Serum visfatin level in prediabetics and its relation to left ventricular function

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Introduction
Visfatin is a molecule of clinical relevance, released mainly from visceral fat (hence it named as such) and could be a promising biomarker with diagnostic and prognostic significance in metabolic syndrome. Very little is known about visfatin and its relation with prediabetes.
Objective
The present study was conducted to demonstrate the relationship between serum visfatin level and prediabetes and its relation to left ventricular function.
Patients and methods
We studied 60 prediabetic patients recently diagnosed according to ADA criteria 2014 and classified into two groups according to the BMI. They were compared with 30 healthy matched controls. All groups underwent complete history taking, general examination, laboratory investigations (including homeostasis model assessment-insulin resistance and serum visfatin level), and two-dimensional transthoracic echo Doppler study at baseline and 8 months thereafter only for the patient groups.
Results
This study showed that there is a positive correlation between serum visfatin level and prediabetes and left ventricular function.
Conclusion
Serum visfatin is an early and strong predictor of prediabetes and left ventricular dysfunction.

Keywords:
left ventricular dysfunction, prediabetes, visfatin

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Introduction

Visfatin history

Visfatin was first identified as pre-B cell colony-enhancing factor (PBEF), to be secreted by human peripheral blood active lymphocytes, and it acts as a cytokine with immune regulatory action. PBEF was identified by Fukuhara *et al*., as visfatin, a novel adipokine secreted by fat cells. Analysis of the amino acid sequence of visfatin revealed it to be identical with PBEF and nicotinamide phosphoribosyltransferase; hence, three different biological names, with three different functions for a single protein (the names are used interchangeably) [1].

Visfatin is a 52-kDa protein that is active as a dimer, with each monomer containing 491 amino acids, with 19 β-strands and 13 α helices, and is organized into two structural domains [2]. Dimerization is essential for the catalytic activity of the enzyme. The gene is located on the long arm of chromosome 7 between 7q22.1 and 7q31.33 [3].

Research on visceral adipose tissue has confirmed that it is not simply a reservoir for excess nutrients but an active and dynamic organ capable of secreting a variety of highly active and huge number of harmful systemic bioactive mediators of proatherogenic and pro-inflammatory adipocytokines and chemokines (adipose tissue-derived factors), for example, leptin, adiponectin, resistin, transforming growth factor β1, tumor necrosis factor alpha, monocyte chemotactic protein 1, plasminogen activator inhibitor, interleukin-6, complement factors, e-selectin, endothelin, and fibroblast growth factor, as well as free fatty acids and visfatin, which may influence through endocrine, paracrine, and vasocrine effects. These substances are released not just by adipocytes but also by the connective tissue matrix and immune cells of obese white adipose tissue [4].

Bone marrow, macrophages, liver, and muscle have been reported to be the tissues with the highest expression levels of this protein, followed by brain,

kidney, spleen, testis, and lung [5]. High circulating visfatin levels have been observed in rheumatoid arthritis [6], acute lung injury [7], inflammatory bowel disease [5], clinical sepsis [3], and severe generalized psoriasis [8].

Visfatin is upregulated in neutrophils and monocytes after exposure to inflammatory stimuli. Visfatin synthesis is up-regulated by several factors, including inflammation, hyperglycemia, hypoxia, glucocorticoids, tumor necrosis factor alpha, IL 6, and GH and downregulated by insulin, somatostatin, and statins [9].

Visfatin levels with obesity and type II diabetes mellitus

Many studies show that more the BMI (obesity) more the visfatin levels, and levels decrease after weight loss. Visfatin levels have been shown to be increased in children with more BMI [10]. Visfatin levels were shown to be increased in females with visceral obesity [1]. This is in agreement with the study carried out by Adeghate [9], who reported that there may be a direct relationship between levels of visfatin and obesity.

Insulin-mimetic properties of visfatin

The binding affinity of visfatin to insulin receptor (IR) was found to be similar compared with that of insulin [1]. Visfatin exhibits insulin-mimetic properties, such as increasing glucose uptake and lipogenesis and decreasing hepatic glucose production. It has been shown that vistatin helps in the regulation of glucose homeostasis, as it is necessary for β cell function [11].

Insulin-sensitizing effect of visfatin

The insulin-sensitizing effect of visfatin appears to be additive to the effect of insulin [1]. On the contrary, Chen *et al*. [12] suggest that visfatin causes IR phosphorylation, activation of the downstream signaling molecules, and stimulatory effects on peroxisome proliferator-activated receptor gamma and adiponectin gene expression, resulting in decreased glucose and insulin levels [1].

Thus, circulating visfatin is increased in type II diabetes mellitus (DM) owing to the following:

(1) Progressive pancreatic β-cell deterioration, suggesting that the increase in the level of visfatin is a compensatory mechanism that develops aimed at ameliorating the functional consequences of endogenous insulin deficiency in patients with longer standing type II DM [13].
(2) A compensatory mechanism for the decreased insulin sensitivity [14].
(3) Oxidative stress [9].
(4) Impairment in visfatin signaling in target tissues or dysregulation of its biosynthesis in response to hyperglycemia, hyperinsulinemia, or adipocytokines in the condition of diabetes [12].

Serum visfatin level was significantly increased in the obese patients and in the diabetics with the highest rise in the obese diabetics [12]. Moreover, Abd Rabo *et al*. [15] and Shelbaya *et al*. [15,16] showed that visfatin levels were higher in obese diabetic patients than in nonobese diabetic patients and obese controls (visfatin levels were also significantly higher in nonobese diabetic patients than in nonobese controls), suggesting that serum visfatin level has a link between obesity and type II DM.

Visfatin seems to play an important role in the pathogenesis of IR, diabetes, dyslipidemia, inflammation, and atherosclerosis. Interestingly, visfatin levels and not adiponectin or resistin levels were associated with type II DM [12]. Visfatin may be used as a promising predictor for obesity, IR, diabetes status, metabolic syndrome, and cardiovascular disease [17].

Visfatin and left ventricular functions

It is well established that the association between visceral fat and IR is related to increased cardiovascular risk. Visfatin has multiple functions in the cardiovascular system. It stimulates growth of vascular smooth muscle cells and endothelial angiogenesis. Visfatin can also directly affect vascular contractility [18].

Torres *et al*. [19] concluded that there is a strong correlation between left ventricular mass (LVM) and epicardial adipose tissue (EAT) thickness. Several mechanisms might explain this relationship. EAT augmentation is associated with higher intramyocardial lipid content (myocardial steatosis), which might induce both adverse effects of (a) local (structural) remodeling, with cardiac morphological changes including cardiomyopathy, and (b) systemic effect of lipotoxicity [20]. EAT could induce systemic IR, which in turn can promote left ventricular hypertrophy via direct mitogenic action of insulin postreceptor pathway in myocardial cells [21].

Patients and methods

Patients

Sixty adult patients (28 men and 32 women) recently diagnosed as having prediabetes were enrolled in the study and classified into two groups:

(1) Group I: 30 patients with BMI more than or equal to 30 kg/m^2; 17 patients were female and 13 patients were males (aged between 17 and 55 years).
(2) Group II: 30 patients with BMI 25–30 kg/m^2; 15 patients were female and 15 patients were males (aged between 16 and 52 years).

A third group (group III) included 30 normal healthy participants as control with normal BMI, where 15 were female and 15 were males (aged between 18 and 50 years) for comparison.

All patients enrolled in the study were from outpatient clinic of Bab-Elsharyia University Hospital, Cairo, Egypt. The study started from the beginning of August 2018 to the end of March 2019.

Exclusion criteria

One or more of the following were the exclusion criteria:

(1) A well-established diagnosis of type II DM, with one or more of the following: fasting blood sugar (FBS) (≥125 mg/dl), 2-h postprandial blood surge (≥200 mg/dl), and/or glycosylated hemoglobin (HbA1c) (≥6.5%).
(2) Systemic hypertension (≥130/85 mmHg) or on antihypertensive therapy.
(3) Drug that would be able to affect metabolic variables (e.g. glucocorticoids, anticonvulsants, hypolipidemic agents, and oral contraceptives), smoking, or modest to severe alcoholic.
(4) Current or past history of evidenced endocrinopathies.
(5) Chronic cardiovascular (valvular heart diseases, congenital heart disease, cardiomyopathy, etc.), respiratory, renal, hepatic (with negative HCV-Ab and HBsAg), bone, or blood affection.
(6) Urolithiasis or thromboembolic events.
(7) Chronic infection or other major diseases.

Methods

All participants were subjected to written informed consent before enrollment. Approval of the ethical committee of the faculty was obtained. The study was arranged to be a cross-sectional comparative study.

All participants were subjected to a detailed history and physical examination. A brief medical history was taken to gather demographic data, such as age, sex, and associated personal and family background. Weight and height were measured with the participants wearing only their underwear. BMI was calculated as weight (kg) divided by height (m^2). Using the IDF criteria, WC (cm) was measured at its narrowest part of the body midway between the underside of the lowest rib and the iliac crests with patients standing. Blood pressure was taken after at least 10 min of rest, using the auscultation method through a standard mercury sphygmomanometer. Three measurements were performed, and the average of the blood pressure measurements was calculated.

(1) Prediabetes were diagnosed according to ADA 2014 criteria for diagnosis of prediabetes, which were formed from one or more of the following:
   (a) FBS (100–125 mg/dl).
   (b) 2-h postprandial blood surge (140–200 mg/dl).
   (c) HbA1c (5.7–6.4%).
(2) Laboratory investigations were done at the baseline and after 8 months of lifestyle modification mentioned in Diabetes Prevention Programs: FBS, 2-h postprandial blood sugar (2hPPBS), HbA1c, serum visfatin, homeostasis model assessment-insulin resistance (HOMA-IR), and lipid profiles after a 12-h overnight fast [total cholesterol TC), triglycerides (TG), low-density lipoprotein cholesterol (LDLc), and high-density lipoprotein cholesterol (HDLc)].
(3) For all participants, after an overnight fasting, 10 ml of peripheral venous blood was collected in clean vacutainer tube, and serum was separated and divided into two Eppendorf tubes: one tube for measurement of routine tests and the other tube was stored at −70°C for further measurement of serum insulin and visfatin levels.
(4) Over-night fasting insulin was assessed using enzyme-linked immunosorbent assay (ELISA) kit by Thermo Fisher Scientific (Thermofischer, Waltham, Massachusetts, USA). The human insulin solid-phase sandwich ELISA is designed to measure the amount of the target bound between a matched antibody pair. A target-specific antibody has been precoated in the wells of the supplied microplate. Samples, standards, or controls are then added into these wells and bind to the immobilized (capture) antibody. The sandwich is formed by the addition of the second (detector) antibody; a substrate solution is added that reacts with the enzyme–antibody–target complex to produce measurable signal. The intensity of this signal is directly proportional to the concentration of target present in the original specimen.
(5) IR was evaluated through HOMA according to the method of Matthews *et al*. [22] (1 and 2) (HOMA-IR=insulin (μU/ml)×fasting glucose (mmol/l)/22.5).

(6) Serum visfatin levels were assessed using RayBio Visfatin Enzyme Immunoassay Kit, RayBiotech (RayBiotech, Inc., 3607 Parkway Lane, Suite 200, GA 30092, USA). Human Visfatin ELISA kit is an in-vitro ELISA for the quantitative measurement of human visfatin in serum (human visfatin concentration is low in normal serum/plasma, and may not be detectable in this assay), plasma, and cell culture supernatants. This assay employs an antibody specific for human visfatin coated on a 96-well plate. Standards and samples are pipetted into the wells, and visfatin present in a sample is bound to the wells by the immobilized antibody. The wells are washed and biotinylated anti-human visfatin antibody is added. After washing away unbound biotinylated antibody, HRP-conjugated streptavidin is pipetted to the wells. The wells are again washed, and a TMB substrate solution is added to the wells and color develops in proportion to the amount of visfatin bound. The stop solution changes the color from blue to yellow, and the intensity of the color is measured.

(7) Echocardiographic measurement was done by a single-experienced cardiologist, who performed a focused two-dimensional and Doppler transthoracic echocardiography. Standard M-mode echocardiograms of the LV liners internal dimension measurement were recorded from the parasternal long-axis view carefully perpendicular to the LV long axis and measured at the level of mitral valve leaflet tips guided by two-dimensional image. All echocardiographic readings were made and interpreted according to the American Society of Echocardiography guidelines [3].

(a) LVM (g) was calculated using the anatomically validated formula of Devereux *et al*. [23] LV mass was calculated in grams using the following formula:

$$0.8 \times \left(1.04\left[(\mathrm{LVID} + \mathrm{IVSd} + \mathrm{LVPWd})^3 - \mathrm{LVID}^3\right]\right) + 0.6$$

where (a) LVID=left ventricular internal dimension.

(b) IVSd=interventricular septal thickness.

(c) LVPWT=left ventricle posterior wall thickness.

(d) LVM was normalized for height to the 2.7 power (LVM/H 2.7) (6) [5].

(e) The left ventricular mass index (LVMI) (g/$m^{2.7}$) was calculated by the formula, LVM/(height)$^{2.7}$. It was corrected for body height in meters to the allometric power of 2.7 that linearizes the relation between LVM and height and identifies the effect of excess body weight to calculate LVMI. Based on values of LVMI and relative wall thickness (RWT) calculated from the equation, RWT=2×LVPWd/LVEDD, RWT >0.42 was classified as concentric LV hypertrophy.

(f) The left ventricle diastolic function was measured using trans-mitral flow and tissue Doppler echocardiography.

(1) (M) E=peak velocity of early diastolic filling flow across mitral valve.

(2) (M) A=peak velocity of late diastolic filling flow across mitral valve.

(3) LV dimension at end diastole (mm) (LVEDD).

(g) The left ventricle ejection fraction (LVEF) was calculated over five consecutive beats (7) [4] by subtracting the end systolic volume from the end diastolic volume, and dividing the result by the end diastolic volume (×100).

(h) Epicardial fat thickness (EFT) was measured using a standard two-dimensional echocardiography, which was performed in all participants using a 2.5–3.5-MHz transducer. Definition of EFT was considered as the echo-free space (hypoechoic space) between the visceral layer of the pericardium and the outer wall of the myocardium anterior (vertical) to the right ventricular free at end-systole in three cardiac cycles' image in the left lateral decubitus position, as average from the parasternal long axis and short axis views, which allows for the most accurate measurement according to previous methods. Because EFT measurement might be inconsistent with measurement locations, two settings of echocardiographic at different times (not >1 week) were examined in some of the studied cases. If measurements by the two-setting differed by more than 10% for any of the variables, the patient was not included; if the difference was less than 10%, the measurements were averaged.

(8) The pervious radiological parameters were assayed at the baselinefor all participants and 8 months thereafter only for the cases.

(9) All participants in the case groups were followed regularly throughout the study. A number of cases discontinued the follow-up and therefore

were excluded, with a final 60 cases completing the study.

(10) During the follow up period (8 months), the life lifestyle modification mentioned in Diabetes Prevention Programs were applied to our patients with particular attention to the following:
   (a) Optimizations of the lifestyle and behavioral state as follows:
      (1) Before any details, the patient is informed that weight reduction and physical activity give high possibility for reversal (remission) of the DM to a normal state, and at the same time, higher BMIs increase the risk of cardiovascular disease and all-cause mortality (positive energy to encouraged for weight loss).
      (2) Inform the patient about his BW target (written in his follow up chart) and how to reach to it (subcaloric requirement and physical activity). Proper assessment and planning of the amount and type of food stuff was done according to the patient's BW, physical activity, family resources, health status, lifestyle level, and preferences i.e. family-centered approach lick ADA-2019.
      (3) Patients were permitted overconsumption of a reduced-calorie diet (vegetables and fruit) particularly at beginning to overcome the hunger.
      (4) All instruction regarding the lifestyle educated were provided by the internist himself/herself and not by assistant and through verbal (mainly), written and visual/audio manner, to ensure adherance to lifestyle regimen throughout the study.
      (5) As a multidisciplinary DM team including a physician, DM nurse educator, registered dietitian and psychologist or social worker, is not yet available in our country, all of the aforementioned tasks are carried out by the physician (internist), in addition to blood glucose control and self management education.
      (6) Physical activity was done for all patients according to his sex and social and educational state (which ranged from regular walking 'not <30 mint/d' to strenuous physical activity) at least 4 days/week, all through the follow-up period.

(7) Psychological assessment and support was provided by the internist. However, the most valuable antidepressant for that group of patients is a good patient/physician relationship through continuous and regular monthly follow-up visits.

(8) All the aforementioned described instructions are ongoing processes.

(9) Regular and mandatory follow-up every 1–2 months was done for the following:
   (a) Assessment of FBS, 2hPPPG, and BW with documentation in the patient follow-up chart.
   (b) Rapid reviewing about the lifestyle modifications.
   (c) Excellent follow-up visit adherence.

(10) However, patients who missed more than 2 successive monthly visits or three separate visits were excluded.

Statistical analysis

Recorded data were analyzed using the statistical package for social sciences, version 20.0 (SPSS Inc., Chicago, Illinois, USA). Quantitative data were expressed as mean±SD. Qualitative data were expressed as frequency and percentage.

The following tests were done:

(1) Independent-samples *t* test of significance was used when comparing between two means.
(2) Paired sample *t* test of significance was used when comparing between related sample.
(3) A one-way analysis of variance when comparing between more than two means.
(4) Post-hoc test: least significant difference was used for multiple comparisons between different variables.
(5) Pearson's correlation coefficient (*r*) test was used to assess the degree of association between two sets of variables
(6) The confidence interval was set to 95%, and the margin of error accepted was set to 5%. So, the *P* value was considered significant as the following:
   (a) *P* value less than or equal to 0.05 was considered significant.
   (b) *P* value less than or equal to 0.001 was considered as highly significant.
   (c) *P* value more than 0.05 was considered insignificant.

Results

The Results situated directly after the patient and methods and before the discussion.

Discussion

Very little is known about visfatin and its relation with prediabetes, cardiovascular risks, and the component of

metabolic syndrome. Many researches in the past decade reported that serum visfatin level was significantly increased in the obese patients and in the diabetics, with the highest rise in the obese diabetics, suggesting that serum visfatin level has a link between obesity and type II DM [12].

Our results revealed a high statistically significant difference between the parameters of metabolic syndrome (FBS, 2hPPBS, HbA1c, TG, TC, HDLc, LDLc, BMI, fasting insulin level, and HOMA-IR score), visfatin serum level, EAT, and parameters of left ventricular function (LVM, LVMI, M (E), M (A), LVEDD, and LVEF) in all groups at the baseline ($P<0.001$; Table 1).

Regarding the comparison between all parameters at baseline and after intervention in group I, there is a high statistically significant difference between the parameters of metabolic syndrome (including 2hPPBS, HbA1c, TG, TC, HDLc, LDLc, fasting insulin level, and HOMA-IR score), serum visfatin level, EAT, and parameters of left ventricular function (LVM, LVMI, M (E), M (A), LVEDD, and LVEF) ($P<0.001$; Table 2), and a significant difference regarding FBS and BMI ($P<0.05$; Table 2).

The comparison between all parameters at baseline and after intervention in group II revealed high statistically significant difference regarding all parameters ($P<0.001$; Table 3).

The comparison between groups I and II after intervention revealed high statistically significant differences regarding TG, TC, LDLc, serum visfatin level, EAT, and most parameters of left ventricular function (LVM, LVMI, M (E), LVEDD, and LVEF) in both groups ($P<0.001$; Table 4) and significant difference regarding HDL, BMI and M (A) ($P<0.05$; Table 4), whereas there is no statistically significant difference regarding FBS, 2hPPBS, HbA1c, fasting insulin level, and HOMA-IR score ($P>0.05$; Table 4).

In concordance with our results, Choi *et al.* [24] showed that the level of plasma visfatin was higher in obese participants as compared with that in nonobese participants. They also showed that plasma visfatin can be lowered after body weight reduction by an exercise program, and this result also held for nonobese patients [24].

Similarly, Araki *et al.* [25] reported that the plasma visfatin level was higher in the obese patients than in the controls.

These results are alike the results of Manco *et al.* [26], which revealed a decrease in circulating visfatin found in morbidly obese who lost more than 20% of their BMI, and also, increased plasma visfatin concentrations in morbidly obese patients are reduced after gastric banding.

Of the same view, García-Fuentes *et al.* [27] reported that the mean serum visfatin level of patients with metabolic syndrome was significantly higher than the mean level of patients without metabolic syndrome ($P<0.01$). As the number of components of metabolic syndrome increased, the concentration of serum visfatin also increased.

In quite agreement with our results, Abd Rabo *et al.* [15] showed high significant increase of serum visfatin levels in all diabetic patients when compared with healthy controls. Similar findings were reported by Sandeep *et al.* [28] and Shelbaya *et al.* [16].

On the contrary, other studies reported that obese patients had significantly lower visfatin levels compared with patients with normal body weight [29].

The present study revealed a positive correlation between serum visfatin level and 2hPPBS, HbA1c, TG, TC, LDLc, fasting insulin level, HOMA-IR score, EAT, and parameters of left ventricular function (LVM, LVMI, and LVEDD) and a negative correlation with HDL, M (E), M (A), and LVEF at baseline in group I, whereas no correlation between serum visfatin level and FBS and BMI (Table 5).

The correlation study done after intervention in group I also revealed a positive correlation regarding TG, TC, LDLc, EAT, and parameters of left ventricular function (LVM, LVMI, LVEDD) and negative correlation with the remaining parameters of left ventricular function: M (E), M (A), and LVEF. No correlation was found between visfatin level and FBS, 2hPPBS, HbA1c, fasting insulin level, HOMA-IR score, HDL, and BMI (Table 5).

The correlation study done at baseline in group II revealed a positive correlation with TG, TC, LDLc, EAT, and parameters of left ventricular function (LVM, LVMI, and LVEDD) and negative correlation with HDL and LVEF, whereas no correlation with the remaining parameters. The same results were obtained after intervention except for HDL, which shows no correlation with visfatin after intervention (Table 6).

Table 1 Comparison among the three groups at baseline

Parameters	Group I (*N*=30)	Group II (*N*=30)	Group III (*N*=30)	ANOVA	*P* value
FBS (mg/dl)					
Mean±SD	106.50±10.86	107.63±10.31	86.00±7.57ab	47.406	<0.001*
Range	87–125a	87–123a	74–100a		
2hPPBS (mg/dl)					
Mean±SD	160.20±16.27	158.03±12.38	127.00±9.20ab	61.760	<0.001**
Range	137–196a	139–191a	102–139a		
HbA1c%					
Mean±SD	5.93±0.32	5.88±0.30	4.87±0.32ab	110.664	<0.001**
Range	5.3–6.4a	5.3–6.4a	4.3–5.5a		
Fasting insulin level (μIU/ml)					
Mean±SD	7.77±2.69	6.78±2.19	3.94±0.81ab	28.151	<0.001**
Range	4.2–15.6a	3.8–11.3a	2.7–5.5a		
HOMA-IR score					
Mean±SD	2.09±0.90	1.84±0.73	0.84±0.21ab	28.088	<0.001**
Range	1.04–4.74a	0.82–3.43a	0.51–1.32a		
TG (mg/dl)					
Mean±SD	185.97±40.24	149.13±19.94a	106.40±21.59ab	57.474	<0.001**
Range	139–328a	118–209a	69–144a		
TC (mg/dl)					
Mean±SD	226.63±39.22	183.83±20.94a	152.93±19.19ab	52.574	<0.001**
Range	175–314a	149–228a	112–198a		
HDLc (mg/dl)					
Mean±SD	45.90±9.59	53.43±4.55a	59.03±4.92ab	28.590	<0.001**
Range	31–64a	45–61a	51–71a		
LDLc (mg/dl)					
Mean±SD	143.50±41.45	100.57±23.67a	72.62±19.38ab	43.236	<0.001**
Range	84–232a	59–149a	44.6–111.8ab		
Visfatin (ng/ml)					
Mean±SD	22.43±4.66	14.93±3.75a	6.90±1.40ab	143.767	<0.001**
Range	13.1–31.4a	8.4–24.1a	3.9–9.5a		
BMI (kg/m^2)					
Mean±SD	31.88±1.34	27.70±1.10a	20.48±1.39ab	604.696	<0.001**
Range	30.4–35.4a	25.5–29.5a	18.2–24.1a		
EAT (mm)					
Mean±SD	6.63±0.90	5.26±0.68a	3.22±0.72ab	147.504	<0.001**
Range	4.8–8.6a	3.9–6.5a	1.8–4.9a		
LVM (g)					
Mean±SD	168.51±15.79	113.64±13.98a	97.24±16.04ab	178.561	<0.001**
Range	138.4–194.3	87.9–142.3a	73.5–132.5a		
LVMI (g/m$^{2.7}$)					
Mean±SD	61.07±11.18	51.58±5.90a	50.48±5.61a	15.964	<0.001**
Range	45.9–86.5a	41.3–63.1a	40.3–62.3a		
M (E) (cm/s)					
Mean±SD	73.57±9.44	81.37±7.80a	83.33±7.70a	11.475	<0.001**
Range	57–91a	69–93a	66–93a		
M (A) (cm/s)					
Mean±SD	60.30±11.92	66.77±8.53a	69.40±5.24a	8.149	<0.001**
Range	38–76a	50–80a	54–76a		
LVEDD (mm)					
Mean±SD	54.07±5.66	48.30±3.64a	46.80±3.90a	21.889	<0.001**
Range	45–64a	41–56a	41–55a		
LVEF%					
Mean±SD	62.93±7.39	70.03±6.49a	75.03±6.23ab	24.529	<0.001**
Range	51–81a	59–82a	59–84a		

2hPPBS, 2-h postprandial blood sugar; ANOVA, analysis of variance; EAT, epicardial adipose tissue; *F*, one-way analysis of variance; FBS, fasting blood sugar; HbA1c, glycosylated hemoglobin; HDLc, high-density lipoprotein cholesterol; HOMA-IR, homeostasis model assessment-insulin resistance; LDLc, low-density lipoprotein cholesterol; LVEDD, left ventricular dimension at end diastole; LVEF, left ventricle ejection fraction; LVM, left ventricular mass; TC, total cholesterol; TG, triglycerides. *Post hoc*: a, significant difference with group I; b, significant difference with group II. *P* value more than 0.05, NS; **P* value less than 0.05, significant; ***P* value less than 0.001 highly significant.

Table 2 Comparison between data of group I at baseline and after intervention

Parameters	Group I		Paired sample *t* test		
	Before	After	Mean difference	*t* test	*P* value
FBS (mg/dl)	106.50±10.86	103.50±8.97	−3.00	3.021	0.005*
2hPPBS (mg/dl)	160.20±16.27	151.00±12.81	−9.20	6.675	<0.001**
HbA1c%	5.93±0.32	5.73±0.29	−0.20	6.700	<0.001**
Fasting insulin level (μIU/ml)	7.77±2.69	6.49±2.14	−1.28	6.221	<0.001**
HOMA-IR score	2.09±0.90	1.68±0.66	−0.41	5.627	<0.001**
TG (mg/dl)	185.97±40.24	159.83±25.71	−26.14	7.868	<0.001**
TC (mg/dl)	226.63±39.22	204.30±28.59	−22.33	7.740	<0.001**
HDLc (mg/dl)	45.90±9.59	53.63±8.02	7.73	−11.797	<0.001**
LDLc (mg/dl)	143.50±41.45	118.67±31.61	−24.83	8.507	<0.001**
Visfatin (ng/ml)	22.43±4.66	16.48±4.50	−5.95	21.909	<0.001**
BMI (kg/m^2)	31.88±1.34	28.90±5.09	−2.98	3.255	0.003*
EAT (mm)	6.63±0.90	5.74±0.84	−0.89	25.904	<0.001**
LVM (g)	168.51±15.79	160.24±15.91	−8.27	13.490	<0.001**
LVMI (g/m$^{2.7}$)	61.07±11.18	58.85±10.67	−2.22	4.740	<0.001**
M (E) (cm/s)	73.57±9.44	75.33±9.51	1.76	−6.168	<0.001**
M (A) (cm/s)	60.30±11.92	62.17±11.65	1.87	−7.263	<0.001**
LVEDD (mm)	54.07±5.66	52.03±5.87	−2.04	10.142	<0.001**
LVEF%	62.93±7.39	65.00±7.23	2.07	−11.154	<0.001**

2hPPBS, 2-h postprandial blood sugar; EAT, epicardial adipose tissue; FBS, fasting blood sugar; HbA1c, glycosylated hemoglobin; HDLc, high-density lipoprotein cholesterol; HOMA-IR, homeostasis model assessment-insulin resistance; LDLc, low-density lipoprotein cholesterol; LVEDD, left ventricular dimension at end diastole; LVEF, left ventricle ejection fraction; LVM, left ventricular mass; *t*, paired sample *t* test; TC, total cholesterol; TG, triglycerides. *P* value more than 0.05, NS; **P* value less than 0.05, significant; ***P* value less than 0.001 highly significant.

Table 3 Comparison between data of group II at baseline and after intervention

Parameters	Group II		Paired sample *t* test		
	Before	After	Mean difference	*t* test	*P* value
FBS (mg/dl)	107.63±10.31	102.93±7.40	−4.7	5.379	<0.001**
2hPPBS (mg/dl)	158.03±12.38	150.13±9.69	−7.9	8.008	<0.001**
HbA1c%	5.88±0.30	5.73±0.24	−0.15	7.389	<0.001**
Fasting insulin level (μIU/ml)	6.78±2.19	6.09±1.63	−0.69	5.037	<0.001**
HOMA-IR score	1.84±0.73	1.57±0.53	−0.27	5.597	<0.001**
TG (mg/dl)	149.13±19.94a	135.47±15.86	−13.66	7.954	<0.001**
TC (mg/dl)	183.83±20.94a	173.10±17.77	−10.73	6.576	<0.001**
HDLc (mg/dl)	53.43±4.55a	59.47±5.46	6.04	−15.550	<0.001**
LDLc (mg/dl)	100.57±23.67a	86.53±21.05	−14.04	7.863	<0.001**
Visfatin (ng/ml)	14.93±3.75a	11.08±3.14	−3.85	22.787	<0.001**
BMI (kg/m^2)	27.70±1.10a	25.89±0.95	−1.81	22.079	<0.001**
EAT (mm)	5.26±0.68a	4.52±0.65	−0.74	23.790	<0.001**
LVM (g)	113.64±13.98a	106.93±12.55	−6.71	8.681	<0.001**
LVMI (g/m$^{2.7}$)	51.58±5.90a	50.28±5.38	−1.3	5.112	<0.001**
M (E) (cm/s)	81.37±7.80a	83.37±6.88	2	−6.361	<0.001**
M (A) (cm/s)	66.77±8.53a	69.20±8.06	2.43	−9.825	<0.001**
LVEDD (mm)	48.30±3.64a	46.40±3.83	−1.9	12.318	<0.001**
LVEF%	70.03±6.49a	72.03±6.42	2	−9.832	<0.001**

2hPPBS, 2-h postprandial blood sugar; EAT, epicardial adipose tissue; FBS, fasting blood sugar; HbA1c, glycosylated hemoglobin; HDLc, high-density lipoprotein cholesterol; HOMA-IR, homeostasis model assessment-insulin resistance; LDLc, low-density lipoprotein cholesterol; LVEDD, left ventricular dimension at end diastole; LVEF, left ventricle ejection fraction; LVM, left ventricular mass; *t*, paired sample *t* test; TC, total cholesterol; TG, triglycerides. *P* value more than 0.05, NS; **P* value less than 0.05, significant; ***P* value less than 0.001 highly significant.

From these results, there is an obvious strong positive correlation between serum visfatin level and EAT in group I and II both at baseline and after intervention, whereas there is no correlation with BMI, denoting that visfatin plasma level mainly originated from visceral than other body fat.

These finding are supported by Berndt *et al*. [30], who reported that differences in visfatin mRNA

Table 4 Comparison between groups I and II after intervention

Parameters	Group I (*N*=30)	Group II (*N*=30)	*t* test	*P* value
FBS (mg/dl)				
Mean±SD	103.50±8.97	102.93±7.40	0.071	0.790
Range	90–124a	90–119a		
2hPPBS (mg/dl)				
Mean±SD	151.00±12.81	150.13±9.69	0.087	0.769
Range	128–183a	139-–179a		
HbA1c%				
Mean±SD	5.73±0.29	5.73±0.24	0.000	1.000
Range	5.2–6.2a	5.2–6.2a		
Fasting insulin level (μIU/ml)				
Mean±SD	6.49±2.14	6.09±1.63	0.653	0.422
Range	3.5–10.9a	3.7–10.3a		
HOMA-IR score				
Mean±SD	1.68±0.66	1.57±0.53	0.541	0.465
Range	0.86–3.34a	0.92–3.03a		
TG (mg/dl)				
Mean±SD	159.83±25.71	135.47±15.86	19.524	<0.001**
Range	119–243a	99–168a		
TC (mg/dl)				
Mean±SD	204.30±28.59	173.10±17.77	25.772	<0.001**
Range	167–279a	138–201a		
HDLc (mg/dl)				
Mean±SD	53.63±8.02	59.47±5.46	10.842	0.002*
Range	42–71a	51–71a		
LDLc (mg/dl)				
Mean±SD	118.67±31.61	86.53±21.05	21.480	<0.001**
Range	78–196a	44–123a		
Visfatin (ng/ml)				
Mean±SD	16.48±4.50	11.08±3.14	29.045	<0.001**
Range	8.4–24.3a	5.9–19.8a		
BMI (kg/m^2)				
Mean±SD	28.90±5.09	25.89±0.95	10.131	0.002*
Range	3.1–33.1a	23.9–27.5a		
EAT (mm)				
Mean±SD	5.74±0.84	4.52±0.65	38.973	<0.001**
Range	4.2–7.3a	3.1–5.7a		
LVM (g)				
Mean±SD	160.24±15.91	106.93±12.55	207.689	<0.001**
Range	128.7–182.9a	85.4–131.2a		
LVMI (g/m$^{2.7}$)				
Mean±SD	58.85±10.67	50.28±5.38	15.398	<0.001**
Range	41.3–80.6a	41.5–61.2a		
M (E) (cm/s)				
Mean±SD	75.33±9.51	83.37±6.88	14.059	<0.001**
Range	59–92a	70–93a		
M (A) (cm/s)				
Mean±SD	62.17±11.65	69.20±8.06	7.399	0.009*
Range	40–77a	53–84a		
LVEDD (mm)				
Mean±SD	52.03±5.87	46.40±3.83	19.386	<0.001**
Range	43–62a	40–55a		
LVEF%				
Mean±SD	65.00±7.23	72.03±6.42	15.875	<0.001**
Range	54–83a	61–84a		

2hPPBS, 2-h postprandial blood sugar; EAT, epicardial adipose tissue; FBS, fasting blood sugar; HbA1c, glycosylated hemoglobin; HDLc, high-density lipoprotein cholesterol; HOMA-IR, homeostasis model assessment-insulin resistance; LDLc, low-density lipoprotein cholesterol; LVEDD, left ventricular dimension at end diastole; LVEF, left ventricle ejection fraction; LVM, left ventricular mass; *t*, independent sample *t* test; TC, total cholesterol; TG, triglycerides. *P* value more than 0.05, NS; **P* value less than 0.05, significant; ***P* value less than 0.001 highly significant.

Table 5 Correlation between visfatin and other parameters in group I before and after intervention, using Pearson correlation coefficient

Parameters	Visfatin (ng/ml) before		Visfatin (ng/ml) after	
	r	*P* value	*r*	*P* value
FBS (mg/dl)	0.350	0.058	0.351	0.057
2hPPBS (mg/dl)	0.504	0.005*	0.356	0.053
HbA1c%	0.454	0.012*	0.281	0.133
Fasting insulin level (μIU/ml)	0.420	0.021*	0.303	0.104
HOMA-IR score	0.434	0.017*	0.353	0.056
TG (mg/dl)	0.692	<0.001**	0.574	<0.001**
TC (mg/dl)	0.546	0.002*	0.409	0.025*
HDLc (mg/dl)	–0.478	0.007*	–0.323	0.082
LDLc (mg/dl)	0.491	0.006*	0.357	0.048*
BMI (kg/m^2)	–0.117	0.537	–0.207	0.272
EAT (mm)	0.899	<0.001**	0.878	<0.001**
LVM (g)	0.715	<0.001**	0.682	<0.001**
LVMI (g/m$^{2.7}$)	0.411	0.024*	0.424	0.019*
M (E) (cm/s)	–0.687	<0.001**	–0.679	<0.001**
M (A) (cm/s)	–0.699	<0.001**	–0.746	<0.001**
LVEDD (mm)	0.720	<0.001**	0.728	<0.001**
LVEF%	–0.681	<0.001**	–0.680	<0.001**

2hPPBS, 2-h postprandial blood sugar; EAT, epicardial adipose tissue; FBS, fasting blood sugar; HbA1c, glycosylated hemoglobin; HDLc, high-density lipoprotein cholesterol; HOMA-IR, homeostasis model assessment-insulin resistance; LDLc, low-density lipoprotein cholesterol; LVEDD, left ventricular dimension at end diastole; LVEF, left ventricle ejection fraction; LVM, left ventricular mass; *r*, Pearson correlation coefficient; TC, total cholesterol; TG, triglycerides. *P* value more than 0.05, NS; **P* value less than 0.05, significant; ***P* value less than 0.001 highly significant.

Table 6 Correlation between visfatin and other parameters in group II before and after intervention, using Pearson correlation coefficient

Parameters	Visfatin (ng/ml) before		Visfatin (ng/ml) after	
	r	*P* value	*r*	*P* value
FBS (mg/dl)	0.267	0.154	0.302	0.104
2hPPBS (mg/dl)	0.297	0.110	0.152	0.422
HbA1c%	0.319	0.086	0.175	0.354
Fasting insulin level (μIU/ml)	0.222	0.237	0.166	0.382
HOMA-IR score	0.234	0.214	0.188	0.320
TG (mg/dl)	0.706	<0.001**	0.619	<0.001**
TC (mg/dl)	0.477	0.008*	0.507	0.004*
HDLc (mg/dl)	–0.387	0.034*	–0.314	0.092
LDLc (mg/dl)	0.380	0.038*	0.418	0.021*
BMI (kg/m^2)	0.323	0.082	0.189	0.317
EAT (mm)	0.806	<0.001**	0.746	<0.001**
LVM (g)	0.700	<0.001**	0.635	<0.001**
LVMI (g/m$^{2.7}$)	0.603	<0.001**	0.619	<0.001**
M (E) (cm/s)	–0.097	0.610	–0.104	0.583
M (A) (cm/s)	–0.057	0.764	–0.003	0.987
LVEDD (mm)	0.457	0.011*	0.473	0.008*
LVEF%	–0.635	<0.001**	–0.548	0.002*

2hPPBS, 2-h postprandial blood sugar; EAT, epicardial adipose tissue; FBS, fasting blood sugar; HbA1c, glycosylated hemoglobin; HDLc, high-density lipoprotein cholesterol; HOMA-IR, homeostasis model assessment-insulin resistance; LDLc, low-density lipoprotein cholesterol; LVEDD, left ventricular dimension at end diastole; LVEF, left ventricle ejection fraction; LVM, left ventricular mass; *r*, Pearson correlation coefficient; TC, total cholesterol; TG, triglycerides. *P* value more than 0.05, NS; **P* value less than 0.05, significant; ***P* value less than 0.001 highly significant.

expression between visceral and subcutaneous adipose tissue in humans were also not significant, with high levels of expression in visceral fat cells.

On the contrary, Esteghamati *et al*. [31] concluded that the elevation of visfatin levels in type II DM is independent of obesity and IR and is mainly determined by levels of fasting glucose and TGs.

This is in contrast to the study carried out by Gursoy *et al.* [32] and Shelbaya *et al.* [16], who found a significant positive correlation between visfatin levels and BMI.

Moreover, we notice that serum visfatin level positively correlated with LVM, LVMI, and LVEDD in both groups at baseline and after intervention, and it has a strong negative correlation with LVEF, which denotes a deleterious effect of visfatin on overall left ventricular function. Our results are similar to the result of Erten *et al.* [33], who had concluded that visfatin might have negative effects on left ventricular diastolic function parameters, but unlike our results, they found no effect of visfatin on LVMI.

In agreement with our results, Araki *et al.* [25] reported that the serum visfatin level significantly correlated with TG, insulin, and the HOMA-IR. Moreover, El-Shafey *et al.* [34] found a significant positive correlation between serum visfatin level and both serum insulin and HOMA-IR.

The aforemetioned described results also coincide with the results of García-Fuentes *et al.* [27] who reported that visfatin concentration was positively correlated with fasting glucose level, fasting insulin level, HOMA-IR, TC, and TG level and concluded that plasma visfatin level is a specific marker for visceral fat accumulation and for IR in obese.

Moreover, Abd Rabo *et al.* [15] and Sandeep *et al.* [28] reported that obese diabetic patients showed a significant positive correlation between serum visfatin levels and HOMA-IR.

In contrast, Takebayashi *et al.* [35] found no correlation between diabetes and levels of visfatin.

Conclusion

(1) Serum visfatin is a good indicator for visceral fat more than total body fat.
(2) Visfatin may be used as a promising predictor for IR, metabolic syndrome, and cardiovascular disease risks.
(3) Visfatin has a deleterious effect on LV function.

Recommendations

(1) More studies are needed, with prolonged period of follow-up and on larger number of patients for proper assay of the visfatin level and its prolonged effect on type II DM and ventricular function.
(2) More insight on the effect of visfatin on the other parameters of myocardial structure and function is needed.

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Conflicts of interest
There are no conflicts of interest.

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