Increased Serum Visfatin Levels in Patients with Type2 Diabetic Patients

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Abstract: Background: Obesity is highly associated with insulin resistance and the increased risk of type 2 diabetes and cardiovascular diseases. Visfatin is a cytokine that is highly expressed in visceral fat. It's expression in visceral fat is increased in obese subjects. Visfatin exerts insulin-mimetic effects and was as effective as insulin in reducing hyperglycemia in insulin-deficient diabetic mice. Objective: To study serum visfatin level in patients with type2 diabetes mellitus and to clarify its possible relationship with insulin resistance and glycemic control. **Patients and Methods**: Eighty cases (60 type2 diabetic patients and 20 apparently healthy subjects) were subjected for estimation of visfatin and fasting insulin by ELISA technique together with routine laboratory investigations including fasting blood glucose, cholesterol, triglycerides, HDL-cholesterol, LDL-cholesterol and HbA1C. **Results:** Fasting blood glucose, fasting insulin level, HOMA-IR, HbA_1C and visfatin levels were significantly higher in diabetic than control group. HBA1C, fasting serum glucose and serum visfatin were significantly higher in uncontrolled than controlled diabetic subgroups. Weight, BMI and serum visfatin were significantly higher in overweight diabetic subgroup than normal BMI diabetic subgroup. A positive significant correlation was found between serum visfatin & HbA_1C levels in the diabetic group. Conclusion: The increased serum visfatin concentration may be a compensatory mechanism aimed at ameliorating the functional consequences of insulin deficiency. The increased visfatin concentration may also promote insulin sensitivity by its stimulatory effects on insulin receptors.

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1. Introduction

The term diabetes mellitus describes a metabolic disorder of multiple aetiology characterized by chronic hyperglycemia with disturbances of carbohydrate, fat and protein metabolism resulting from defects in insulin secretion, insulin action, or both. The effects of diabetes mellitus include long term damage, dysfunction and failure of various organs[(1)].

Type 2 is the most common form of diabetes and is characterized by disorders of insulin action and insulin secretion, either of which may be the predominant feature. Both are usually present at the time that this form of diabetes is clinically manifest. By definition, the specific reasons for the development of these abnormalities are not yet known[(2)]. Nevertheless, such patients are at increased risk of developing macrovascular and microvascular complications[(3)].

The majority of patients with this form of diabetes are obese, and obesity itself causes or aggravates insulin resistance[(4)]. Insulin resistance is often found in people with visceral adiposity (i.e. a high degree of fatty tissue underneath the abdominal muscle wall - as distinct from subcutaneous adiposity or fat between the skin and the muscle wall, especially elsewhere on the body, such as hips or thighs), hypertension, hyperglycemia and dyslipidemia involving elevated triglycerides, small dense low-density lipoprotein (sdLDL) particles, and decreased HDL cholesterol levels. With respect to visceral adiposity, a great deal of evidence suggests two strong links with insulin resistance. First, unlike subcutaneous adipose tissue, visceral adipose cells produce significant amounts of proinflammatory cytokines such as tumor necrosis factor-alpha (TNF-α), and Interleukins-1 and -6, etc[(5)]. Additionally, insulin resistance is found in hypertension, hyperlipidemia, and ischemic heart disease, entities commonly found in association with diabetes[(6)], again raising the question as to whether insulin resistance results from different pathogenetic disease processes or is unique to the presence of type 2 diabetes[(7)].

In numerous experimental models, these proinflammatory cytokines profoundly disrupt normal insulin action in fat and muscle cells, and may be a major factor in causing the whole-body insulin resistance observed in patients with visceral adiposity. A great deal of attention into the production of proinflammatory cytokines has focused on the IKK-beta/NF-kappa-B pathway, a protein network that enhances transcription of cytokine genes. Second, visceral adiposity is related to an accumulation of fat in the liver, a condition known as nonalcoholic fatty liver disease (NAFLD). The result of NAFLD is an excessive release of free fatty acids into the blood stream (due to increased lipolysis), and an increase in hepatic glucose production, both of which have the effect of exacerbating peripheral insulin resistance and increasing the likelihood of type 2 diabetes mellitus[(5)].

Insulin resistance is also occasionally found in patients who use insulin. In this case, the production of antibodies against insulin leads to lower-than-expected glucose level reductions after a specific dose of insulin. With the development of human insulin and analogues in the 1980s and the decline in the use of animal insulin (e.g. pork, beef), this type of insulin resistance has become uncommon[8].

Obesity is highly associated with insulin resistance and the increased risk of type 2 diabetes and cardiovascular diseases[9]. The accumulation of adipose tissue in the abdominal visceral depot is especially correlated with insulin resistance[10]. Visfatin, also known as pre-B cell colony-enhancing factor, is a cytokine that is highly expressed in visceral fat and was originally isolated as a secreted factor that synergizes with IL-7 and stem cell factors to promote the growth of B cell precursors[11]. **Fukuhara *et al.*** [12] found that visfatin expression in visceral fat is increased in obese subjects and that plasma concentration of visfatin correlated much more strongly with the amount of visceral fat than that of subcutaneous adipose tissue. Visfatin exerts insulin-mimetic effects that are dose dependent and quantitatively similar to those of insulin in stimulating muscle and adipocyte glucose transport and in inhibiting hepatocyte glucose production. In keeping with its insulin-mimetic effects, visfatin was as effective as insulin in reducing hyperglycemia in insulin-deficient diabetic mice. Visfatin was also found to be bound to and activate insulin receptor, causing receptor phosphorylation and the activation of downstream signaling molecule. However, visfatin and insulin did not compete for binding to the insulin receptor, indicating that the two proteins were recognized by different regions of the receptor[12]. The aim of the present work is to study serum visfatin level in patients with type2 diabetes mellitus and to clarify its possible relationship with insulin resistance and glycemic control.

2. Subjects and Methods:

The study was conducted on 80 subjects aged from 35-60 years; they were divided into two groups; group I *(patient group)* and group II (*control group*). Group I (*patient group*) included sixty type 2 diabetic patients (45 males & 15 females). They were recruited from internal medicine outpatient clinic of Benha University Hospital. This group was further subdivided according to body mass index (BMI), insulin resistance (IR) and glycemic control. Group II *(control group)* included twenty age and sex matched apparently healthy subjects (12 males & 8 females). Exclusion criteria were patients with diabetes mellitus on insulin treatment, patients with other endocrine disorders, patients with hepatic, renal, cardiac disease or chronic infections and pregnant females or those receiving oral contraceptives.

The following was done for all subjects included in the study:

A. Full clinical history.
B. Anthropometric measurements:
   - Weight and height.
   - Body Mass Index (weight in kilograms divided by height in squared meters).
C. Laboratory investigations:
   Blood samples were drawn from all subjects after overnight fasting (10-16 hours) by veinpuncture:
   1. Two milliliters were anticoagulated using EDTA for determination of HbA_1C.
   2. Two milliliters were anticoagulated using sodium fluoride for determination of fasting blood glucose level.
   3. Four milliliters were placed in plain test tubes and allowed to clot for 30 minutes in water bath at 37°C and then centrifuged for 15 minutes at 1000 xg. Serum was then subdivided into two aliquots:
      a. The first aliquot was used for lipid profile assay.
      b. The second aliquot was used for insulin and visfatin assays. This aliquot was kept at -70°C for subsequent assay.

Methodology:

1. Fasting blood glucose, cholesterol, triglycerides, and HDL-cholesterol were performed by automated enzymatic methods (Cobas Integra 400 analyzer, Roche, Germany). LDL cholesterol were calculated according to Friedwald formula:

LDL cholesterol = Total cholesterol – HDL cholesterol – TG/5.

2. Fasting insulin level was assessed through chemiluminescence immunoassay technique using Autobio, Zhengzhou, China kit. The insulin chemiluminescence test is a solid phase two-site immunoassay.
3. Glycated hemoglobin (HbA_1C) level was assessed through HPLC technique using Bio - Rad, Hercules, USA kit.
4. Serum visfatin level was assessed through enzyme-linked immunosorbent assay (ELISA) supplied by Adipogen, Soul, Korea. Monoclonal antibody specific for human visfatin had been precoated onto microtiter plate. Standards and samples were pipetted into the wells and any visfatin present is bound by immobilized antibody. The wells are washed and biotinylated anti-human visfatin was added. After washing away unbound biotinylated antibody, hoarse radish peroxidase conjugated anti-rabbit IgG was added. After washing, a substrate solution was added. The color developed in proportion to the amount of visfatin bound. The color development was stopped and the intensity of color was measured at 450 nm.

Calculation of homeostasis model assessment (HOMAIR): [fasting blood glucose (mmol/L) × fasting blood insulin (μU/ml)/22.5].

Statistical Methods:

The collected data was organized, tabulated and statistically analyzed using SPSS software statistical computer package version 16. For quantitative data, mean and standard deviation were calculated. Student "t" test: used to test the significance of the difference between two groups.

The association of serum visfatin level with continuous variables was tested with Pearson's correlation. P value was considered significant if $P< 0.05$ & not significant if $P> 0.05$.

3. Results:

Parameters including fasting blood glucose, fasting insulin level, HOMA-IR, HbA_1C and visfatin levels were significantly higher in diabetic than control group while parameters including age, weight, height, BMI, total cholesterol, triglycerides, HDL-cholesterol & LDL-cholesterol levels showed non significant difference between both groups.

A positive significant correlation was found between serum visfatin & HbA_1C levels in the diabetic group and no significant correlations were found between serum visfatin and all other parameters in the same group.

HBA1C, fasting serum glucose and serum visfatin were significantly higher in uncontrolled than controlled diabetic subgroups while no significant differences were found between age, weight, height, BMI, fasting insulin, HOMA-IR, total cholesterol, triglycerides, HDL-cholesterol & LDL-cholesterol in the same subgroups.

Weight, BMI and serum visfatin were significantly higher in overweight diabetic subgroup than normal BMI diabetic subgroup. No significant differences were found between age, height, HbA_1C, fasting blood glucose, fasting insulin, HOMA-IR, total cholesterol, triglycerides, HDL-cholesterol & LDL-cholesterol in the same subgroups.

Table (1): The clinical and laboratory parameters of studied groups:

Parameter	T2DM (N=60) Mean ± SD	Controls (N=20) Mean ± SD	*p* value	*Sig.*
Age (years)	47.4 ± 6.4	46.6 ± 5.8	0.607	NS
Weight (kg)	85.0 ± 12.5	83.7 ± 10.8	0.688	NS
Height (meters)	1.71 ± 6.9	1.73 ± 6.6	0.525	NS
BMI (kg/m^2)	28.5 ± 4.2	27.4 ± 0.7	0.460	NS
Fasting glucose (mg/dl)	159 ± 54.0	95 ± 9.0	0.001	S
Fasting Insulin (μU/mL)	17.0 ± 8.6	9.2 ± 4.9	0.001	S
HOMA-IR	6.2 ± 2.9	2.2 ± 1.2	0.001	S
HbA_1C (%)	8.1 ± 2.3	4.9 ± 0.7	0.001	S
Total cholesterol (mg/dl)	206 ± 41	180 ± 30	0.0819	NS
Triglycerides (mg/dl)	154 ± 77	145 ± 66	0.641	NS
HDL cholesterol (mg/dl)	48 ± 14	47 ± 14	0.783	NS
LDL cholesterol (mg/dl)	127 ± 33	117 ± 25	0.068	NS
Visfatin (ng/ml)	22.9 ± 17.5	14.4 ± 4.2	0.036	S

p value is significant (S) if < 0.05 and non significant (NS) if > 0.05.

Table (2): Visfatin level correlations in the diabetic group:

Parameter	*p* value	Significance
Age (years)	0.062	NS
Weight (kg)	0.027	S
Height (meters)	0.165	NS
BMI (kg/m^2)	0.042	S
HbA1C (%)	0.001	S
Fasting Blood Glucose (mg/dl)	0.175	NS
Insulin (μU/mL)	0.762	NS
HOMA-IR	0.625	NS
Total cholesterol (mg/dl)	0.385	NS
Triglycerides (mg/dl)	0.621	NS
HDL-cholesterol (mg/dl)	0.062	NS
LDL-cholesterol (mg/dl)	0.173	NS

p value is considered significant (S) if <0.05 and non significant (NS) if > 0.05.

Table (3): The clinical and laboratory parameters of controlled & uncontrolled diabetic subgroups:

Parameter	Uncontrolled subgroup (N=27) Mean ± SD	Controlled subgroup (N= 33) Mean ± SD	*P* value	Sig.
Age (years)	48.9 ± 6.7	46.2 ± 5.9	0.0988	NS
Weight (kg)	85.9 ± 12.0	84.2 ± 12.8	0.5823	NS
Height (meters)	1.71 ± 0.07	1.71 ± 0.06	0.7190	NS
BMI(kg/m^2)	29.2 ± 4.6	28.7 ± 3.8	0.6355	NS
HbA1C(%)	10.0 ± 1.9	6.6 ± 0.9	<0.001	S
Fasting Blood Glucose (mg/dl)	182 ± 65	139 ± 32	0.0015	S
Fasting Insulin (µU/mL)	16.3 ± 8.8	17.6 ± 8.5	0.5641	NS
HOMA-IR	6.6 ± 2.8	5.9 ± 2.9	0.264	NS
Total cholesterol (mg/dl)	210 ± 44	202 ± 39	0.4586	NS
Triglycerides (mg/dl)	166 ± 86	145 ± 69	0.2982	NS
HDL-cholesterol (mg/dl)	48 ± 17	47 ± 11	0.7843	NS
LDL-cholesterol (mg/dl)	129 ± 34	126 ± 32	0.7267	NS
Serum Visfatin (ng/ml)	32.0 ± 18.8	15.4 ± 12.1	0.01	S

p value is considered significant (S) if <0.05 and non significant (NS) if > 0.05.

Table (4): The clinical and laboratory parameters of normal & overweight diabetic subgroups:

Parameter	Normal BMI group (N=10) Mean ± SD	Overweight group (N= 50) Mean ± SD	*p* value	Sig.
Age (years)	47.7 ± 4.8	47.3 ± 6.7	0.8603	NS
Weight (kg)	69.6 ± 4.5	88.0 ± 11.3	<0.001	S
Height (meters)	1.73 ± 0.04	1.71 ± 0.07	0.3870	NS
BMI(kg/m^2)	23.2 ± 1.4	30.1 ± 3.5	<0.001	S
HbA1C(%)	8.5 ± 2.7	8.0 ± 2.2	0.53	NS
Fasting Blood Glucose (mg/dl)	152 ± 40	160 ± 57	0.6745	NS
Fasting Insulin (µU/mL)	15.1 ± 9.9	17.4 ± 8.4	0.4458	NS
HOMA-IR	5.3 ± 3.1	6.4 ± 2.8	0.2696	NS
Total cholesterol (mg/dl)	185 ± 46	210 ± 39	0.0766	NS
Triglycerides (mg/dl)	135 ± 42	158 ± 82	0.3931	NS
HDL-cholesterol (mg/dl)	40 ± 13	49 ± 13	0.0504	NS
LDL-cholesterol (mg/dl)	117 ± 36	129 ± 32	0.2931	NS
Serum Visfatin (ng/ml)	11.7 ± 12.3	25.1 ± 17.6	0.0256	S

p value is considered significant (S) if <0.05 and non significant (NS) if > 0.05.

4. Discussion:

Not all adipokines are diabetogenic. Some of them may be protective against insulin resistance and T2DM. The best example is adiponectin, which has insulin-like effects in liver and muscle and also acts as an insulin sensitizer[13]. The adipocyte production of adiponectin is decreased in insulin resistant states, and a low circulating adiponectin level is an independent risk factor for T2DM[13].

An adipose-tissue-derived protein termed visfatin was described with putative antidiabetogenic properties[13]. Visfatin was reported to be expressed almost exclusively in visceral adipose tissue and has insulin-like metabolic effects[12]. Visfatin molecule was previously identified as a growth factor for early B-lymphocytes termed pre-B cell colony enhancing factor (PBEF)[11]. However, the visfatin gene is expressed in adipocytes, where it is subjected to regulation[14]. Furthermore, in humans the gene is expressed predominantly in visceral as compared with subcutaneous human adipose tissue[15]. These findings are exiting news and could provide a novel mechanism by which visceral fat accumulation can promote the development of T2DM[16]. In particular, effects of visfatin on the liver could be of importance for T2DM and other insulin-resistant disorders because of the portal delivery.

According to the results of this study, age, sex, weight, height and BMI total cholesterol, triglycerides, HDL-cholesterol and LDL-cholesterol were not significantly different between the patient and control group while HbA_1c, fasting blood glucose, fasting insulin level & HOMA-IR were significantly higher in the patient group.

According to the results of this study, a significantly higher visfatin/PBEF/Nampt levels were found in the diabetic group when compared with controls. This coincides with ***Dogru et al.,*** [17] who studied visfatin levels in 40 subjects with newly diagnosed diabetes or glucose intolerance and found that visfatin levels were higher in the diabetic patients when compared to controls, but not when compared to glucose intolerant patients (pre-diabetes). Results obtained in this study also coincides with ***Chen et al.,*** [18] who reported that in patients with T2DM (61 patients with T2DM and 59 sex- and age-matched controls), visfatin/PBEF/Nampt plasma levels were significantly increased in T2DM compared with controls, and a significant correlation between plasma visfatin/PBEF/Nampt and T2DM persisted even after adjustment for known biomarkers influencing glucose metabolism, such as age, gender, BMI, WHR, SBP (systolic BP), DBP (diastolic BP), lipid profile and smoking status . The results also coincide with those obtained by ***Lopez-Bermejo et al.,*** [19] who reported that circulating visfatin/PBEF/Nampt was increased in subjects with known T2DM compared with non-diabetic subjects, but not in newly diagnosed subjects with T2DM compared with non-diabetic subjects. Interestingly, visfatin/PBEF/Nampt levels were significantly increased in patients with long-standing T1DM (Type 1 diabetes mellitus) compared with subjects with T2DM or non-diabetic subjects.

Zhang et al., [20] studied a group of 814 diabetic patients from the USA and a group of non-diabetic controls (n = 320). They found a significant association between -948C> A and T2DM (p = 0.021). In a non-diabetic population (n = 630), the same -948C allele that conferred increased risk of T2DM was significantly associated with higher plasma levels of fibrinogen and C-reactive protein (p =0.0022 and 0.0038, respectively). However, no significant associations were observed with BMI, waist circumference, serum glucose levels, or fasting insulin levels. They suggested that the visfatin gene may play a role in determining T2DM susceptibility, possibly by modulating chronic, low-grade inflammatory responses.

Elevated visfatin level in patients with T2DM may be explained by the impairment of visfatin signaling in targets tissues or the dysregulation in biosynthesis in response to hyperglycemia, hyperinsulinemia, or adipocytokines in state of diabetes[18].

On the other hand, ***Erick Ingelesson et al.,*** [21], reported the absence of statistically significant associations between plasma visfatin and diabetes, obesity (generalized or abdominal and subcutaneous or visceral fat), or dyslipidemia. Potential explanations of ***Erick Ingelesson et al.,*** [21] negative findings include that the study group was a community-based cohort study, whereas prior investigations were smaller case-control studies of patients with diabetes or obesity or based on patients referred to a hospital for abdominal surgery. In addition, ***Bottcher et al.,*** [22] did not find any association with either T2DM, in a cohort of 503 diabetic subjects and 476 healthy controls, or with T2DM-related traits in 626 non-diabetic subjects from Germany. However, they found an association between the -948 G > T single-nucleotide polymorphism (SNP) and fasting insulin levels in non-diabetic subjects (p < 0.05). The ratio of visceral/subcutaneous visfatin mRNA expression was associated with all three genetic polymorphisms studied (rs9770242, -948G > T, rs4730153).

Regarding other types of diabetes, some investigators have reported higher plasma visfatin in individuals with gestational[23] and type 1[19,24] diabetes. However, other studies have noted opposite findings, e.g., lower plasma visfatin in gestational diabetes[18] while another study, ***Toruner et al.,*** [25] demonstrated decreased visfatin in patients with T1DM and inverse relationship between HbA_1c and visfatin levels**.**

Current data suggests that visfatin is important to normal insulin secretion, but its relationship with diabetes risk and progression is still a matter of debate. Thus, visfatin may be a compensatory mechanism or part of the pathophysiology of diabetes.

Regarding the diabetic group & according to the results of this study, there was no correlation between plasma visfatin/PBEF/Nampt concentrations on one hand, and age, gender, fasting blood glucose and fasting insulin level on the other hand. This coincides with ***Berndt et al.,*** [26], ***Haider et al.,*** [24], ***Pagano et al.***[27], , ***Dogru et al.,*** [17] ***and Varma et al.,*** [28].

There was no correlation between plasma visfatin/PBEF/Nampt concentrations on one hand, and total cholesterol, triglycerides, HDL-cholesterol, LDL-cholesterol, levels on the other hand. ***Chen et al.,*** [18], reported that plasma visfatin level was significantly associated with total cholesterol, triglycerides, HDL-cholesterol and LDL-cholesterol in simple regression analysis but not in multiple regression analysis.

Our results confirmed that plasma visfatin /PBEF/ Nampt correlates positively with BMI in the diabetic group. This finding coincides with a separate study by ***Berndt et al.,*** [26] in a population of 189 subjects who showed that plasma visfatin/PBEF/Nampt concentrations correlated positively and significantly with BMI and percentage body fat, as well as visfatin/PBEF/Nampt mRNA expression in VAT (visceral adipose tissue). ***Berndt et al.,*** [26] reported a negative correlation between circulating visfatin/PBEF/Nampt levels and mRNA expression in subcutaneous fat. Plasma visfatin/PBEF/Nampt concentrations were not associated with visceral fat mass, which had been calculated by CT (computed tomography) scans in a subgroup of 73 subjects.

Brendt et al., [26] explained these findings through a reciprocal regulatory mechanism of subcutaneous visfatin gene expression by increased plasma visfatin concentration. In addition, ***Hammarstedt et al.,*** [29], in a small study composing six healthy subjects and seven untreated patients with T2DM, reported that plasma visfatin/PBEF/Nampt levels and BMI had a weak positive correlation in both groups, whereas there was no correlation between visfatin/PBEF/Nampt concentrations and WHR or waist circumference.

On the other hand ***Lopez-Bermejo et al.,*** [19], ***Haider et al.,)***[24], ***Chen et al.,)***[18], ***Dogru et al.,)***[17] ***and Varma et al.,*** [28] reported absence of correlation between plasma visfatin and BMI and explained this finding by the differential regulation of VF expression in the different adipose depots. Hence, the increase in VAT VF with obesity may be balanced by the decrease in SAT VF, such that plasma VF is not affected by increasing BMI. ***Pagano et al.,*** [27] reported a negative correlation between circulating visfatin/PBEF/Nampt levels and BMI. In contrast, no association between plasma visfatin/PBEF/Nampt and waist circumference, fat mass, was found in lean, as well as obese, subjects.

Regarding glycemic control and according to the results of this study, visfatin level correlates positively with HbA_1c level in the diabetic group. In addition, in the diabetic group, both visfatin & HbA_1c were significantly higher in uncontrolled subgroup than the controlled one. This finding coincides with ***Lopez-Bermejo et al.,*** [19] ***and Zhu et al.,*** [30] who reported a significant correlation between visfatin levels and HbA_1c levels in diabetic patients and reported a reduction in visfatin concentrations from 25.0±6.5 ng/ml at baseline to 20.3±4.7 ng/ml (p<0.01) after 3 months of intensive glycemic control, while HbA_1c levels decreased from 9.0±1.8% to 6.2±0.7% (p<0.01). ***Toruner et al.,)***[25] reported the presence of a significant correlation between visfatin and hemoglobin A_1c (HbA_1c) even after the adjustment for age, sex, body mass index and duration of diabetes ($r = -0.48$, $p = 0.005$) in the patient group and multivariate analysis showed that significant determinants of visfatin concentrations were HbA_1c and duration of diabetes ($r^2 = 0.27$).

The relationship between visfatin levels and insulin resistance surrogates was also investigated in this study. However, it was not possible to demonstrate correlation of visfatin with HOMA-IR. This coincides with ***Lopez-Bermejo et al.,*** [19], ***Berndt et al.,*** [26], ***Drogu et al.,*** [17] ***and Chang et al.,*** [31] who reported that HOMA-IR did not show correlation with visfatin expression on visceral adipose tissue but was positively associated with visfatin expression in subcutaneous adipocytes.

In conclusion: Diabetic subjects had higher plasma visfatin levels than those of control subjects. Plasma visfatin positively correlated with HbA_1c and BMI and not correlated with gender, age, fasting plasma insulin, total cholesterol, triglycerides, HDL-cholesterol, LDL-cholesterol, fasting blood glucose and HOMA-IR in the diabetic subjects.

These results indicate that visfatin may play a role in the pathogenesis of T2DM through the unresponsiveness to visfatin actions and the contribution of visfatin to β-cell deterioration in diabetic patients or the increased serum visfatin concentration may be a compensatory mechanism aimed at ameliorating the functional consequences of insulin deficiency. The increased visfatin concentration may also promote insulin sensitivity by its stimulatory effects on insulin receptors.

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