Relation of Osteoprotegerin, Visfatin and Ghrelin to Metabolic Syndrome in Type 2 Diabetic Patients

Manal Basyouni Ahmed, [(1)*] Maha Imam Ahmed Ismail, [(1)] Abdel-Raheim M. Meki [(2)]

Department of Biochemistry, Faculty of Medicine, Qassim University, KSA, Permanent address: Medical Biochemistry Dept., Faculty of Medicine, Ain Shams University Cairo, Egypt. [(1)]
Department of Biochemistry, Faculty of Medicine, Assuit University, Assuit, Egypt [(2)]

Abstract

Background: It is now realized that insulin resistance plays a principal role in initiating the pathologic manifestations of the metabolic syndrome (MetS).

Objectives: The aim of this study was to assess the possible role of osteoprotegerin, visfatin and ghrelin in the pathogenesis of MetS among type2 diabetes mellitus (T2DM).

Design and methods: Serum blood samples were obtained from 116 subjects (39 T2DM; 48 T2DM with MetS; 29 healthy controls). Glycemic status and lipid profile were assessed by enzymatic method. Osteoprotegerin, visfatin, ghrelin and insulin were measured by ELISA method.

Results: Osteoprotegerin and visfatin were significantly higher, while ghrelin was significantly lower in diabetic patients compared to healthy control group ($p<0.05$). Moreover, Osteoprotegerin and visfatin showed significant higher levels in T2DM patients with MetS than those without MetS ($p<0.05$). The best cut-off values for the investigated markers were determined by ROC curve.Osteoprotegerin (1.06 ng/mL), visfatin (32.27 ng/mL) and ghrelin (33.65 pg/mL) presented sensitivity of76%, 92% and 39.1%; respectively and specificity of41%, 69.2% and 62.9%; respectively, in predicting MetS among T2DM. Among the investigated parameters, Visfatin was the one which predicts MetS among diabetic patients [AUC=0.88, $p<0.05$].

Conclusion: Osteoprotegerin, visfatin and ghrelin might be implicated in the pathogenesis of diabetes. Moreover, osteoprotegerin and visfatin may have additional potential role in the development of the metabolic syndrome. Visfatin was superior among studied parameters in predicting MetS among T2DM**.**

Keywords: Osteoprotegerin, Visfatin, Ghrelin, Diabetes, Insulin Resistance, Type2 diabetes mellitus and Metabolic Syndrome

Correspondence:

Manal Basyouni Ahmed
Associate Professor of Medical Biochemistry
Faculty of Medicine, Qassim University, KSA
Cell Phone: 0583503468
E-mail: manal_basiony@yahoo.com
*Permanent address:
Medical Biochemistry Dept.,
Faculty of Medicine,
Ain Shams University, Cairo, Egypt

Introduction

Metabolic syndrome (MetS) is characterized by the variable co-existence of hyperinsulinemia, obesity, dyslipidemia, and hypertension. Obesity and insulin resistance are key components of the clustering of risk factors known as the metabolic syndrome. The number of patients with MetS is expanding worldwide; the prevalence in developed and developing countries is comparable, ranging from 15.2% to 43.7%. [1]

Osteo Osteoprotegerin (OPG) is a secreted glycoprotein belonging to the tumor necrosis factor receptor super family. It is mainly secreted by bone but is also secreted by a variety of different tissues including endothelial and smooth muscle cells. [2] The role of OPG in the pathogenesis of metabolic syndrome, type 2 diabetes and cardiovascular diseases is still studied. It acts as a blocking receptor by binding to the receptor activator of nuclear factor–κB ligand and preventing it from binding to the receptor activator of nuclear factor–κB. [3]

Among novel adipocytokines, visfatin was originally identified as pre-B cell colony-enhancing factor and is also known as nicotinamide phosphoribosyl transferase (NAMPT), an enzyme involved in the NAD+ salvage pathway. [4] It is preferentially expressed in visceral adipose tissue and possessed insulin-mimetic bioactivity. [5] Following the recent isolation and characterization of visfatin, there has been a rapidly growing interest in this protein, its potential properties and subsequent role in the development of T2DM and obesity. [6] Visfatin has insulin-like metabolic effects on glucose metabolism but has a distinct binding site on insulin receptors. [4] However, visfatin exerts pro inflammatory and immunomodulating properties that contributing to its association with metabolic parameters. [7]

Ghrelin is a 28 amino acids hormone is secreted by many tissues, but its main source is the gastric mucosa. [8] Ghrelin stimulates growth hormone secretion and inhibits the release of calcium and insulin from pancreas. [9] During the last years both basic research and genetic association studies have revealed association between the ghrelin gene and obesity, metabolic syndrome or type 2 diabetes. [10]

An expanding body of data indicates the association between insulin resistance, adipocytokines, and consequent diabetic complication. However, to our knowledge, few previous studies investigated the association between osteoprotegerin and adipocytokines (visfatin, and ghrelin) with metabolic syndrome in type 2 diabetic patients. Thus, we investigated the association of these parameters with T2DM and studied their relation to glycemic control and lipid profile in addition to evaluate their possible pathogenic role for MetS among patients with T2DM.

Materials and Methods

1. Study subjects

Eighty seven diabetic Saudi patients were recruited from the Outpatient Clinic of Qassim University, KSA between January 2013 and September 2013. Patients were further divided into: 39 patients with T2DM (mean age 45.8± 6.2years) and 48 patients with T2DM and MetS (mean age 49.9 ±6.4years). The patients were compared to 29 healthy subjects (mean age 41.1± 8.3 years). All diabetic patients were on oral hypoglycemic drugs. The control subjects had age and sex matched with diabetic patients. All individuals were subjected to complete full history and clinical examination. Metabolic syndrome was diagnosed according to the criteria of the International Diabetes Federation (IDF). [11] Exclusion criteria were the presence of type 1 DM, acute and chronic infections, malignancy, hepatic or renal disease, diabetic retinopathy, nephropathy and smoking. The control group had no history of endocrine dysfunctions; hypertension and coronary heart diseases. An informed consent was obtained from all included subjects. Permission and ethical approval to conduct the study was sought and granted by the University Deanship of Scientific Research, College of Medicine, Qassim University (Project No. SR-D-2013-1877).

2. Blood sample collection

Overnight blood samples (5 to 10 mL) were collected either on Na_2-EDTA tubes (1mg/mL) for fasting blood glucose (FBG) and HbA1c% determination [12] or in plain

tubes for serum recovery by centrifugation at 3000 rpm for 10 minutes. Sera were aliquoted and stored at -20°C until measurements of other parameters.

3. Biochemical analyses

Fasting blood glucose (FBG) was determined immediately enzymatically using kits provided byBeckman Instruments, Inc., Brea, USA. Glycated hemoglobin (HbA_{1c}) was measured on a DCA 2000 BioAnalyzer according to manufacturer's instructions (Bayer, Elkhart, USA)**.** Lipid profile parameters [total cholesterol (TC), high density lipoprotein cholesterol (HDL-c) and triglycerides (TG)] were evaluated using colorimetric assay (StanbioLiquiColor Procedure, USA). Human serum osteoprotegerin (Uscn Life Science Inc, USA; sensitivity= 0.06 ng/mL), visfatin (Biosource International, Inc., USA, sensitivity =2ng/mL), ghrelin (SPI-Bio bertin pharma, European, sensitivity =6pg/ mL) and insulin (ChemuxBioScince, Inc, USA, sensitivity =2 µIU/mL) were determined using specific ELISA kits according to recommendation of the manufactures.

4. Calculations

Standing height and body weight were measured with the subjects dressed in light indoor clothing without shoes. Body mass index (BMI) was calculated as weight divided by the square of the height (kg/m^2). The Participates considered obese when BMI ≥ 30 kg/m^2 according World Health Organization (WHO), 2007. [13]

5. Statistical Analysis

Statistical analysis was performed using SPSS for Windows (Statistical Package for the Social Sciences, version 16.0; SSPS Inc. Chicago, IL, USA). Clinical and laboratory data were presented mean ± SD and/or median and mean rank. Statistical comparison was made using the parametric test, ANOVA (followed by post Hoc test) for the comparison of variables which were normally distributed or non-parametric test Mann-Whitney U (to compare two groups) and Kruskal-Wallis test (to compare three groups) for the comparison of variables which were not normally distributed. Pearson tests were used for the evaluation of correlations among the variables according to the distribution of variables. The threshold value for optimal sensitivity and specificity were determined by receiver operating characteristic (ROC) curve, which was constructed by calculating the true-positive fraction {sensitivity [%]), false-positive fraction (100-specificity [%]), and Area Under the Curve (AUC)} of the above-mentioned markers at several cut-off points.P<0.05 was accepted as indicative of statistical significance.

Results

Table (1) depicts the demographic data of the study groups. BMI showed no significant difference between healthy and diabetic group, while diabetic patients with metabolic syndrome had significantly higher BMI than healthy group and other diabetic patients ($p<0.05$). Moreover, the blood pressure (systolic and diastolic) was significantly higher in diabetic patients compared to healthy group ($p< 0.05$), and in T2DM with MetS patients than those without MetS ($p< 0.05$). Moreover, Fasting blood glucose ($p<0.01$), glycosylated hemoglobinA_{1c} ($p<0.01$), Insulin, HOMA-IR ($p<0.01$), cholesterol ($p<0.05$), and triglycerides ($p<0.01$) showed higher significant differences among diabetic patients compared to control group, and among T2DM with MetS compared to others T2DM ($p<0.05$). MeanwhileT2DM with MetS showed a significant higher LDL levels than control group ($p< 0.01$) and higher an atherogenic index than control group ($p< 0.01$) and other diabetic patients ($p< 0.05$). However, HDL-C showed significant lower levels in T2DM with MetS compared to other groups ($p< 0.05$), (Table 2). Furthermore, levels of osteoprotegerin andvisfatin were significantly higher in diabetic patients compared to health control and were significant higher in T2DM with MetS compared to those without Mets, $p< 0.05$. While ghrelin was significantly lower in diabetic patients compared to control group ($p< 0.01$), but was non-significantly among subgroups of diabetic patients (Table3). Table 4 showed that osteoprotegerin and visfatin levels were significantly higher in diabetic, metabolic syndrome patients compared to healthy individuals, while ghrelin showed significant

lower levels. Moreover, ghrelin was significantly higher in females, while osteoprotegerin and visfatin were significantly higher in obese subjects.

Fig. 1 and Table 5 showed ROC curve analysis for osteoprotegerin, visfatin and ghrelin to calculate cut-off point to discriminate between diabetic patients with and without metabolic syndrome. The best cut-off point of osteoprotegerin was at 1.06 ng/mL(sensitivity = 76% and specificity = 41%; p = 0.14), Visfatinat32.27ng/mL (sensitivity= 92% and specificity = 69.2%; p = 0.01) and Ghrelinat33.65pg/mL(sensitivity = 39.1% and specificity = 62.2.9%; p = 0.57), table (6).

Correlation analysis among the investigated serum parameters revealed a significant positive correlation between osteoprotegerin and visfatin with advancing age of patients (p<0.05), systolic blood pressure (p<0.01), blood pressure (p<0.01), BMI(P<0.01), FBG (P<0.01), HbA1c (p<0.01), insulin resistance(p<0.01), TG (p<0.01), cholesterol (p<0.05), atherogenic index (p<0.05) and with each other (p<0.01) and negatively correlated to HDL (p<0.05). Additional significant correlations were found between visfatin and waist to Hip ratio (p<0.01). Moreover, ghrelin showed significant negative correlation with advancing age of patients (p<0.01), blood pressure (p<0.01), FBG (P<0.01), HbA1c (p<0.01), insulin resistance (p<0.01), TG (p<0.01), LDL (p<0.05), osteoprotegerin (p<0.01) and visfatin (p<0.01). However, apositive significant correlation was found between ghrelin and HDL (p<0.05), (table 6).

Table (1): Demographic data of the studied groups

Parameters	Healthy Control (n=29)	T2DM (n=39)	T2DM with MetS (n=48)
Age (years)	41.1± 8.3	45.8± 6.2	49.9 ±6.4
Male (%) **Female (%)**	12 (41.4%) 17 (58.6%)	19 (48.7%) 20 (51.2%)	25 (52.1%) 23 (47.9%)
BMI (kg/m^2)	30.7± 6.6	30.1± 4.8	35.9± 4.1 $^{A*, B*}$
Systolic Blood Pressure (mmHg)	107.3± 11.9	139.5± 12 ^{A*}	150.8± 11.1 $^{A*, B*}$
Diastolic Blood Pressure (mmHg)	73.0± 8.4	83.5± 11 ^{A*}	95.6± 5.1 $^{A*, B*}$
Waist to hip ratio	0.9± 0.18	0.87±0.15	1.2± 0.21 $^{A*, B*}$

Data is presented as % frequency, mean ± standard deviation, *p< 0.05 is significant, ^{A}: Significance versus Healthy control. ^{B}: Significance versus type 2 diabetes. (Post hoc tests were used after ANOVA).

BMI: Body Mass Index.

Table (2): Glycemic status and lipid profile parameters (Mean± SD) in various studied groups.

Parameters	Healthy Control (n=29)	T2DM (n=39)	T2DM with MetS (n=48)
FBG (mg/dl)	83.9 ± 7.1	176.9± 59.6 ^{A*}	222.8 ±55.8 $^{A*, B*}$
HbA1c (%)	5.3 ± 0.62	7.0± ١.١ ^{A*}	8.8± ١.٦ $^{A*, B*}$
Insulin (µlU/mL)	3.3 ± 1.3	18.4± 9.9 ^{A*}	52.6± ١٧.٧ $^{A*, B*}$
HOMA-IR	0.69± 0.34	9.75± 6.4 ^{A*}	33.6± 16.1 $^{A*, B*}$
Total Cholesterol (mg/dl)	152.0± 38.6	184.6± 42.1 ^{A*}	213.8 ± 33.6 $^{A*, B*}$
TG (mg/dl)	76.2 ± 38.9	138.1 ± 41.7 ^{A*}	243.2± 61.3 $^{A*, B*}$
HDL-C (mg/dl)	58.5 ± 17.1	50.7 ± 11.9	33.1 ± 2.5 $^{A*, B*}$
LDL-C (mg/dl)	88.1 ± 37.8	105.3 ± 41.3	122.2 ± 38.4 ^{A*}
Atherogenic Index	0.39 ± 0.08	0.42 ± 0.16	0.71 ± 0.2 $^{A*, B*}$

Data is presented as mean ± standard deviation *p< 0.05 is significant, ^{A}: Significance versus Healthy control. ^{B}: Significance versus type 2 diabetes. (Post hoc tests were used after ANOVA).

FBG: Fasting Blood Glucose, HbA1c: Glycosylated hemoglobin, HOMA-IR: insulin resistance, TG: Triglycerides, HDL-C: High density Lipoprotein-cholesterol, LDL-C: Low density Lipoprotein-cholesterol.

Table (3): Levels of osteoprotegerin, visfatin and ghrelin in diabetic patients with and without metabolic syndrome compared to control group

Parameters	Healthy Control (n=29)	T2DM (n=39)	T2DM with MetS (n=48)
Osteoprotegerin (ng/mL)			
Mean± SD	0.9± 0.19	1.22± 0.47	1.53± 0.6
Median	0.9	1.17	1.4
mean rank	28.3	47.1	55.86
Statistics	……..	P: 0.00 ^{A*}	P:0.00 ^{A*}
			P:0.025 ^{B*}

Visfatin(ng/mL) **Mean± SD** **Median** **mean rank** **Statistics**	**18.4± 6.0** **18.0** **24.0** **……**	**28.2± 15.1** **24.0** **39.9** **P: 0.048** [A*]	**58.9± 29.9** **54.0** **71.28** **P:0.00** [A*] **P:0.00** [B*]
Ghrelin (pg/ mL) **Mean± SD** **Median** **mean rank** **Statistics**	**108.7± 34.5** **110** **67.9** **……**	**31.7± 6.3** **32.2** **31.5** **P: 0.01** [A*]	**30.8± 6.8** **30.7** **29.0** **P:0.00**[A*] **P:0.85**[B]

[A]: Significance versus Healthy control. [B]: Significance versus type 2 diabetes (Mann-Whitney non parametric test is used to compare mean ranks between groups; *p<0.05 is significant).

Table (4): Clinical Characteristics and Levels (Mean Rank) of osteoprotegerin, visfatin and ghrelin of the Study Patients

Parameters	Osteoprotegerin (ng/mL)	Visfatin (ng/mL)	Ghrelin (pg/ mL)
Sex			
Males	**46.56**	**44.83**	**35.7**
Females	**42.7**	**44.21**	**46.26**
Statistics	**X^2:0.5**	**X^2:0.013**	**X^2: 3.9**
	P:0.46	**P:0.91**	**P: 0.046***
Body mass index			
Non-obesity	**27.26**	**27.87**	**33.14**
Obesity	**38.14**	**38.14**	**30.39**
Statistics	**X^2:5.4**	**X^2:4.49**	**X^2: 0.35**
	P: 0.02*	**P: 0.034***	**P: 0.55**

Diabetes mellitus			
No	**28.38**	**24.0**	**67.96**
yes	**50.55**	**52.19**	**30.55**
Statistics	**X^2: 13.17**	**X^2:21.3**	**X^2:42.1**
	P: 0.00*	**P:0.00***	**P:0.00***
Metabolic Syndrome			
No	**39.1**	**32.95**	**53.07**
yes	**53.07**	**66.56**	**39.12**
Statistics	**X^2:5.79**	**X^2:33.6**	**X^2: 8.0**
	P:0.016*	**P:0.00***	**P: 0.005**

Statistically significant ($p < 0.05$) by Mann-Whitney test.

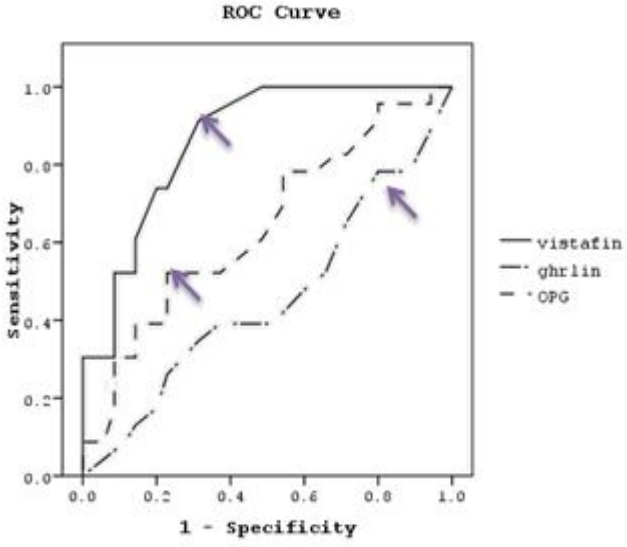

Fig. 1: Receiver-operating characteristic (ROC) curve of osteoprotegerin (OPG) visfatin and ghrelin serum levels for the prediction of MetS among patients with T2DM.

Table (5): Serum osteoprotegerin, visfatin and ghrelin to diagnosis metabolic syndrome among diabetic patients

Variable	Sensitivity (%)	Specificity (%)	AUC	P
Osteoprotegerin cutoff=1.06ng/mL	**76**	**41**	**0.61**	**0.14**
Visfatin cutoff=32.27ng/mL	**92**	**69.2**	**0.88**	**0.01***
Ghrelin cutoff = 33.65pg/mL	**39.1**	**62.9**	**0.46**	**0.57**

AUC: Area under curve, *p<0.05 is significant.

Table (6): Pearson correlation coefficient (r) between osteoprotegerin, visfatin and ghrelin to Clinical Variables in the diabetic Patients

Parameters	Osteoprotegerin (ng/mL)	Visfatin (ng/mL)	Ghrelin (pg/mL)
Age (years)	r: 0.283* P: 0.01	r: 0.247* P: 0.025	r: -0. 44* P< 0.001
Systolic blood pressure(mmHg)	r: 0.325* P: 0.005	r: 0.396* P: 0.001	r:- 0. 65* P< 0.001
Diastolic blood pressure(mmHg)	r: 0.312* P: 0.008	r: 0.378* P: 0.001	r:- 0.47* P< 0.001
BMI	r: 0.335* P: 0.006	r: 0.416* P: 0.001	r: 0.196 P: 0.12
Waist to Hip ratio	r: 0.33 P: 0.029	r: 0.48* P: 0.001	r: 0.13 P: 0.38
FBG (mg/dl)	r: 0.31* P: 0.001	r: 0.413* P< 0.001	r: -0.60* P< 0.001
HbA1c (%)	r: 0.348* P: 0.005	r: 0.54* P< 0.001	r: -0.55* P< 0.001
Insulin (µlU/mL)	r: 0.393* P< 0.001	r: 0.805* P< 0.001	r: -0.47* P: 0.00

Insulin resistance	r: 0.425* P< 0.001	r: 0.691* P< 0.001	r:- 0.40* P< 0.001
Total cholesterol (mg/dl)	r: 0.219 P:0.038	r: 0.323* P: 0.002	r: -0.402 P:0.001
TG (mg/dl)	r: 0.331* P< 0.002	r: 0.73* P< 0.001	r:- 0.49* P< 0.001
HDL-C (mg/dl)	r: -0.229* P< 0.032	r: -0.398* P< 0.001	r: 0.25* P: 0.023
LDL-C (mg/dl)	r: -0.02 P: 0.84	r: 0.133 P: 0.217	r:- 0.23 P: 0.034
Atherogenic Index	r: 0.217* P: 0.042	r: 0.559* P< 0.001	r:- 0.219* P: 0.049
ghrelin	r: 0.-348* P: 0.001	r:-0.383* P< 0.001	…….
visfatin	r: 0.317* 0.003	…….	…….

FBG: Fasting Blood Glucose, HbA1c: Glycosylated hemoglobin A1c, HOMA-IR: insulin resistance, TG: Triglycerides, HDL-C: High density Lipoprotein-cholesterol, LDL-C: Low density Lipoprotein-cholesterol.
*p< 0.05 is significant.

Discussion

In our previous researches, we clarified the potential role of oxidized LDL (OX-LDL) and adhesion molecules (VCAM-1, ICAM-1) in type 2 diabetes mellitus patients. [17] We tried in this study todetermine the relation of serum osteoprotegerin and some adipokines as visfatin and ghrelin to glycemic control in T2DM and also to evaluate their roles to pathogenesis of metabolic syndrome among diabetic patients.

We found the serum levels of osteoprotegerin (OPG) were significantly higher in diabetic patients than in healthy group and in diabetic patients with MetS than those without MetS. Similarly, other researchers found that OPG was correlated to HbA_{1c} and fasting plasma glucose in diabetes [2, 18].Xiang et al. [19] reported that osteoprotegerin levels were related to inflammatory markers such as C- reactive protein in type 2 diabetic patients. This may explain elevated serum concentrations of OPG in obesity and metabolic syndrome with a subclinical inflammation. [20, 21] On the other hand, other authors did not find any statistical difference of OPG between subjects with or without metabolic syndrome. [3]

As an active endocrine organ, adipose tissue communicates with other central and peripheral organs by synthesis and secretion of a host of molecules that we generally refer to as adipokines. [20] In the present study, serum levels of visfatin showed a significant elevation in diabetic patients compared to the healthy participants. Moreover visfatin was significantly higher in T2DM with MetS than those without MetS. Several reports confirmed our finding by showing increased circulatingvisfatin levels inT2DM patients, [7, 22] however, other studies did not support this result consistently. [23-25] Regardless of this discrepancy, serum visfatin was reported to be elevated in patients with overweight/obesity problems and in subjects with metabolic syndrome. [26, 27] In contrast to our data, Chen et al [7] showed that visfatin is not related to most anthropometric parameters and metabolic syndrome related parameters. While, Deng and Scherer [20] reported that levels of some adipokines correlate with specific metabolic states and had the potential to impact directly upon the metabolic homeostasis of the system. Looking for the underlying mechanisms of visfatin's regulation strongly support the pro-inflammatory function of visfatin, [4, 24] that leads to the development of metabolic syndrome. [27]

The strong positive significant correlations between osteoprotegerin and visfatin with

advancing age of patients, obesity, fasting blood glucose, HbA1c and insulin resistance and with each other, confirm their role in pathogenesis of T2DM. Meanwhile, their positive correlation with diastolic blood pressure, TG and cholesterol and negative correlation with HDL-cholesterol indicates that they could be implicated in changes leading to MetS. This is confirmed by their significant higher levels among diabetic patients with MetS compared to other diabetic patients. These data are in concordance to many investigators [28, 29] who found that visfatin was positively associated with insulin resistance. However, Xiang et al [19] did not find any relation between plasma osteoprotegerin and BMI, total cholesterol, triglycerides, LDL-cholesterol, or HDL-cholesterol. In contrast, OPG was positively correlated with insulin resistance in an obese population [30] and in men with T2DM. [31]

Regarding ghrelin in this study, it was significantly lower in diabetic patients compared to healthy individuals. Moreover, it was negatively correlated to advancing age of patients, FBG, HbA1c, insulin resistance. Despite the significant positive correlation that found between ghrelin and HDL and the significant negative correlation with blood pressure, TG, LDL, osteoprotegerin and visfatin, ghrelin showed no significance difference between two T2DM subgroups. Other observational studies have reported that low ghrelin levels are associated with insulin resistance, type II diabetes and to the number of components of MetS. [7, 32, 33] This is mostly explained by higher BMI in subjects with lower ghrelin levels because adiposity influences all other features of the metabolic syndrome. [34] The best possible explanation for the high ghrelin level in diabetic patients group supposes a competition between the factors that increase ghrelin level (insulin deficiency) and factors that decrease ghrelin level (obesity, glucose, and hyperinsulinemia). The high percentage of insulin resistance in diabetic patients may support this explanation. [32]

Gender difference showed no significant data among our investigated parameter, except for ghrelin that was significantly higher in females. That was in accordance with Farajallah et al [33] who reported that higher ghrelin level was negatively associated with measures of obesity, HbA1c, and blood pressure in females and positively associated with increased insulin resistance in Arab males.

A receiver operating characteristic (ROC) curve was utilized in this study to identify a cut-off value of studied biomarkers that best predict the presence of MetS among T2DM patients. The best cut-off point of osteoprotegerin was 1.06 ng/mL witha sensitivity of 76%, a specificity of 41% and without a significant prediction value. Forvisfatin the best cut-off point was 32.27 ng/mL with a sensitivity of 92%, a specificity of 69.2% and a significant prediction value. For ghrelin the best cut-off point was 33.65 pg/mLwith a sensitivity of 39.1% and a specificity of 62.9% that was not significant in prediction MetS. Despite the presence of simpler and established biomarkers and indices for detecting MetS, we wanted to test the predictive ability of the currently studied biomarkers for detecting MetS among T2DM and their possible role in pathogenesis process. The combined sensitivity and specificity together with area under ROC curve ellicted visfatin to be superior among other investigated parameters for the detection of MetS. Since visceral obesity is known as the central core of metabolic syndrome, [34, 35] the significant positive correlation between visfatin with BMI and abdominal obesity detected in this study may be the possible explanations for its significance in diagnosing metabolic syndrome. In support, Kim et al [36] using a multiple logistic regression analysis revealed that, visfatin was found to be an independent factor that associated with metabolic syndrome after an adjustment for confounding variables including age, BMI, and HOMA-IR. Others suggested that visfatin may be promising for predicting obesity, diabetes status, insulin resistance, metabolic syndrome and cardiovascular disease. [37]

Conclusion

Our findings indicate that serum osteoprotegerin and visfatin are elevated in T2DM with decrease in ghrelin levels that may support the hypothesis that these parameters are associated with impaired glucose metabolism. Moreover, the high sensitivity and specificity of visfatin at the calculated cut-off point to predict MetS, suggests its patho

physiological role which might be useful in therapeutic intervention.

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