# Serum visfatin in type 2 diabetes mellitus

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**Received** 6 November 2012
**Accepted** 27 November 2012

**Egyptian Journal of Internal Medicine**
2013, 25:27–32

**Introduction**
Obesity is commonly associated with insulin resistance and hyperinsulinemia and is the most important risk factor for type 2 diabetes. Visfatin is an adipokine that exerts insulin-mimetic effects that stimulate muscle and adipocyte glucose transport and inhibit hepatocyte glucose production.

**Purpose**
The aim of this study was to assess levels of visfatin and its relationship to obesity and insulin resistance in type 2 diabetes mellitus.

**Patients and methods**
This study included 40 patients with type 2 diabetes as the patient group: 20 of them were obese (BMI $\geq$ 30) and 20 were not (BMI $<$ 25). Forty apparently healthy individuals matched for age and sex were included as the control group: 20 of them were obese (BMI $\geq$ 30) and the other 20 were not (BMI $<$ 25). All patients and controls underwent history taking, physical examination including determination of BMI, and the following laboratory investigations: determination of levels of fasting blood glucose, 2 h postprandial blood glucose, serum cholesterol, triglycerides, fasting insulin, and fasting visfatin; kidney and liver function tests and calculation of homeostasis model of assessment-insulin resistance (HOMA-IR) were also performed. Neither the patients nor controls suffered from any chronic disease other than diabetes.

**Results**
The results of this study revealed a highly significant increase in the fasting serum insulin level, HOMA-IR, and fasting serum visfatin level among diabetic patients ($26.10 \pm 6.04$ μIU/ml, $12.18 \pm 5.24$, $36.70 \pm 6.86$ ng/ml, respectively) when compared with controls ($12.10 \pm 3.45$ μIU/ml, $2.42 \pm 0.79$, $13.63 \pm 3.98$ ng/ml, respectively; $P < 0.01$). Fasting insulin levels, HOMA-IR, and visfatin levels were significantly higher in obese diabetic patients ($31.13 \pm 4.34$ μIU/ml, $14.71 \pm 6.22$, $42.36 \pm 4.11$ ng/ml, respectively) than in obese controls ($14.31 \pm 3.11$ μIU/ml, $2.89 \pm 0.77$, $16.72 \pm 3.16$ ng/ml, respectively; $P < 0.01$). Visfatin levels were higher in nonobese diabetic patients than in nonobese controls. Moreover, visfatin levels were higher in obese diabetic patients ($31.04 \pm 3.49$ ng/ml) than in nonobese diabetic patients ($10.54 \pm 1.53$ ng/ml; $P < 0.01$). The present study revealed a highly significant positive correlation between levels of visfatin and fasting insulin in both obese and nonobese diabetic patients. Although there was a significant positive correlation between visfatin levels and HOMA-IR, there was no significant correlation between visfatin levels and BMI in obese diabetic patients.

**Conclusion**
Visfatin levels are increased in patients with type 2 diabetes regardless the degree of adiposity.

**Keywords:**
insulin resistance, obesity, type 2 diabetes mellitus, visfatin

Egypt J Intern Med 25:27–32

1110-7782

## Introduction

The prevalence of obesity is increasing in most societies, even among young adults and children. Obesity is the single most important risk factor for the development of type 2 diabetes mellitus (type 2 DM) [1].

Adipose tissue produces several proteins (adipokines) such as leptin, adiponectin, and resistin that modulate insulin sensitivity and play an important role in the pathogenesis of insulin resistance and diabetes [2]. However, the mechanisms by which fat tissue induces insulin resistance and the role of adipokines in the pathogenesis of type 2 DM have not been established [3].

Visfatin is an adipokine (protein) expressed mainly by the visceral adipose tissues (hence the name); it has insulin-like action and its plasma concentration is closely related to the amount of visceral fats. Visfatin can be detected in visceral adipose tissues and to a much lower extent in subcutaneous adipose tissues [4]. It is also

highly expressed in human liver, muscles, and macrophages [5].

Visfatin is produced by many tissues and cells, including adipose tissue, white blood cells, macrophages, and colonic and mammary epithelial cells; it is also present synovial fluid and plasma [6].

Visfatin is involved in regulation of the cell cycle [6]. It is secreted by activated lymphocytes and is upregulated in neutrophils and monocytes after exposure to inflammatory stimuli; it also promotes the growth of B-cell precursors and is therefore known as pre-B-cell colony-enhancing factor [7].

Visfatin induces the production of cytokines such as interleukin-6 and tumor necrosis factor-α in human leukocytes. Its plasma level increases during chronic inflammatory conditions such as psoriasis, arthritis, and obesity [6].

Visfatin is a nuclear as well as a cytoplasmic protein. It increases the lifespan of aging human vascular smooth muscle cells [8].

Visfatin enhances neovascularization in the chorioallantoic membrane and stimulates migration and invasion of the endothelial cells and tube development in the human umbilical vein [9].

Visfatin exhibits insulin-mimetic properties, causing a glucose lowering effect. It increases glucose uptake and lipogenesis and decreases glucose production by hepatocytes. Visfatin improves insulin sensitivity, resulting in decreased glucose and insulin levels. The insulin sensitizing effect of visfatin appears to be additive to the effect of insulin. Visfatin and insulin do not compete to bind to the insulin receptors, indicating that the two proteins are recognized by different regions of the receptors [10]. Visfatin may be used as promising predictor for obesity, insulin resistance, diabetes status, metabolic syndrome, and cardiovascular disease [11]. Elevation of visfatin levels in type 2 DM is independent of obesity and insulin resistance and is mainly determined by levels of fasting glucose and triglycerides [12].

The aim of this study was to assess levels of visfatin and its relationship with obesity and insulin resistance in type 2 DM.

## Patients and methods

This study included 40 patients with type 2 DM [diagnosed on the basis of a fasting blood glucose (FBG) level of $\geq 126$ mg/dl and 2 h postprandial blood glucose (PBG) level of $>140$ mg/dl]. Twenty of them were obese diabetic patients (BMI $\geq 30$ kg/m$^2$); 17 women and three men with ages ranging from 35 to 70 years, with a mean age of $55.60 \pm 9.27$ years. The other 20 patients were nonobese (BMI $< 25$ kg/m$^2$). Forty healthy individuals were also included as controls; 20 of them were obese: 12 women and eight men matched for age, and the other 20 were nonobese. All patients were selected from the Department of Internal Medicine, Al-Azhar University and Matareya Teaching Hospitals.

All patients and controls were subjected to medical history taking, complete physical examination including determination of BMI (the weight in kilograms divided by the square of the height in meters), and laboratory investigations: determination of levels of FBG, 2 h PBG, serum cholesterol and triglycerides; liver function tests and kidney function tests were also performed.

About 3 ml of fasting (12 h) venous blood was withdrawn from each study participant and left to clot. Thereafter, the serum was separated by centrifugation and the FBG level was immediately determined using a Hitachi auto analyzer (Hitachi 736; Hitachi, Japan). The remaining serum was stored at $-20^\circ$C for determination of the following parameters: serum levels of cholesterol, triglyceride, insulin, and visfatin.

Two hours after a meal, 2 ml of blood was withdrawn from each study participant and aliquoted into a tube containing fluoride for determination of PBG.

Determination of FBG, PBG, serum cholesterol, and serum triglyceride levels was carried out on a Hitachi auto analyzer (Hitachi 736; Hitachi)using colorimetric techniques. The level of fasting serum insulin was measured using a radioimmunoassay kit supplied by BioSource Europe (Nivelles, Belgium) [13].

Insulin sensitivity was assessed using a homeostasis model of assessment-insulin resistance (HOMA-IR), which uses the formula [(fasting insulin (μIU/ml) × FBG (mg/dl)]/405 [13].

The level of serum visfatin was determined using a competitive enzyme immunoassay kit (Phoenix Pharmaceutical Inc., California, USA) [14].

Statistical data were analyzed using Microsoft Excel 2003 and SPPS version 10 (SPSS Inc., Chicago, Illinois, USA). Quantitative data were described in terms of range of minimum and maximum and mean and standard deviation. Comparative statistical analysis was carried out using Student's-*t* test and the Spearman correlation coefficient.

A *P*-value of more than 0.05 was considered nonsignificant.

A *P*-value of less than 0.05 was considered significant.

A *P*-value of less than 0.01 was considered highly significant.

## Results

There was an insignificant increase in the BMI and a highly significant increase in the levels of FBG, PBG, cholesterol, triglycerides, fasting insulin and visfatin as well as in HOMA-IR of all diabetic patients compared with all nondiabetic controls (Table 1).

There was a highly significant increase in the levels of FBG, PBG, cholesterol, triglycerides, fasting insulin, and visfatin and in HOMA-IR in obese diabetic patients compared with obese controls (Table 2).

There was an insignificant increase in the BMI and levels of cholesterol and triglycerides, whereas there was a highly significant increase in the levels of FBG, PBG, fasting insulin, and visfatin as well as in HOMA-IR in nonobese diabetic patients compared with nonobese controls (Table 3).

There was an insignificant increase in the levels of FBG and PBG, whereas there was a highly significant increase in the BMI, serum levels of cholesterol, triglycerides, fasting insulin, and visfatin, and in HOMA-IR of obese diabetic patients compared with nonobese diabetic patients (Table 4).

In the obese diabetic patients (Table 5), there was no significant correlation between serum levels of visfatin and BMI (Fig. 1), levels of FBG, PBG, serum cholesterol, and triglycerides, whereas there was a significant positive correlation between serum levels of visfatin and fasting insulin levels ($P<0.01$; Fig. 2) and HOMA-IR ($P<0.05$; Fig. 3).

In the nonobese diabetic patients, there was insignificant correlation between serum visfatin levels and BMI (Fig. 4), HOMA-IR (Fig. 5), and serum levels of FBG, PBG, cholesterol, and triglycerides (Table 6), whereas there was a highly significant correlation between levels of visfatin and fasting insulin levels ($P<0.01$; Table 6; Fig. 6).

**Table 1 The studied parameters in all diabetic patients compared with controls**

| Parameters | All diabetic patients (mean ± SD) | All controls (mean ± SD) | *P*-value |
|---|---|---|---|
| BMI (kg/m$^2$) | 29.37 ± 6.88 | 27.29 ± 4.47 | >0.05 |
| FBG (mg/dl) | 186.50 ± 53.97 | 81.33 ± 10.27 | <0.01 |
| PBG (mg/dl) | 247.00 ± 61.96 | 107.33 ± 10.66 | <0.01 |
| Serum cholesterol (mg/dl) | 207.98 ± 52.34 | 168.00 ± 41.09 | <0.01 |
| Serum triglycerides (mg/dl) | 137.85 ± 38.94 | 95.08 ± 24.12 | <0.01 |
| Fasting insulin (μIU/ml) | 26.10 ± 6.04 | 12.10 ± 3.45 | <0.01 |
| HOMA-IR | 12.18 ± 5.24 | 2.42 ± 0.79 | <0.01 |
| Serum visfatin (ng/ml) | 36.70 ± 6.86 | 13.63 ± 3.98 | <0.01 |

HOMA-IR, homeostasis model of assessment-insulin resistance; FBG, fasting blood glucose; PBG, postprandial blood glucose.

**Table 2 The studied parameters in obese diabetic patients compared with obese controls**

| Parameters | Obese diabetic patients (mean ± SD) | Obese controls (mean ± SD) | *P*-value |
|---|---|---|---|
| FBG (mg/dl) | 188.40 ± 68.62 | 81.80 ± 11.35 | <0.01 |
| PBG (mg/dl) | 245.55 ± 76.43 | 110.50 ± 10.62 | <0.01 |
| Serum cholesterol (mg/dl) | 229.00 ± 53.40 | 169.05 ± 41.45 | <0.01 |
| Serum triglycerides (mg/dl) | 159.50 ± 31.24 | 92.30 ± 18.51 | <0.01 |
| Fasting insulin (μIU/ml) | 31.13 ± 4.34 | 14.31 ± 3.11 | <0.01 |
| HOMA-IR | 14.71 ± 6.22 | 2.89 ± 0.77 | <0.01 |
| Serum visfatin (ng/ml) | 42.36 ± 4.11 | 16.72 ± 3.16 | <0.01 |

HOMA-IR, homeostasis model of assessment-insulin resistance; FBG, fasting blood glucose; PBG, postprandial blood glucose.

**Table 3 The studied parameters in nonobese diabetic patients compared with nonobese controls**

| Parameters | Nonobese diabetic patients (mean ± SD) | Nonobese controls (mean ± SD) | *P*-value |
|---|---|---|---|
| BMI (kg/m$^2$) | 23.27 ± 1.01 | 23.24 ± 1.21 | >0.05 |
| FBG (mg/dl) | 184.60 ± 35.52 | 80.85 ± 9.35 | <0.01 |
| PBG (mg/dl) | 239.45 ± 43,81 | 104.00 ± 9.90 | <0.01 |
| Serum cholesterol (mg/dl) | 186.45 ± 42.91 | 166.95 ± 41.77 | >0.05 |
| Serum triglycerides (mg/dl) | 116.20 ± 33.92 | 97.85 ± 28.91 | >0.05 |
| Fasting insulin (μIU/ml) | 21.08 ± 1.69 | 9.90 ± 2.14 | <0.01 |
| HOMA-IR | 9.65 ± 2.09 | 1.96 ± 0.49 | <0.01 |
| Serum visfatin (ng/ml) | 31.04 ± 3.49 | 10.54 ± 1.53 | <0.01 |

HOMA-IR, homeostasis model of assessment-insulin resistance; FBG, fasting blood glucose; PBG, postprandial blood glucose.

**Table 4 The studied parameters in obese diabetic patients compared with nonobese diabetic patients**

| Parameters | Obese diabetic patients (mean ± SD) | Nonobese diabetic patients (mean ± SD) | *P*-value |
|---|---|---|---|
| BMI (kg/m$^2$) | 35.79 ± 3.72 | 23.27 ± 1.01 | <0.01 |
| FBG (mg/dl) | 188.40 ± 68.62 | 184.60 ± 35.52 | >0.05 |
| PBG (mg/dl) | 245.55 ± 76.43 | 239.45 ± 43,81 | >0.05 |
| Serum cholesterol (mg/dl) | 229.00 ± 53.40 | 186.45 ± 42.91 | <0.01 |
| Serum triglycerides (mg/dl) | 159.50 ± 31.24 | 116.20 ± 33.92 | <0.01 |
| Fasting insulin (μIU/ml) | 31.13 ± 4.34 | 21.08 ± 1.69 | <0.01 |
| HOMA-IR | 14.71 ± 6.22 | 9.65 ± 2.09 | <0.01 |
| Serum visfatin (ng/ml) | 42.36 ± 4.11 | 31.04 ± 3.49 | <0.01 |

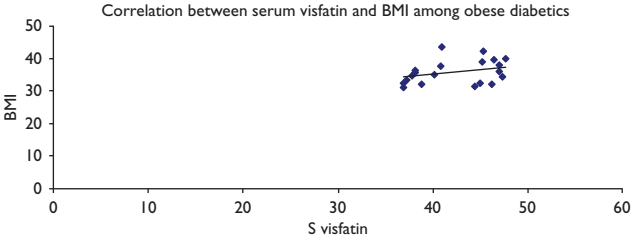
HOMA-IR, homeostasis model of assessment-insulin resistance; FBG, fasting blood glucose; PBG, postprandial blood glucose.

**Table 5 Correlation between the studied parameters and visfatin levels in obese diabetic patients**

| Parameters | Serum visfatin | | |
|---|---|---|---|
| | *R* | *P* | Significance |
| BMI (kg/m$^2$) | 0.336 | >0.05 | Not significant |
| FBG (mg/dl) | 0.260 | >0.05 | Not significant |
| PBG (mg/dl) | 0.227 | >0.05 | Not significant |
| Serum cholesterol (mg/dl) | 0.008 | >0.05 | Not significant |
| Serum triglycerides (mg/dl) | 0.367 | >0.05 | Not significant |
| Fasting insulin (μIU/ml) | 0.981 | <0.01 | Highly significant |
| HOMA-IR | 0.516 | <0.05 | Significant |

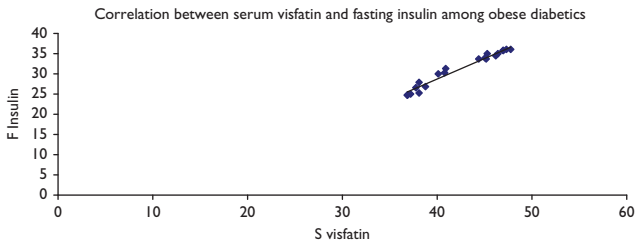
HOMA-IR, homeostasis model of assessment-insulin resistance; FBG, fasting blood glucose; PBG, postprandial blood glucose.

**Figure 1**



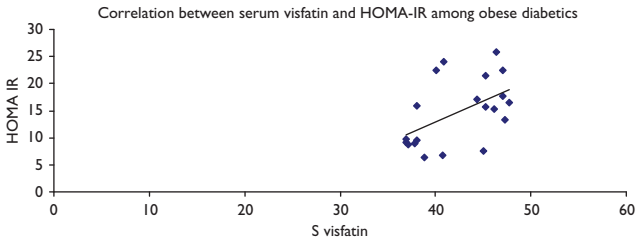

Nonsignificant positive correlation between visfatin levels and BMI among obese diabetic patients.

**Figure 2**



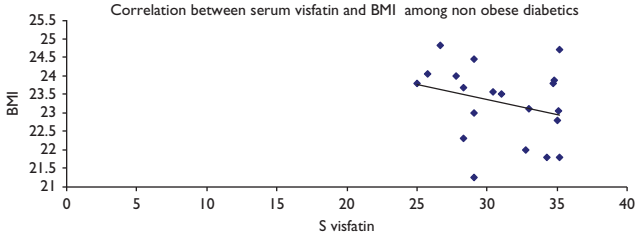

Highly significant positive correlation between levels of visfatin and fasting insulin among obese diabetic patients.

**Figure 3**




Significant positive correlation between visfatin level and HOMA-IR among obese diabetic patients. HOMA-IR, homeostasis model of assessment-insulin resistance.

**Figure 4**



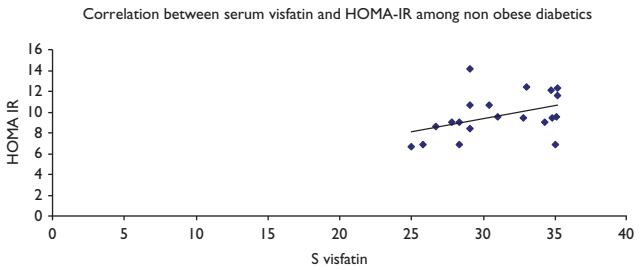

Nonsignificant positive correlation between visfatin levels and BMI among nonobese diabetic patients.

Visfatin levels (Fig. 7), fasting insulin levels (Fig. 8), and HOMA-IR (Fig. 9) were high in the obese and nonobese diabetic patients, and they were higher in the obese controls than in nonobese controls.

## Discussion

In the present study, fasting insulin levels and HOMA-IR showed a highly significant increase in all diabetic patients compared with healthy controls. This result is similar to those of the studies carried out by Chen *et al.* [3] and Varma *et al.* [15], who reported that the precise etiology of insulin resistance is unknown; however, many studies have suggested that lipotoxicity or ectopic fat accumulation may be responsible for insulin resistance.

**Figure 5**



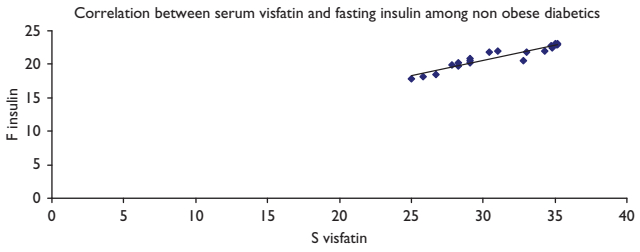

Nonsignificant positive correlation between visfatin levels and HOMA-IR among nonobese diabetic patients. HOMA-IR, homeostasis model of assessment-insulin resistance.

**Table 6 Correlation between the studied parameters and visfatin levels in nonobese diabetic patients**

| | Serum visfatin | | |
|---|---|---|---|
| Parameters | *R* | *P* | Significance |
| BMI(kg/m$^2$) | −0.284 | >0.05 | Not significant |
| FBG (mg/dl) | 0.120 | >0.05 | Not significant |
| PBG(mg/dl) | −0.170 | >0.05 | Not significant |
| Serum cholesterol(mg/dl) | −0.031 | >0.05 | Not significant |
| Serum triglycerides(mg/dl) | 0.097 | >0.05 | Not significant |
| Fasting insulin(μIU/ml) | 0.942 | <0.01 | Highly significant |
| HOMA-IR | 0.423 | >0.05 | Not significant |

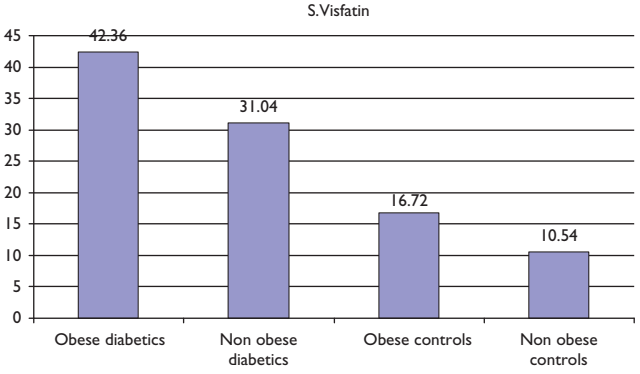
HOMA-IR, homeostasis model of assessment-insulin resistance; FBG, fasting blood glucose; PBG, postprandial blood glucose.

**Figure 6**



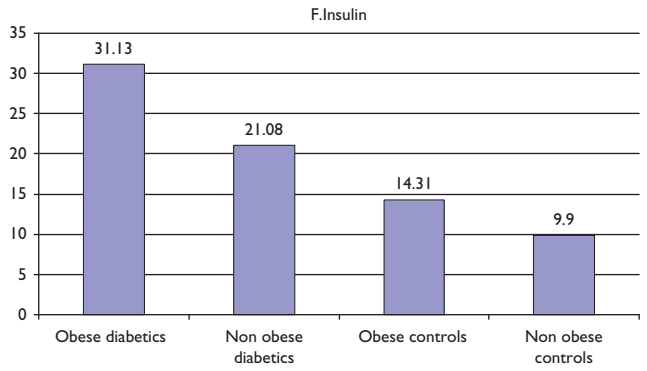

Highly significant positive correlation between levels of visfatin and fasting insulin among nonobese diabetic patients.

**Figure 7**



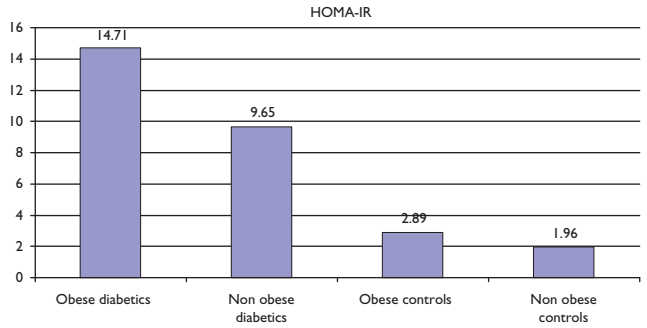

Visfatin levels in the studied groups.

**Figure 8**




Fasting insulin levels in the studied groups.

**Figure 9**




Homeostasis model of assessment-insulin resistance in the studied groups.

In the present study, fasting insulin levels were higher in obese diabetic patients than in obese controls. This is in agreement with the results of Zahorska *et al.* [16].

In the present study, serum visfatin levels showed a highly significant increase in all diabetic patients when compared with healthy controls. Similar findings were reported by Hammarsted *et al.* [17], Sandeep *et al.* [18], Abdullah and Barakat [19], Rosa *et al*. [20], and Shelbaya *et al.* [21].

According to our results, visfatin levels were higher in obese diabetic patients than in obese controls. This is in agreement with the results of Miao *et al.* [3], who suggested that elevated visfatin levels in patients with type 2 DM may be because of an impairment in visfatin signaling in target tissues or dysregulation of its biosynthesis in response to hyperglycemia, hyperinsulinemia, or adipocytokines in the condition of diabetes. Moreover, serum visfatin levels were higher in obese diabetic patients than in nonobese diabetic patients. This is in agreement with the study carried out by Adghate [6], who reported that there may be a direct relationship between levels of visfatin and obesity.

In the present study, visfatin levels were also significantly higher in nonobese diabetic patients than in nonobese controls. This is similar to the results of Shelbaya *et al.* [21]. This may be explained by increased insulin resistance and hyperinsulinemia in diabetic patients as a compensatory mechanism because visfatin has insulin like action on the insulin receptors but on site different than that on which the insulin acts [21].

In our study, the obese diabetic patients showed a nonsignificant positive correlation between visfatin levels and BMI. This is in agreement with the results of Chen *et al.* [3] Pangono *et al.* [22], and Dogru *et al.* [23], who found no correlation between visfatin levels and BMI. Moreover, Abdullah and Barakat [19] found that visfatin levels were increased in obese patients with type 2 DM, regardless of BMI. These findings may indicate that elevation of visfatin levels in patients with type 2 DM is independent of obesity and insulin resistance, which is in agreement with the results of Esteghamati *et al*. [12].

In contrast to the study carried out by Berndt *et al.* [24], Curat *et al.* [5], Gursoy *et al.* [25], and Salah *et al.* [21] found a significant positive correlation between visfatin levels and BMI.

In our results, obese diabetic patients showed a significant positive correlation between serum visfatin levels and HOMA-IR; this is in agreement with the results of Sandeep *et al.* [18], who found a strong correlation between serum visfatin levels and HOMA-IR.

The mechanism by which hyperglycemia induces increase in circulating visfatin levels is not clear, but it may be due to oxidative stress, increased apoptosis, or destruction of B lymphocytes [6].

Finding a significant positive correlation between serum levels of visfatin and fasting insulin in diabetic patients (obese and nonobese) and HOMA-IR in obese diabetic patients and between a higher level of serum visfatin and fasting serum insulin level and HOMA-IR in nonobese diabetic patients compared with nonobese healthy controls makes us suggest that elevation in levels of circulating visfatin is a compensatory mechanism for the decreased insulin sensitivity in patients with type 2 DM. This is in agreement with the results of Rosa *et al.* [20], who suggested that increased visfatin levels may be a part of the pathophysiology of diabetes. Visfatin exhibits insulin-mimetic properties, such as increasing glucose uptake and lipogenesis and decreasing hepatic glucose production. It also improves insulin sensitivity, resulting in decreased glucose and insulin levels. The insulin sensitizing effect of visfatin appears to be additive to the effect of insulin [10].

In contrast, Takebayashi *et al.* [26] found no correlation between diabetes and levels of visfatin.

Visfatin may be used as promising predictor for obesity, insulin resistance, diabetes status, metabolic syndrome, and cardiovascular disease [11].

## Conclusion

Visfatin levels are increased in patients with type 2 DM regardless the degree of adiposity as a compensatory

mechanism for the increased insulin resistance and insufficient insulin action that may represent a new target in the treatment of type 2 diabetes in the future.

## Acknowledgements

### Conflicts of interest

There are no conflicts of interest.

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