared with groups 2 and 3 ($P < .01$ for all). The previous study showed the same results.[18] HbA1c levels were also observed to be statistically higher and significant when compared with patients without metabolic syndrome and healthy control. Previously Tamer et al[18] also found statistically significant when HbA1c was compared with patients without metabolic syndrome and healthy control. Patients with metabolic syndrome may have worsen anthropometric and biochemical parameters.

Also, TC and TG levels of T2DM patients with metabolic syndrome were observed to be significantly high when compared to T2DM patients without metabolic syndrome and healthy control ($P < .01$ for all). Moreover, the serum leptin levels and insulin levels were significantly high ($P < .01$ for all) in group 1 as compared to groups 2 and 3. T2DM patients with metabolic syndrome may have cardiometabolic risk.

Correlation between leptin and other parameters measured in this study showed no significant differences regarding the age of participants, but higher and significant differences ($P < .01$) concerning BMI, FBS, PPBS, HbA1c, TC, TG, and insulin were found. The most important role of this finding of our study was the positive relationship between serum leptin and serum insulin, that is, increased serum leptin with increases in insulin levels, our study found the same results as those of ADA criteria.[26] Therefore, in IR syndrome, if there is a hyperinsulinemic state, we predict that there are high leptin levels. Leptin resistance is more common in obese people which also lead to IR, implying that leptin plays a role in T2DM pathogenesis.[13,28] According to Welsh et al,[29] leptin is a predictor of T2DM risk factors in men. Higher leptin levels indicated a higher risk of T2DM,[30] These are the potential pathway by which leptin levels in T2DM are linked to IR.[13] Serum leptin is a good indicator of IR syndrome.

Our study showed a positive relation between serum insulin and leptin with BMI. The other study[13] was also shown, that the positive correlation between serum leptin and serum insulin, and BMI suggests that body fat or obesity plays role in the development of IR syndrome's hyperleptinemia and hyperinsulinemia. Despite leptin's anti-obesity properties, the findings of multiple studies show a strong correlation between circulating leptin concentrations and obesity.[31] Serum levels of leptin were found to be very high in the obese population and body fatness and obesity were found to be a positive association.[32] This is also to Adil Omar's[33] finding, which found that leptin levels were high in both the non-diabetic and diabetic obese groups, and it had a direct link to BMI and waist circumference (WC). A previous study also found a positive correlation between serum leptin and insulin levels with metabolic syndrome.[34] Contrary to previous studies, Martin et al found a direct positive association between obesity and serum leptin, hyperinsulinemia, and IR but not strong relation to other components of metabolic syndrome[35] on other hand, previously concluded that serum leptin, through obesity marker, does not significantly end towards the multifactor causation of interactions between adipocytokines are proposed to be involved in the defect in IR, and any single molecule alone including leptin may have not significant associations with the level of IR.[36] Increased leptin levels in obese, diabetic patients may indicate leptin resistance; and since leptin is a strong regulator of insulin sensitivity/glucose homeostasis, it is possible that when leptin resistance develops it may worsen IR.

There are several limitations of the study, for example, a small sample size and the single center settings. Also, antidiabetic treatment on leptin level was not evaluated. The study does not show evidence of cause and effect, and since group 1 is also clearly obese it makes it difficult to distinguish the effects of leptin resistance *versus* those of obese and its associate metabolic complications on insulin profile and sensitivity. For example, the same could be stated regarding TC or TGs levels based on data presented in the manuscript. The study group is only involved with 113 patients' cases.

5. Conclusions

The study describes the metabolic profile of diabetic patients with or without metabolic syndrome, and compares these two groups with healthy controls. Their major findings are that diabetic patients that also exhibit obesity have higher levels of cholesterol, triglycerides, insulin, and leptin when compared to leaner diabetic patients and non-diabetic controls. The study proposes that since leptin levels show positive correlation with insulin levels, then, it could be inferred that elevated leptin levels may predict the degree of IR in diabetic patients. Although serum leptin has limited role in diagnosis and treatment of diabetes mellitus, the clinical significance of this article is broad.

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Author contributions

Conceptualization: Huihui Li.
Investigation: Huihui Li.
Methodology: Yanfei Zhao, Huihui Li.
Project administration: Yanfei Zhao.

Resources: Yanfei Zhao.
Software: Yanfei Zhao.
Supervision: Yanfei Zhao.
Writing – original draft: Huihui Li.
Writing – review & editing: Huihui Li.

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