The Relation Between Metabolic Parameters, Some Cardiovascular Risk Factors and Visfatin in Hyperlipidemic Female Patients

Hiperlipidemik Kadın Hastalarda Visfatinin Metabolik Parametreler ve Bazı Kardiyovasküler Risk Faktörleri ile İlişkisi

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ABSTRACT Objective: Hyperlipidemia is a modifiable major risk factor in primary and secondary prevention of cardiovascular diseases. Visfatin, predominantly expressed and secreted by adipose tissue in both humans and mice, is shown to play a regulatory role in lipid metabolism. The relationship between visfatin and metabolic parameters, insulin resistance and obesity have only recently begun to be examined. In our study, we intended to show the relation of visfatin with metabolic parameters and some cardiovascular risk factors in hyperlipidemic female patients. **Material and Methods:** The study included 60 hyperlipidemic female patients. Twenty-six of the patients were nonobese and 34 of them were obese. As well as making physical and antropometric examinations, fasting plasma glucose and insulin, post prandial plasma glucose and insulin, lipid profile, uric acid, homocysteine, C-reactive protein and visfatin levels were measured in all female subjects. **Results:** In our nonobese hyperlipidemic and obese hyperlipidemic groups, plasma visfatin levels were not found to be different. In the obese group only serum uric acid levels were significantly high. In nonobese hyperlipidemic group positive correlations were found between visfatin and trigyceride levels, homeostasis model assessment insulin resistance index. We also demonstrated negative correlations between visfatin levels and low density lipoprotein cholesterol levels in our obese hyperlipidemic group. **Conclusions:** In conclusion, we may speculate that visfatin has a role in lipid abnormalities. But it may not have a role in metabolic parameters, and some cardiovascular risk factors such as uric acid, homocysteine, C- reactive protein, Lipoprotein a in hyperlipidemic subjects.

Key Words: Obesity; atherosclerosis; nicotinamide phosphoribosyltransferase; hyperlipidemia; ınsulin resistance

ÖZET Amaç: Kardiyovasküler hastalıkların primer ve sekonder korumasında hiperlipidemi değiştirilebilir majör bir risk faktörüdür. Esas olarak fare ve insanlarda adipoz dokuda eksprese edildiği ve salgılandığı gösterilen visfatinin lipid metabolizmasında regülatör bir rolü olduğu gösterilmiştir. Metabolik parametreler, insülin rezistansı ve obezite ile visfatinin ilişkisi daha yeni yeni araştırılmaktadır. Bu çalışmada visfatinin hiperlipidemik kadın hastalarımızda metabolik parametreler ve bazı kardiyovasküler risk faktörleri ile ilişkisini göstermeyi planladık. **Gereç ve Yöntemler:** Çalışmamıza 60 hiperlipidemik kadın hastayı aldık. Hastaların 26'sı nonobez, 34'ü obez idi. Tüm kadın hastalarda fizik muayene ve antropometrik ölçümlere ek olarak açlık kan şekeri, açlık insülin, tokluk kan şekeri, tokluk insülin, lipid profili, ürik asit, homosistein, C-reaktif protein ve visfatin seviyelerine bakıldı. **Bulgular:** Hepsi hiperlipidemik olan nonobez ve obez gruplarımızda, plazma visfatin seviyeleri farklı bulunmadı. Sadece, obez grupta serum ürik asit seviyeleri belirgin olarak yüksekti. Nonobez hiperlipidemik grupta visfatin seviyeleri ile trigliserid ve insülin rezistansı ölçümü olan HOMA-IR (homeostasis model assessment) arasında pozitif korelasyon saptandı. Ayrıca obez hiperlipidemik hastalarımızda visfatin seviyeleri ile düşük dansiteli lipoprotein kolesterol, homosistein, C- reaktif protein seviyeleri arasında negatif korelasyon bulduk. **Sonuç:** Sonuç olarak visfatinin lipid abormalliklerinde rolü olduğunu söyleyebiliriz. Ama hiperlipidemik kişilerde metabolik parametreler ve ürik asit, homosistein, C- reaktif protein ve lipoprotein a gibi kardiyovasküler risk faktörleri ile ilişkisi olmayabilir.

Anahtar Kelimeler: Şişmanlık; ateroskleroz; nikotinamid fosforiboziltransferaz; hiperlipidemiler; insülin direnci

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Adipose tissue has recently been identified as an endocrine organ. It releases a lot of adipokines such as tumor necrosis factor-α (TNF-α), plasminogen activator inhibitor type 1 (PAI-1), non-esterified fatty acids, prostaglandins, leptin, adipsin, adiponectin, resistin, angiotensinogen, interleukin 1 and 6.[1-4] In 2005 Fukuhara isolated a novel adipokine named visfatin.[5] This cytokine was identical to Pre-B cell colony-enhancing factor (PBEF). PBEF was originally cloned as a putative cytokine shown to enhance the maturation of B cell precursors in the presence of IL-7 and stem cell factor.[6] Revollo et al.[7] determined biochemically that the mouse PBEF gene product encodes a nicotinamide phosphoribosyltransferase (Nampt) enzyme, capable of modulating intracellular NAD levels. More recently, several groups have reported the crystal structure of Nampt/PBEF/visfatin and they all show that this protein is a dimeric type II phosphoribosyltransferase enzyme involved in NAD biosynthesis.[8,9]

Visfatin is preferentially expressed in visceral fat[5]. Increased body fat, especially visceral fat, is closely linked to insulin resistance.[10] The relationship between visfatin and metabolic parameters such as insulin resistance and dyslipidemia, and also adiposity have only recently begun to be understood. The precise role of visfatin in insulin resistance is not clear. It was demonstrated that both visfatin and insulin had similar affinity for the insulin receptor.[5] However under physiological conditions, the circulating levels of visfatin are lower than insulin. Thus, despite the insulin sensitizing action of visfatin in vitro, visfatin was said to be a biomarker of the insulin resistant state as it is predominantly secreted in visceral adipose tissue, site of insulin resistance. Contrary to the most putative hypothesis, visfatin treatment did not promote insulin resistance, but actually exhibited insulin mimetic properties resulting in a glucose lowering effect.[11]

It is stil unclear whether circulating visfatin levels are associated with increased visceral fat mass or increased total fat mass. There are conflicting results about visfatin and obesity.[12-18] A number of studies showed that visfatin is linked with circulating lipid parameters such as high density lipoprotein cholesterol (HDL-C), low density lipoprotein cholesterol (LDL-C) and triglyceride (TG).[17,19-22]

We thought that it would be interesting to examine metabolic and anthropometric parameters, cardiovascular risk factors in hyperlipidemic patients, so in this study, in order to seek answers about the relation of visfatin with lipid profile, metabolic parameters and some cardiovascular risk factors, we investigated visfatin levels and above mentioned parameters in hyperlipidemic patients by grouping them as nonobese and obese.

MATERIAL AND METHODS

SUBJECTS

Our subject population was composed of 60 females aged from 25-65 years. They were selected among the patients who visited the outpatient Clinic of Ankara Education and Research Hospital from July 2008 to October 2008. We chose the subjects who had only lipid anormalities in their blood analysis, whose physical examinations and other blood analysis parameters were normal.. Although no gender difference was determined in visfatin levels[14,17] we examined only females in order to obtain a homogenous group. 26 of them were nonobese and 34 of them were obese.

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

Patients with male gender, hypertension, diabetes mellitus, glucose intolerance, conditions which may effect metabolic parameters (such as tiroid 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, whereas hip was measured at the greatest circumference around the buttocks, by a non elastic mesure. Waist to hip ratio (WHR) were calculated.

Body mass index (BMI) was calculated as weight in kilograms divided by the square of height in meters. The reference interval of BMI is defined as obesity as a BMI of more than 30 kg/m^2.

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

This sudy was performed according to the Helsinki decleration 2008. **The local ethics committee approved this study and all the subjects gave written informed consent.**

LABORATORY METHODS

Plasma glucose, total cholesterol, TG and HDL-C concentrations were determined by enzymocalorimetric spectrophotometric method in a Roche/Hitachi molecular PP autoanalyser. 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 resistance was calculated from the fasting plasma insulin (μunite / ml) x fasting plasma glucose (mmol/l)/22. 5 formula as homeostasis model assessment (HOMA).

Homocysteine concentrations were determined according to the method of HPLC using Agilend 1100 device. High sensitivity C-reactive protein (CRP) was measured by immunnephelometric tests by Beckman-Cutler device. Uric acid was measured by calorimetric, Lp a and microalbumin were measured by nephelometric methods.

For the measurements of visfatin, after fasting blood samples were drawn, they 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 were presented as mean ± SD. Student t- test was used to compare the groups in a parametric way. One way variation analysis (ANOVA) 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 26 hyperlipidemic nonobese (Group 1), and 34 hyperlipidemic obese female patients (Group 2). All the demographic and laboratory findings of the groups were compared and demonstrated in Table 1.

The age, the levels of FBG, PPBG, FI, PPI, total cholesterol, triglceride, LDL and HDL- cholesterol, Lp-a, hsCRP, homocysteine and visfatin were found to be statistically insignificant in the obese and nonobese hyperlipidemic patients. Uric acid levels of the obese group was also significantly high ($p< 0.05$) (Table 1).

In order to seek correlations between all our parameters (age, BMI, total body fat, waist, hip circumference, WHR, FBG, PPBG, FI, PPI, total cholesterol, triglceride, LDL and HDL- cholesterol, Lp-a, hsCRP, homocysteine and visfatin) we made correlation analysis in obese and nonobese groups. In our nonobese patients we found positive correlation between the levels of visfatin and TG, HOMA-IR ($r= 0.453$, $r= 0.542$, $p< 0.02$, $p< 0.01$ respectively) There were also positive correlation between homocysteine levels and LDL-C, uric a levels ($r= 0.453$, $r= 0.505$, $p< 0.02$, $p< 0.01$ respectively), and positive correlation between hsCRP and uric acid levels($r= 0.440$, $p< 0.05$). HOMA-IR was also positively correlated with TG levels of the nonobese hyperlipidemic patients($r= 0.673$, $p< 0.01$). In our obese hyperlipidemic patients there were negative correlation between visfatin and LDL-C ($r=-0.419$, $p< 0.05$). We could not find any positive or negative correlations among any other parameters in nonobese and obese patients.

TABLE 1: Characteristics of Group 1 ve Group 2.

	Group 1 (n= 26)	Group 2 (n= 34)	P
Age (yr)	48.6 ± 10.1	51.7 ± 9.4	NS
FBG (mg/dl)	92.7 ± 17.5	98.6 ± 8.7	NS
PPBG (mg/dl)	114.7 ± 22.1	120.5 ± 22.8	NS
Cholesterol (mg/dl)	248.4 ± 45.6	245.5 ± 39.3	NS
TG (mg/dl)	266.7 ± 58.4	283.3 ± 14.4	NS
LDL-C (mg/dl)	158.7 ± 38.5	149.6 ± 37.3	NS
HDL-C (mg/dl)	46.2 ± 12.5	43.0 ± 9.4	NS
Uric acid (mmol/L)	3.7 ± 1.5	4.5 ± 1.5	<0.05
CRP (mg/dl)	4.5 ± 1.9	4.4 ± 2.0	NS
Homocysteine (µmol/L)	12.6 ± 8.2	12.5 ± 5.7	NS
Lp a (mg/dl)	465.8 ± 31.9	341.6 ± 48.4	NS
FI (µu/ml)	11.2 ± 5.9	12.7 ± 6.2	NS
PPI (µu/ml)	23.5 ± 13.2	34.3 ± 16.3	NS
HOMA-IR	2.6 ± 1.5	3.1 ± 1.6	NS
Visfatin (ng/ml)	31.2 ± 2.6	21.6 ± 2.0	NS

Data are presented as mean ± SD. NS: nonsignificant. Group 1: hyperlipidemic nonobese females, Group 2: hyperlipidemic obese females.

FBG: fasting blood glucose, PPBG: post prandial blood glucose, TG: triglyceride, LDL-C: 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-IR: homeostasis model assessment-insulin resistance.

DISCUSSION

Human visfatin gene is located at 7q22.3, which has been reported to be a linkage region for insulin resistance syndrome related phenotypes such as hyperinsulinemia, obesity-related traits, impaired glucose tolerance, dyslipidemia, and hypertension.[23] It was stated that a single nucleotide polymorphism at three different loci of visfatin gene was associated with TG and total cholesterol levels,[24] and a specific variant of visfatin gene was associated with cholesterol levels.[25] These reports imply that visfatin may play an important role in lipid metabolism. So, we decided to test the possible link between visfatin and metabolic parameters, cardiovascular risk factors in hyperlipidemic subjects.

In our hyperlipidemic patients obese or nonobese, visfatin levels were found to be similar. Some authors found elevated plasma visfatin levels in obese subjects,[8,12-15] but plasma visfatin level was also shown to be reduced in obesity.[17] Our result may indicate that visfatin may have a role in hyperlipidemia, but if hyperlipidemia exists visfatin levels does not differ, when obesity is concerned. Moreover; visfatin was shown to be down regulated by short- term overfeeding,[18] we think that it is very difficult to interpret the levels of visfatin in our overfed obese and hyperlipidemic subjects.

Keeping in mind that HDL-C plays an important role in estimating the risk for cardiovascular disease and increasing levels of HDL-C provide a protective effect, Smith et al. reported that serum visfatin level correlated positively to HDL-C and apolipoprotein A1, the major component of HDL, in Asian Indians.[21] In the study of Pagano et al., the relation between visfatin and lipid profile was not analysed but, his 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.[17] Wang et al. supported these findings; as in their study visfatin correlated positively with HDL-C and negatively with triglyceride suggesting that this benefical lipid profile might be associated with NAD metabolism.[8]

Similar to our nonobese hyperlipidemic subjects, Sun et al. had found positively correlated TG levels with visfatin levels of their healthy young men.[18] We found positive correlation between visfatin and TG in our only hyperlipidemic otherwise healthy nonobese patients, but not in our obese hyperlipidemic patients. As elevated serum TG is agreed to be a marker of the metabolic syndrome, our results warrent explanation.

We also demonstrated that visfatin levels were negatively correlated with LDL-C levels in obese hyperlipidemic patients. Like our study, Chen et al found no correlation between visfatin levels and anthropometric parameters in male subjects, but demonstrated negative correlation with LDL-C levels and visfatin in female subjects[20]. As inhibition of cholesterol ester protein increases HDL-C level and decreases LDL-C levels, we may explain our results about LDL-C via inhibition of cholesteryl ester transfer protein. As our subjects were female, we think that estrogen may modulate the effect of cholesterol ester protein.

We were not able to show the correlation between HDL-C and visfatin like some recent studi-

es,[8,17,20] it may be related to the comparably low levels of HDL-C in our population. The reason why different lipid parameters were correlated with visfatin levels in our nonobese and obese hyperlipidemic patients, warrents explanation. This puzzle may be clarified by further and larger studies.

Visfatin was highly expressed in visceral, compared with subcutaneous adipose tissue.[5] As visceral adipose tissue is strongly associated with insulin resistance, we thought that if a correlation between visfatin plasma concentrations and/or visfatin gene expression in visceral adipose tissue existed, we may demonstrate a relation between HOMA-IR, insulin levels and visfatin. However we could not show any difference in our hyperlipidemic obese or hyperlipidemic nonobese groups as insulin resistance parameters were concerned, like the study of Pagano et al.[17] We also did not determine any correlation between visfatin and insulin resistance paremeters in our obese hyperlipidemic subjects, but there was positive correlation between visfatin levels and HOMA-IR in nonobese hyperlipidemic subjects, but not in obese hyperlipidemic ones. These results do not clarify the area of conflicting results about visfatin and insulin resistance but we can say that visfatin may play a role in lipid metabolism and insulin resistance, but the extent and the mechanism of this role needs to be examined.

We did not find correlation between BMI and visfatin in our hyperlipidemic subjects. As visfatin is shown to be correlated with visceral fat, this result did not surprise us, but we did not find any correlation between WHR, waist circumference and body fat like the study of Berndt et al.[14] The lack of an association between WHR, waist circumference, total body fat, BMI and plasma visfatin concentrations in our study may suggest that circulating visfatin concentrations is not associated with the place of fat accumulation or might also not related to increased fat mass in hyperlipidemic subjects. We wonder if we can speculate that in hyperlipidemic patients obesity did not make any difference.

Recently uric acid,[26] CRP,[27] homocysteine[28] and Lp a[29] have been accepted to be cardiovascular risk factors. We also investigated the relation between visfatin and these risk factors. Only uric acid levels of the obese hyperlipidemic group was significantly high. We did not demonstrate any positive or negative correlation between visfatin and uric acid or CRP or homocysteine or Lp a in our obese or nonobese hyperlipidemic subjects. As uric acid levels may be related to overfeeding we may say that cardiovascular risk of the hyperlipidemic patients may not differ with obesity.

In conclusion we speculate that the role visfatin in obesity and insulin resistance is complicated, but we can say that it may play a role in lipid metabolism. Our data do not support a role for visfatin in the development of insulin resistance, obesity and in the presence of a number of cardiovascular risk factors in hyperlipidemic subjects.

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