



Study of Elevated Visfatin Levels in Obese Diabetic and Non-diabetic Subjects

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ABSTRACT

Visfatin is an adipokine highly expressed in visceral fat tissues and has insulin mimetic properties. Our aim is to investigate serum levels of visfatin in obese patients with and without diabetes mellitus type 2. 34 obese patients with T2DM and 27 apparently healthy obese people and 25 apparently healthy controls were enrolled. Visfatin levels were measured along with glucose, glycosylated hemoglobin, insulin, lipid profile and hsCRP levels, also BMI and WHR were measured. Serum visfatin levels were significantly higher in obese diabetic subjects compared with non-diabetic subjects (2.03ng/ml vs. 0.93ng/ml, $p < 0.05$). Serum Visfatin levels were also significantly higher in obese subjects compared with controls, there were a positive correlation of visfatin with WHR and HDL while there were negative correlations of visfatin with LDL, TG, and there was no significant correlation between visfatin and BMI, insulin, glucose, HbA1c in the studied groups. These results indicate to an association with obesity and a possible relationship with the pathogenesis of T2DM.

Keywords: Adipokines, PBEF, Visfatin.

INTRODUCTION

Obesity is the most prevailing diseases in the present, which is described as accumulation of adipose tissues which is now known as a storage of excess fat and energy, but also it is now considered to be a major endocrine organ secreting adipocytokines which are thought to be the missing link between diabetes and insulin resistance, the mechanism in which it induces insulin resistance and the role of adipocytokines in the pathogenesis of T2DM has not been well established.¹ Visfatin, also known as pre B colony enhancing factor PBEF, 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.² However, the biological activity of Visfatin is poorly understood it is secreted by activated lymphocytes, monocytes and neutrophils, it has been recently found that Visfatin expression in visceral fats is increased in obese subjects and that plasma concentrations of Visfatin correlated much more strongly with amount of visceral fat than that of adipose tissue.³

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 production⁴, Intravenous injection of recombinant visfatin in mice decreased plasma glucose in a dose dependent fashion, it was also as effective as insulin in reducing hyperglycemia in insulin deficient diabetic mice⁵, Visfatin was also found to be bound to an active insulin receptor, causing receptor phosphorylation and the activation of downstream signaling molecules. However, visfatin and insulin did not compete on binding to the insulin receptor indicating that

the two proteins were recognized by different regions of the receptor.⁶ (figure 1).

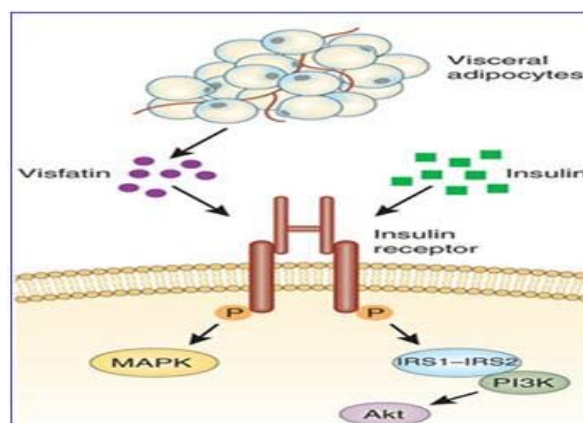


Figure 1: Visfatin binding to insulin receptor

Visfatin showed significant elevations in patients with type 2 diabetes mellitus and these elevations were present in patients taking hypoglycemic agents and in non-treated new patients, this might refer to the fact that visfatin elevations are not related to treatment⁷ however Visfatin is elevated in parallel with β cells deterioration.⁸

Thus, Visfatin might play a role in glucose homeostasis and might contribute to the pathogenesis of diabetes; we investigated the role of visfatin in diabetes; we measured plasma visfatin levels in obese diabetic and non-diabetic persons in Syrian population.

SUBJECTS AND METHODS

Subjects

After the approval by the ethics committee of the faculty of pharmacy, Damascus university, Syria, the study and its purpose was explained to all the participants and their consent was obtained, the study was implemented From June 2008 to December 2008 involving 86 subjects divided into three groups: 34 diabetic obese patients who regularly visited the Syrian association for diabetic care, 27 obese apparently healthy persons, subjects without clinical evidence of major disease were recruited from unselected population that underwent routine medical checkup and 25 apparently healthy people were used as control group.

All patients underwent careful physical examination, subjects having cancer, hepatic or renal failure, heart disease were excluded. Standing high and weight were measured with the patient barefoot in light clothing, body mass index (BMI) was calculated as weight divided by squared height (kg/m^2). Individuals with a BMI of 30 or more are considered obese, while those with a BMI of 25 to 29, 9 are considered overweight along with wrist hip ratio was measured the hip circumferences were measured to the nearest 0.1 cm at the narrowest point between the lowest rib and the uppermost lateral border of the right iliac crest the hips were measured at their widest point. Blood pressure measurements were made after subjects had remained in sitting position for 10 minutes. Measurements were made twice; with a 5 minutes rest period and mean value of measurements was used.

Methods

After overnight fasting (14 hours), blood samples were collected between 08:00 and 09:00 in the morning. Each sample was divided into two parts one part was kept as whole blood for assay of glycohaemoglobin (HbA1) using a kit provided by (Human) and the other part was left to clot and then centrifuged at 2500g for 10 min, the serum was then divided into two parts stored at -80 for further analysis of other parameter the first was for Visfatin titration using (Human Visfatin ELISA kit ALPCO, USA) with sensitivity: 30pg/ml, the second part was for analyzing fasting serum glucose (FSG), Creatinine, total cholesterol (TC), triglycerides (TG), high density lipoprotein cholesterol (HDL-C) levels were measured using precipitation method, low precipitation method was calculated by (Cholesterol CHOD/PAP method), high-sensitivity C Reactive protein (hsCRP) (Human hsCRP turbidimetry, Behring) and Insulin using (Human insulin ELISA kit, Roche) the procedure provided with these kits were applied exactly as mentioned. The insulin resistance index was calculated using the formula of HOMA-IR where $\text{HOMA-IR} = \text{fasting insulin } (\mu\text{U}/\text{ml}) \times \text{fasting glucose}/405$. Low values of HOMA-IR indicate high insulin sensitivity, whereas high values indicate low insulin sensitivity (insulin resistance).

Statistical analysis

Microsoft office Excel 2003 and SPSS version (12.0) was used to handle and analyze data, results are presented as means \pm SD, a P value of <0.05 was accepted to indicate statistical significance and Person's test to study correlation between data.

Results

We found in our study a significant static difference ($p < 0.05$) between mean Visfatin values of obese diabetic subjects 1.733ng/ml and the control group 0.926ng/ml.

We found also a significant statistical difference between the mean Visfatin value in the non-diabetic obese group 1.76ng/ml and the control group 0.926ng/ml (figure 2).

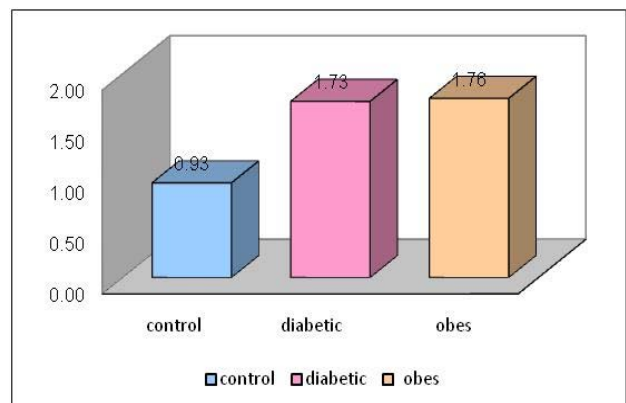


Figure 2: Mean visfatin values in the study groups

In studying the correlation between Visfatin and the other parameters we found in both of the studied group a positive correlation between Visfatin and WHR (figure 3) and a positive correlation between Visfatin and HDL (figure 4) and a positive correlation between Visfatin and hsCRP too (figure 5).

While there were a negative correlation between Visfatin and both of TG and LDL in the obese non diabetic group and in obese diabetic group (figure 6) (figure 7).

There were no correlation between Visfatin and each of glucose, glycelated hemoglobin, Insulin and BMI in the obese diabetic group.

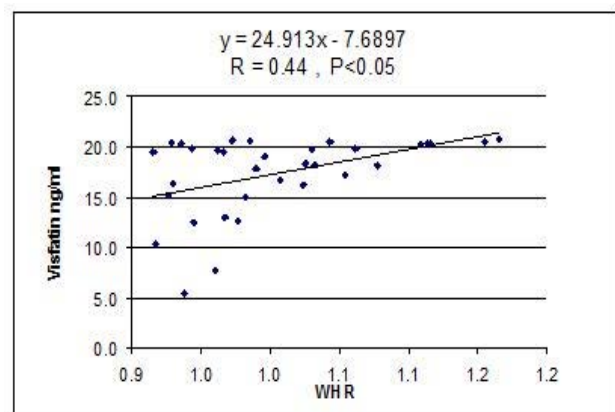


Figure 3: Correlation between visfatin and WHR

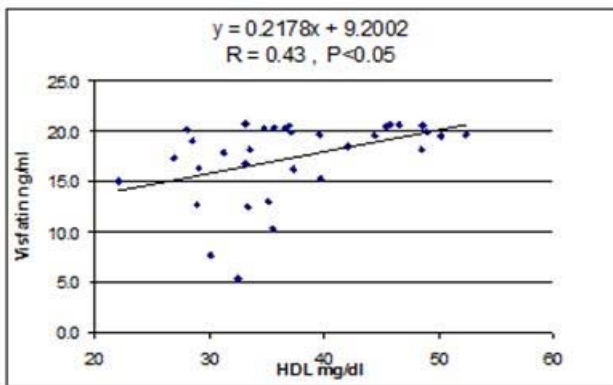


Figure 4: Correlation between Visfatin and HDL

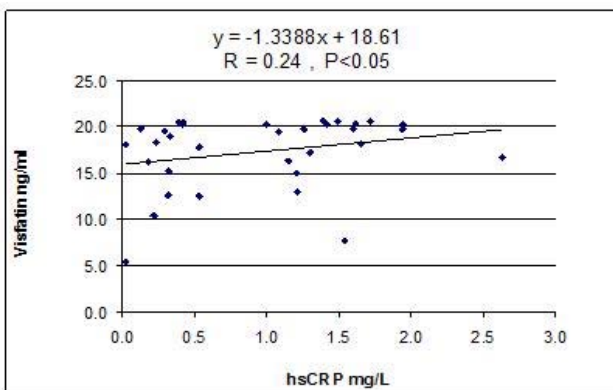


Figure 5: Correlation between visfatin and hsCRP

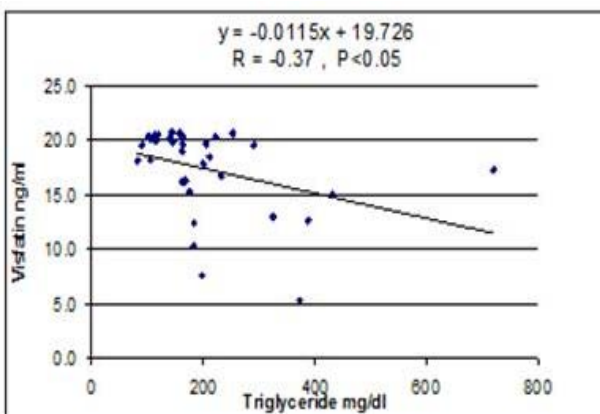


Figure 6: Correlation between Visfatin and TG

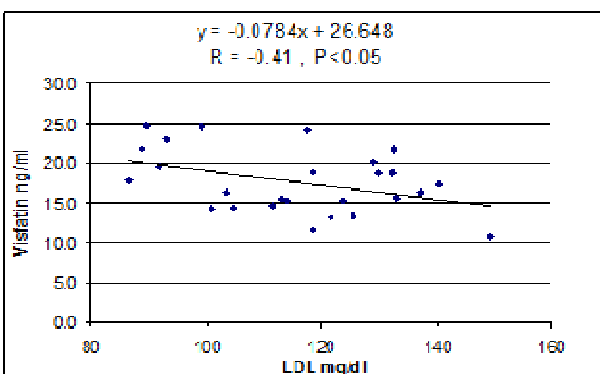


Figure 7: Correlation between Visfatin and LDL

DISCUSSION

Our study is designed to investigate the serum levels of visfatin and its relationship to obesity and insulin resistance and inflammation in obese subjects with or without diabetes mellitus, the non-diabetic obese group in the present study showed significantly higher serum visfatin levels when compared to healthy controls, this corresponds with the fact that Visfatin is an adipokine secreted from the adipose tissue and this secretion is elevated relatively with the size of this tissue⁹, this is in line with the findings of Berdent et al¹⁰, Markwicz et al.,¹¹ This elevation might be considered as a compensation of impaired insulin signal in the early stages of insulin resistance development due to obesity.¹²

We found in our study a significant positive correlation between Visfatin concentrations and WHR this is in compliance with the fact that Visfatin is secreted preferably from visceral fats rather than subcutaneous ones when WHR is the best surrogate of visceral obesity, this is in line with the findings of Fukuhara et al⁴, Berdent et al.,¹⁰

We also found in our study a positive correlation between Visfatin and HDL as the other adipokines do, that is because Visfatin elevation is associated with a better metabolic profile although it is still unknown whether Visfatin influences lipid profile parameter or vice versa.¹³

The positive correlation with CRP and IT-6 would refer to a potential relation between Visfatin and proinflammation this is in line with the finding of Oki et al¹⁴, and Lu et al.,¹⁵

In our study as in those of Berdent et al¹⁰ Alghasham et al¹², Pagano et al¹⁶ and Sandeep et al¹⁷ There were no correlation between Visfatin and each of glucose, HbA1c and insulin. We may suggest that Visfatin elevations are independent to glucose, insulin and insulin resistance which indicate that elevated visfatin levels are related to other factors like inflammation and visceral obesity.¹²

In conclusion, our study confirmed the increased levels of visfatin in obese subjects with or without diabetes those levels were correlated with lipoprotein metabolism and inflammation markers which might represent a compensation mechanism against metabolic disturbance associated with insulin resistance, further well- designed studies are needed to interpret the controversial data on visfatin and uncover its relation to insulin resistance, metabolic disturbances, inflammation and T2DM and its complications.

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