Full Length Research paper

Visfatin in hyperlipidemic female patients

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Hyperlipidemia was a modifiable major risk factor in primary and secondary prevention of cardiovascular diseases. In recent studies it was demonstrated that adipose tissue besides being a store of lipids, was a site that secrete bioactive proteins into the circulation, one of which was visfatin. In clinical trials visfatin levels were found to be related to lipid parameters and obesity. In our study, we intended to show the relation of visfatin with lipid profile and metabolic parameters. The study included 60 female patients and 20 age matched control subjects. As well as making physical and antropometric examinations, fasting plasma glucose and insulin, post prandal plasma glucose and insulin, lipid profile, uric acid, homocysteine, c-reactive protein and visfatin levels were measured in all female subjects. Hyperlipidemic group had significantly higher plasma visfatin levels than control group (p < 0.01). In hyperlipidemic patients positive correlation was found between triglyceride and visfatin levels and negative correlation between low density cholesterol and visfatin levels. Then we classified our patient group with an indirect measure of insulin resistance as homeostasis model assesment 2.7 and homeostasis model assesment < 2.7. We found that the group with homeostasis model assessment 2.7 had significantly high triglyceride, postprandial glucose, post prandial insulin and visfatin levels (p<0.05). In conclusion, our data may point toward a role of visfatin in lipid parameters and insulin resistance.

Key words: Visfatin, atherosclerosis, hyperlipidemia, insulin resistance.

INTRODUCTION

Obesity is strongly associated with insulin resistance, type 2 diabetes mellitus (T2DM), dyslipidemia and increased risk of cardiovascular disease (Grundy, 2004). The accumulation of adipose tissue in abdominal visceral depot is especially correlated with insulin resistance (Varma et al., 2007). Studies have demostrated that adipose tissue secretes different proteins, named adipocytokines, likely have important roles in organising endocrine, metabolic and inflammatory processes which take part in the control of energy homeostasis Depres et al., 2004, Hotamı Iıgil et al., 1993).

After the identification of a protein secreted from lymphocytes, named pre-B-cell colony-enhancing factor (PBEF) (Samal et al., 1994), a novel adipocytokine was isolated in 2005 (Fukuhara et al., 2005). This cytokine, identical to PBEF, was called visfatin, as it was preferentially expressed in visceral fat (Fukuhara et al., 2005). It is also expressed in bone marrow, liver and

muscle and promotes B cell maturation and inhibits neutrophil apoptosis (Samal et al., 1994).

Visfatin is reported to exert insulin-mimetic effects in cultured cells and to lower plasma glucose levels in mice by binding to and activating the insulin receptor (Fukuhara et al., 2005). Its plasma concentration is lower than that of insulin despite having similar receptor-binding affinity. Although, it is shown that plasma levels of visfatin are not effected from fasting and feeding, unlike insulin (Berndt et al., 2005), there are a number of sudies which do not share the same thought (Pagano et al., 2006, Sun et al., 2007).

It is quite a paradox that an insulin-mimetic protein is highly produced by visceral fat in a state of insulin resistance. As increased body fat especially visceral fat is closely linked to insulin resistance and metabolic sendrom (Depres et al. 2006), the relationship between visfatin levels and metabolic syndrome warrants elucidation. Conflicting results were obtained from studies about visfatin and metabolic syndrome, insulin resistance, T2DM, obesity (Varma et al., 2007, Chen et al., 2007, Berndt et al., 2005, Pagano et al., 2006, Sun et

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al., 2007, Smith et al., 2006, Hammarstadt et al., 2006, Filippatos et al., 2007, Zahorska et al., 2007, Sandeep et al., 2007, Haider et al., 2006, Li et al., 2006, Jian et al., 2006, Curat et al., 2006).

Adipocytokines can potentially impact on lipid as well as glucose metabolism. Several authors reported different results about the relation of serum visfatin levels with various lipid parameters (Chen et al., 2007, Pagano et al., 2006, Smith et al., 2006, Wang et al., 2007). Keeping in mind the complex interactions of body fat, insulin resistance and cardiovascular disease we analysed the relationship of plasma visfatin with some parameters of adiposity, insulin resistance and plasma lipid profile in our population.

PATIENTS AND METHODS

Patients

A total of 60 female hyperlipidemic aged from 25-65 years, were recruited from the outpatient Clinic of Ankara Education and Research Hospital from July 2009 to October 2009. 20 aged matched normolipidemic female subjects formed the control group.

Patients with male gender, diabetes mellitus, glucose intolerance, conditions which may effect metabolic parameters(such as thyroid dysfunctions in history or nowadays), pregnancy, chronic diseases, infection, coronary artery disease, and who were taking medicine for hyperlipidemia were excluded.

After detailed physical examination, in all subjects body weight and height were measured. Waist was measured when fasting, in standing position halfway between costal edge and iliac crest, by a non elastic measure.

Body mass index (BMI) was calculated as weight in kilograms divided by the square of height in meters. Body fat were estimated by Tanita body composition analayser TBF -300 after the subjects rested 30 minutes.

Blood was withdrawn after 12h of overnight fasting, at 08.30 a.m. for fasting plasma glucose (FPG), insulin (FI), serum total and high density lipoprotein cholesterol (HDL-C), triglyceride (TG), homocysteine, high sensitive c- reactive protein (CRP), lipoprotein-a (Lp a), uric acid, and visfatin levels. Another blood sample was taken for postprandail plasma glucose (PPPG) and postprandail insulin(PPI) 2 h after breakfast.

We accaepted our patients as hyperlipidemic if their total cholesterol or TG level were above 200mg/dl, or low density lipoprotein cholesterol level was above 130 mg/dl.

The local ethics comitee approved this study and all the subjects gave written informed consent .

Laboratory methods

Plasma glucose, total cholesterol, triglyceride(TG) and HDL cholesterol concentrations were determined by enzymocalorimetric spectrophotometric method in a Roche/Hitachi molecular PP autoanaluser. Low density lipoprotein cholesterol (LDL-C) was calculated by the Friedewald Formula (LDL: Total cholesterol – HDL-TG/5). Insulin was measured by means of DRG Diagnostics (DRG Instruments GmbH, Germany) ELISA kits.

An indirect measure of insulin resistence was calculated from the fasting plasma insulin (unite / ml) x fasting plasma glucose (mmol /l) / 22. 5 formula as homeostasis model assessment (HOMA). 2.7 HOMA levels were accepted as insulin resistant, < 2.7 HOMA levels were accepted as insulin sensitive.

Homocysteine concentrations were determined according to the method of HPLC using Agilend 1100 device. CRP was measured by immunnefolometric tests by Beckman- Cutler device. Uric acid was measured by calorimetric, LP a was measured by nephelometric methods.

For the measurements of visfatin, after fasting blood samples were drawn, were santrifuged 4000 cycle / min in 30 minutes. Plasma was then stored at -80˚C. Plasma visfatin levels were assayed by a commercial visfatin C- terminal (Human) ELISA kit

Statistical analysis

Calculations were performed using SPSS version 11,5 (Customer ID 30000105 930). Data are presented as mean ± SD. Student t-test was used to compare the groups in a parametric way. One way variation analysis (ANNOVA) was used to compare all study groups with each other. Tukey's multiple comparison test was used for post hoc analysis. A p value of < 0.05 was considered as statistically significant. Pearson correlation coefficient was used for the correlation analysis.

RESULTS

This study was performed with 60 hyperlipidemic female patients (GROUP 1), and 20 normolipidemic female control subjects (GROUP 2). All the demographic and laboratory findings of the groups were compared and illustrated in Table 1. As it is anticipated BMI, body fat and waist circumference of the hyperlipidemic group were found statistically higher than normolipidemic ones (respectively p<0.001, p<0.05, <0.05). In the hyper-lipidemic patients total cholesterol, LDL-C, TG and visfatin levels statistically higher than the normolipidemic control group (all p<0.001). We could not find difference between the age, FBG, PPBG, FI, PPI, HOMA, HDL-C, Lp-a, CRP levels of the two groups (Table 1).

We then made the correlation analysis in all hyperlipidemic patients and found statistically significant positive correlation between visfatin and TG, and negative correlation between LDL- C levels. We also found positive correlation between TG and CRP, homocysteine and HOMA and positive correlation between BMI and CRP levels. We could not find any positive or negative correlations among any other paramters, so we did not include them in the table (Table 2).

Then we classified our patient group as HOMA < 2.7, HOMA 2.7, 30 patients dropped into HOMA < 2.7 group, and 30 patients into HOMA 2.7 group. The characteristics of the two groups were demonstrated in Table 3.The age, BMI, body fat, waist circumference, the levels of FBG, total cholesterol, HDL- C, Lp-a, CRP, homocysteine and uric acid were found to be statistically insignificant in the groups with HOMA 2.7 and HOMA< 2.7. The group whose HOMA was 2.7 had significantly high TG and visfatin levels (all p < 0.05), but low LDL-C levels (p < 0.05) . PPBG and PPI levels of

Table 1. Characteristics of Group 1 vs Group 2

	GROUP 1 (n=60)	GROUP 2 (n=20)	P
Age (yr)	50.4± 9.8	43.4 ± 16.8	NS
BMI (kg/m^2)	30.4± 4.1	25.7 ± 5.4	<0.001
Waist circumference (cm)	96.2± 2.0	82.4 ± 3.0	<0.05
Body fat (%)	36.1± 6.5	30.3 ± 11.9	<0.05
FBG (mg/dl)	96.1± 13.4	90.9 ± 9.9	NS
PPBG (mg/dl)	118.0± 22.5	111.1 ± 13.3	NS
Cholesterol(mg/dl)	246.8± 41.9	170.1 ± 23.1	<0.001
TG (mg/dl)	276.1 ± 48.5	97.1 ± 13.2	<0.001
LDL-C(mg/dl)	153.5 ± 37.8	101.2 ± 19.1	<0.001
HDL-C (mg/dl)	44.4± 10.9	49.1 ± 8.8	NS
Uric acid (mmol/L)	4.1± 1.6	4.1 ± 1.5	NS
CRP (mg/dl)	4.0± 2.0	3.4 ± 1.3	NS
Homocysteine (mol/L)	12.6± 6.8	16.2 ± 1.3	NS
Lp a (mg/dl)	393.0± 40.1	270.2 ± 27.7	NS
FI (u/ml)	12.0± 6.1	11.2 ± 5.8	NS
PPI (u/ml)	29.8± 15.9	29.8 ± 18.6	NS
HOMA	2.9 ±1.6	2.6 ± 1.5	NS
Visfatin(ng/ml)	25.6±2.6	9.8 ± 1.2	<0.001

BMI: Body mass index, FBG: fasting blood glucose, PPBG: post prandial blood glucose, TG: triglyceride, LDL: low density lipoprotein cholesterol, VLDL: very low density lipoprotein cholesterol, HDL: high density lipoprotein cholesterol, CRP: high sensitive C- reactive protein, Lp a: lipoprotein a, FI: fasting insulin, PPI: post prandial insulin, HOMA: homeostasis model assessment. Data are presented as mean ± SD. NS: nonsignificant. GROUP 1: hyperlipidemic group, Group 2: normolipidemic control group

Table 2. The correlation analysis of all hyperlipidemic patients

	CRP	Homocysteine	HOMA	Visfatin	TG	BMI	LDL-C
CRP	1				p<0.05 r=0.282	p<0.05 r=0.264	
Homocysteine		1			p<0.05 r=0.27		
HOMA			1		p<0.01 r=0.380	p<0.05 r=0.301	
Visfatin				1	p<0.05 r=0.261		P<0.05 r=-0.307
TG	p<0.05 r=0.282	p<0.05 r=0.27	p<0.01 r=0.380	p<0.05 r=0.261	1		
BMI	p<0.05 r=0.264		p<0.05 r=0.301			1	
LDL-C				P<0.05 r=-0.307			1

BMI: Body mass index, TG: triglyceride, LDL-C: low density lipoprotein cholesterol, CRP: high sensitive C- reactive protein, HOMA: homeostasis   model assessment.

Table 3. Characteristics of HOMA < 2,7and HOMA 2,7   groups

	HOMA < 2.7 (n=30)	HOMA 2.7 (n=30)	P
Age (yr)	51.0±10.8	49.7 ± 8.8	NS
BMI (kg/m^2)	29.8± 4.5	31.1 ± 3.7	NS
Waist circumference (cm)	88.4± 2.0	92.4 ± 5.2	NS
Body fat (%)	35.9± 6.1	36.3 ± 7.6	NS
FBG (mg/dl)	93.0± 17.0	99.1 ± 7.6	NS
PPBG (mg/dl)	111.0± 20.3	124.9 ± 22.7	<0.02
Cholesterol(mg/dl)	252.4± 29.6	241.1 ± 51.3	NS
TG (mg/dl)	233.4 ± 29.0	318.8 ± 15.6	<0.05
LDL-C(mg/dl)	163.5 ± 35.0	143.2 ± 38.2	<0.05
HDL-C (mg/dl)	45.1 ± 11.7	43.7 ± 10.2	NS
Uric acid (mmol/L)	4.0± 1.3	4.2 ± 1.8	NS
CRP (mg/dl)	3.8± 1.8	4.1 ± 2.1	NS
Homocysteine (mol/L)	11.6± 5.9	13.5 ± 7.6	NS
Lp a (mg/dl)	325.3± 64.9	465.5 ± 50.5	NS
FI (u/ml)	12.0± 6.1	11.2 ± 5.8	NS
PPI (u/ml)	23.1± 11.4	37.0 ± 17.1	<0.01
Visfatin(ng/ml)	19.9± 2.8	31.1 ± 2.2	<0.05

BMI: Body mass index, FBG: fasting blood glucose, PPBG: post prandial blood glucose, TG: triglyceride, LDL: low density lipoprotein cholesterol, VLDL: very low density lipoprotein cholesterol, HDL: high density lipoprotein cholesterol, CRP: high sensitive C- reactive protein, Lp a: lipoprotein a, FI: fasting insulin, PPI: post prandial insulin, HOMA: homeostasis model assessment.
Data are presented as mean ± SD. NS: nonsignificant.

the same group were statistically higher than the group with HOMA < 2,7(respectively p < 0,01 and p < 0,02).

DISCUSSION

Studies on adipose tissue reveal that this tissue is not only an energy storing but an endocrine organ that secretes a variety of adipokines (Shah et al 2008, Grundy 2004). With the discovery of new adipokines, our understanding of the connection between adiposity and the metabolic syndrome, T2DM, impaired insulin sensitivity and obesity has improved (Bakhai, 2008, Hofso et al., 2009). Visfatin is a recently discovered adipokine that was shown to mimic the effect of insulin (Fukuhara 2005). Subsequent studies reported conflicting results with regard to its relation with adiposity, subcutaneous or visceral fat and insulin resistance suggesting that its role in the development of obesity and insulin resistance remains unclear.

It was reported that serum visfatin level correlated positively to HDL-C and apolipoprotein A1, the major component of HDL (Smith et al. 2005). In the study of Pagano, obese group that had a significantly lower level of HDL-C and higher level of triglycerides showed a significantly lower level of visfatin compared to the lean group(Pagano et al., 2006). In another study visfatin correlated positively with HDL-C and negatively with triglyceride (Wang et al., 2007). They suggeted that the relation between visfatin and lipid profile may be explained in the light of the cytosolic function of visfatin as a nicotinamide phosphoriboslytransferase, an enzyme involved in nicotinamide adenine dinucleotide (NAD) biosynthesis, which plays an important role as energy and signal transducer.

In the Chen's study, visfatin correlated positively with HDL-C levels and correlated negatively with LDL-C levels in the female subjects (Chen et al., 2007). As inhibition of cholesterol ester protein increases HDL-C level and decreases LDL-C levels, the authors proposed an explanation of visfatin in cholesterol homeostasis to be via inhibition of cholesteryl ester transfer protein.

Sun et al. showed that triglyceride correlated with serum visfatin levels and the correlation was independent of age and body fat. Moreover they also demonstrated that short term overfeeding resulted in a significant reduction of serum visfatin concentrations (Sun et al., 2007).

To explore the link between visfatin and lipid metabolism we analysed the relation of plasma level of

visfatin with some parameters of adiposity, insulin resistance and the circulating blood lipid profile in a group of Turkish population. In our hyperlipidemic patients we found that serum visfatin levels were statistically higher than our normolipidemic subjects. The visfatin levels of the hyperlipidemic group were positively correlated with triglyceride and negatively correlated with LDL-C levels. As we classified our patients as insulin sensitive or resistant (with HOMA < 2.7 and HOMA 2.7 respectively), insulin resistant group had higher visfatin, triglyceride levels but lower LDL- C levels. In concordance with our results, in the literature negative correlation was obtained between serum visfatin and LDL-C levels. This result may be explained by visfatin effect via inhibition of cholesterol ester protein which increases HDL-C level and decreases LDL-C levels (Chen et al., 2007). We were not be able to demonstrate the positive correlation between serum visfatin and HDL-C levels, previously shown in the literature (Chen et al., 2007, Smith et al., 2006, Wang et al., 2007). This discrepancy may be explained by the similarity of low HDL-C levels of both our hyperlipidemic and control groups and both the patients who have and do not have insulin resistance. It was shown that distinctively low HDL-C levels are found in Turkish population (Onat et al., 2003, Akın et al., 1986). The positive correlation between serum visfatin and TG levels, as we demonstrated was also determined recently (Sun et al., 2007). But Wang et al. found negative correlation between serum visfatin and TG levels and proposed that their observations might be associated with NAD metabolism (Wang et al., 2007). The discrepancy of his and our results may be explained by the samples obtained from either fasting or nonfasting state and by the study groups which were obese or non-obese. NAD metabolism in Turkish population may also be a matter of interest. It may be speculated that the regulation of visfatin at physiological conditions in humans may differ from pathological conditions.

After Fukuhara had shown a strong correlation between plasma visfatin and visceral fat mass in humans (Fukuhara et al., 2005), some authors also found an elevated concentration of visfatin in obese subjects (Haider et al., 2006, Wang et al., 2007, Zahorska-Markiewicz et al., 2007), and demonstrated positive correlation between plasma visfatin levels and BMI of the pateints (Berndt et al., 2005, Sandeep et al., 2007, Li et al., 2006).

It is still unclear whether circulating visfatin levels are associated with increased visceral-subcutaneous fat or increased total fat mass. In our hyperlipidemic patients we could not demonstrate any correlation between serum visfatin levels and anthropometric parameters, such as BMI, body fat or waist circumference. As waist circumference and waist hip ratio are good surrogates of visceral fat, we would expect that visfatin levels of our patients would correlate with waist circumference. Because in our hyperlipidemic patients all the anthropom-

etric parameters, such as visceral or total fat parameters, were significantly higher than our control subjects, this may be the reason why we could not show that correlation.

We also found positive correlation between CRP, homosistein, HOMA and TG levels, also BMI and CRP levels of hyperlipidemic patients, in the group where serum visfatin levels were found to be statistically high. These results may confirm that elevated lipid levels and obesity, as well as insulin resistance are linked together with cardiovascular morbidity, as shown by the presumed risk factors such as CRP, homosisteine.

Visfatin levels were found to be increased in T2DM (Hammarstadt et al., 2006, Sandeep et al., 2007, Chen et al., 2006) and gestational DM (Lewandowski et al., 2007), but Berndt found no significant correlation between plasma visfatin concentrations and fasting glucose and insulin concentrations (Berndt et al., 2005). In a study low plasma visfatin levels were demonstrated in patients with T2DM suggesting the dysregulation of visfatin in biosynthesis or in response to hyperglycemia, hyperinsulinemia in state of diabetes (Li et al., 2006). It may also be suggested that visfatin compensates for the impairment of insulin action in the early stage of development of insulin resistance (Zahorska-Markiewicz et al., 2007) . Furthermore, it was also hypothesized that visfatin may be released from dying adipocytes, raising the possibility that it may be released through apoptosis of adipocytes rather than direct mechanistic or metabolic effect (Sandeep et al., 2007). In our study we did not find any correlation between serum visfatin levels and glucose and insulin levels (either fasting or post prandial) in hyperlipidemic patients, but in our insulin resistant group we found significantly higher visfatin levels than those patients who did not have insulin resistance. In this insulin resistant group postprandial glucose and posrprandial insulin levels were also statistically high. We think that if visfatin has an effect on insulin resistance, it may be clarified by further studies.

It may be said that insulin resistance was the reason behind the relation between visfatin and lipid metabolism. When we compared our hyperlipidemic patients with normolipidemic ones, we found higher visfatin levels, but HOMA levels were statistically indifferent (statistically insignificantly higher in hyperlipidemic patients). But in our insulin resistant group visfatin levels were also higher than in the group where insulin resistance were not present. We may speculate that hyperlipidemia may increase visfatin levels, but if insulin resistance was added to hyperlipidemia visfatin levels were augmented.

In summary, we tried to point out the relationship of the interesting protein, visfatin between lipid disorders, obesity, insulin resistance and metabolic syndrome. It is surprising that there is no certainty on the regulation and action of visfatin on these various metabolic events, in the last 10 years. The significant associations positively with triglycerides and negatively with LDL-C, suggest that

visfatin have impact on lipid metabolism in Turkish population. Further studies are warranted.

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