CORRELATES OF VISCERAL AND SUBCUTANEOUS FAT THICKNESS IN NON-DIABETIC OBESE AND MORBIDLY OBESE PATIENTS

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ABSTRACT

Background*: To determine the correlates of visceral and subcutaneous fat thickness in non-diabetic obese and morbidly obese patients*

Methods*: A total of 31 obese female outpatients composed of morbidly obese (n=16, BMI of ≥40kg/m²) and obese (n=15, BMI of 30-39.9kg/m2) patients were included in the present study. Data on age, anthropometrics, blood biochemistry, HOMA-IR, carotid intima-media thickness (CIMT) were recorded in each subject as were plasma resistin (μg/L) and visfatin (μg/ml) levels, epicardial, subcutaneous and abdominal fat thickness (mm). Correlates of visceral and subcutaneous fat thickness were determined via linear regression models with inclusion of severity of obesity, insulin resistance, plasma resistin and visfatin levels and CIMT as variables.*

Results*: Epicardial fat thickness (mm) was 3.1(1.0-10.20) and 8.8(2.60-13.0), CIMT (mm) was 5.8(4.7-8.9) and 5.9(4-8.6), abdominal fat thickness (mm) was 10.8(7.8-16.1) and 13.2(8.7-16.5), subcutaneous fat thickness(mm) was 43.8(28.4-62.9) and 57.4(39.5-72.7), plasma resistin levels (μg/L) were 8.5(4.7-38.1) and 10.8(0.7-26.4) and plasma visfatin levels (μg/ml) were 55.5(5.1-209.5) and 78.2(4.7-228) in obese and morbidly obese patients, respectively. Linear regression analysis revealed that being morbidly obese was likely to increase epicardial fat thickness by 4.33mm(p=0.004) compared with obesity, while for each 1 unit increase in HOMA levels, subcutaneous fat thickness was likely to decrease by 1.16mm(p=0.009).*

Conclusion*: In conclusion, our findings revealed that neither plasma levels for resistin and visfatin nor CIMT correlated with visceral or subcutaneous fat thickness in non-diabetic obese females, while increase in subcutaneous and epicardial fat thickness values were noted with decrease in HOMA-IR and the presence of morbid obesity, respectively.*

Keywords*: Obesity, visceral fat, subcutaneous fat, visfatin, resistin, insulin resistance.*

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Introduction

Aside from being a major risk factor for type 2 diabetes as an energy reservoir, it has recently been appreciated that adipose tissue, mainly the visceral fat, acts as an important secretory organ producing a range of bioactive proteins called adipokines, which could be involved in the pathogenesis of metabolic complications related to obesity[1-3].

Adipose tissue has been related to an increase in cardiovascular risk and morbi-mortality via its ability to produce and release a wide variety of pro-inflammatory cyto-chemokines which play important regulatory functions in a variety of biological processes, including atherosclerosis, apart from their role in insulin resistance[2-5].

Abdominal visceral adipose tissue has been shown to produce bioactive molecules including

visfatin[6], while past reports in patients with overt cardiovascular disease (CVD) have demonstrated a pattern of expression of various inflammatory mediators in epicardial fat similar to that of abdominal visceral adipose tissue such as interleukin-6 (IL-6), tumor necrosis factor-alpha (TNF-a), monocyte chemo-attractant protein 1 (MCP-1), and resistin, and of protective anti-inflammatory and anti-atherogenic proteins, such as adiponectin[2,7-9].

Resistin is a peptide hormone produced by mature adipocytes and regulates whole-body insulin sensitivity which is more highly expressed in visceral white fat than in subcutaneous fat[10]. Another adipokine, visfatin, has been characterized as a peptide expressed in and secreted both from visceral and subcutaneous adipose tissue[2,6] while an increase in both its expression and plasma concentration was noted with increasing levels of obesity[11].

It is recognized that visceral fat contributes to metabolic disorders by altering levels of adipocyte-derived cytokines which are also considered to affect the pathogenesis of arteriosclerosis[12].

Epicardial fat, clinically related to abdominal visceral adiposity[13], was reported to be associated with insulin resistance, increased cardio-metabolic risk, inflammatory markers and coronary artery disease (CAD), and subclinical target organ damage such as carotid intima-media thickness (CIMT) or carotid plaque[14-16].

Although published reports suggest the potential role of adipose tissue as a reliable indicator of cardiovascular risk[17], the clinical relationships between visceral adiposity and inflammatory adipocytokine levels in obesity are not completely understood[2] as is the association of visfatin and resistin levels to and diabetes, obesity, or dyslipidemia that revealed inconsistent results[18,19].

Therefore, the present study was designed to determine the correlates of visceral and subcutaneous fat thickness in non-diabetic obese and morbidly obese patients based on severity of obesity, insulin resistance, plasma resistin and visfatin levels and CIMT.

Methods

Study population

A total of 31 premenopausal obese female outpatients composed of morbidly obese (n=16, BMI of ≥40 kg/m^2) and obese (n=15, BMI of 30-39.9 kg/m^2) patients were included in the present study upon their admission to outpatient clinics in the Department of Endocrinology and Metabolic Disorders at Uludag University Faculty of Medicine. Any individuals with a significant chronic disease or under treatment with medications that might affect body weight and body water content including anti-obesity medications, steroids, thyroid hormone, antipsychotics, antidepressants, anxiolytics, laxatives, oral contraceptives, beta-blockers, diuretics, oral hypoglycemic agents, insulin and hormone replacement therapy were excluded from the study.

Written informed consent was obtained from each subject following a detailed explanation of the objectives and protocol of the study which was conducted in accordance with the ethical principles stated in the "Declaration of Helsinki" and approved by the institutional ethics committee.

Study parameters

Data on age, anthropometric measurements (height, weight, body mass index (BMI), waist circumference, hip circumference and waist-to-hip ratio (WHR)), blood biochemistry (fasting blood glucose, serum lipids, AST, ALT, urea, creatinine, insulin and TSH levels), 75 g oral glucose tolerance test (OGTT), homeostasis model assessment insulin resistance index (HOMA-IR) values, CIMT, plasma resistin (μg/L) and visfatin (μg/ml) levels, epicardial fat thickness (mm), subcutaneous fat thickness (mm) and abdominal fat thickness (mm) were recorded in the obese and morbidly obese groups. Correlates of visceral (epicardial and abdominal) and subcutaneous fat thickness were determined via linear regression models with inclusion of severity of obesity, insulin resistance, plasma resistin and visfatin levels and CIMT as the variables.

Anthropometric measurements

Weight and height were measured in light clothing without shoes. BMI was calculated by dividing weight in kilograms by the square of height in meters. The waist circumference was measured at a level midway between the lowest lateral border of the ribs and the uppermost lateral iliac crest with the subjects standing and breathing normally. All anthropometric measurements were performed twice and the mean value of the two measurements was chosen for analyses. The WHR was then calculated.

Measurement of subcutaneous and abdominal fat thickness

All abdominal ultrasound procedures and measurements of visceral and subcutaneous fat were performed by the same blinded diagnostic imaging specialist at the same radiology center (Bilson Diagnostic Imaging Center, Bursa) using a 3.5 MHz multi-frequency transducer (broad band). Subcutaneous fat thickness was measured using ultrasonography from anterior abdominal wall, while amount of visceral fat was determined via measurement of mesenteric fat tissue thickness. Ultrasound-determined subcutaneous fat was defined as the distance between the skin and external face of the rectus abdominis muscle, and visceral fat was defined as the distance between the internal face of the same muscle and the anterior wall of the aorta.

Measurement of epicardial fat thickness

Epicardial fat thickness was determined echocardiographically. All patients underwent 2D Doppler echocardiography with a Vivid 7 (General Electric, Horten, Norway) echocardiographic machine equipped with a 3.5 MHz transducer. Echocardiographically, epicardial fat is generally identified as the relatively echo-free space between the outer wall of the myocardium and the visceral layer of the pericardium; its thickness is measured perpendicularly on the free wall of the right ventricle at end-systole in 3 cardiac cycles. Because it is compressed during diastole, the EF thickness is best measured at end-systole at the point on the free wall of the right ventricle at which the ultrasound beam is oriented in a perpendicular manner, using the aortic annulus as an anatomic landmark. The average value of 3 cardiac cycles from each echocardiographic view was determined.

CIMT measurement

CIMT was measured via high resolution Duplex scanner (model Vivid 7 Siemens ACUSON X150™ ultrasound system) with probe at a frequency of 10 MHz for B scan based on average of three consecutive measurements.

Insulin resistance

Insulin resistance was calculated using HOMA-IR, according to the following formula: fasting plasma glucose (mmol/L) x fasting serum insulin (mU/mL)/22.5.

Assessment of plasma levels for visfatin and resistin

All of the blood samples were drawn after overnight fasting and centrifuged for 15 minutes at 1000 x g within 30 minutes of collecting. Obtained serum samples stored in aliquots at - 20°C for subsequent visfatin and resistin measurements. RayBio® Visfatin Enzyme Immunoassay (EIA) Kit (RayBiotech, Inc, USA) was used for determination of visfatin in human serum, with an intra-assay CV of <10 %, inter assay CV of 15%. This kit is an in vitro quantitative assay for detecting Visfatin peptide based on the principle of Competitive Enzyme Immunoassay. In this kit the minimum detectable concentration of Visfatin is 0.778 ng/ml, and the detectıon range is 0.1-1,000 ng/ml. Resistin was measured using a commercially available Human Resistin Platinum ELISA kit (eBioscience, Inc. USA) according to the manufacturer's instructions. This kit is an enzyme-linked immunosorbent assay for the quantitative detection of human Resistin.The inter-assay variability is 8.1% and the intra-assay variability is 5.1%.

Statistical analysis

Statistical analysis was made using computer software SPSS version 20.0.0.1 (SPSS Inc. Chicago, IL, USA). Student's t test was used for the analysis of parametric variables and Mann Whitney U test for the numerical variables not normally distributed. Correlates of visceral and subcutaneous fat thickness was determined using linear regression analysis with inclusion of obesity type, HOMA, CIMT, plasma resistin and visfatin levels in the regression model. Data were expressed as "median (min-max)" and percent (%) where appropriate. $p<0.05$ was considered statistically significant.

Results

Baseline characteristics

Baseline clinical and laboratory characteristics of patients are presented in Table 1. Median (min-max) values of HOMA were 3.4 (2.0-23.2) in obese and 3.9 (1.1-17.8) in morbidly obese patients.

Epicardial fat thickness (mm) was 3.1 (1.0-10.20) and 8.8 (2.60-13.0), carotid intima-media thickness (mm) was 5.8 (4.7-8.9) and 5.9 (4-8.6), abdominal fat thickness (mm) was 10.8 (7.8-16.1) and 13.2 (8.7-16.5), subcutaneous fat thickness (mm) was 43.8 (28.4-62.9) and 57.4 (39.5-72.7), plasma resistin levels (μg/L) were 8.5 (4.7-38.1)

and 10.8 (0.7-26.4) and plasma visfatin levels (μg/ml) were 55.5 (5.1-209.5) and 78.2 (4.7-228) in obese and morbidly obese patients, respectively (Table 1).

	Obese (n=15)	Morbidly Obese (n=16)
Age (years)	41.0 (26.0-46.0)	38.5 (23.0-49.0)
Systolic blood pressure (mmHg)	110.0 (100.0-150.0)	120.0 (100.0-150.0)
Diastolic blood pressure (mmHg)	70.0 (60.0-100.0)	75.0 (60.0-100.0)
Anthropometrics		
Height (cm)	160.0 (147.0-169.0)	160.0 (155.0-170.0)
Weight (kg)	94.0 (78.0-104.0)	122.6 (97.0-165.0)
Body massindex (kg/m2)	36.4 (32.5-39.1)	46.7 (40.4-62.1)
Body fat percentage *(%)*	42.0 (36.5-45.6)	46.5 (40.9-53.2)
Waist cimcumference (cm)	111.0 (92-120)	124.5 (110.0-178.0)
Hip cimcumference (cm)	123.0 (114.0-136.0)	141.5 (127.0-172.0)
Waist/hip ratio	0.9 (0.8-1.0)	0.9 (0.8-1.3)
Lipid parameters		
Total cholesterol (mg/dL)	179.0 (79.0-211.0)	188.0 (158.0-265.0)
HDL cholesterol (mg/dL)	44.0 (8.0-55.0)	44.5 (31.0-74.0)
LDL cholesterol (mg/dL)	110.0 (56.0-136.0)	124.5 (92.0-163.0)
Triglyceride (mg/dL)	127.0 (45.0-304.0)	129.5 (57.0-285.0)
Biochemical parameters		
AST *(IU/L)*	19.0 (12.0-33.0)	129.5 (57.0-285.0)
ALT *(IU/L)*	17.0 (12.0-55.0)	19.0 (6.0-63.0)
Urea *(mg/dl)*	24.0 (15.0-30.8)	22.0 (16.0-36.0)
Creatinine *(mg/dl)*	0.7 (0.4-0.9)	0.7 (0.5-0.9)
Uric acid *(mg/dl)*	4.3 (3.0-5.6)	4.5 (3.6-5.8)
Sodium *(mmol/L)*	139.5 (136.0-146.0)	139.0 (135.0-144.0)
Potassium *(mmol/L)*	4.2 (3.9-4.6)	4.2 (3.7-5.2)
Glycemic parameters		
HOMA	3.4 (2.0-23.2)	3.9 (1.1-17.8)
Fasting blood glucose *(mg/dl)*	90.0 (77.0-119.0)	94.5 (75.0-110.0)
Insulin *(μU/ml)*	16.8 (6.9-22.6)	16.7 (4.6-73.7)
OGTT baseline *(mg/dl)*	87.5 (74.0-107.0)	92.0 (77.0-129.0)
OGTT 2nd hour *(mg/dl)*	91.5 (75.0-165.0)	100.0 (78.0-227.0)
Epicardial fat thickness (mm)	3.1 (1.0-10.20)	8.8 (2.60-13.0)
Carotid intima-media thickness (mm)	5.8 (4.7-8.9)	5.9 (4-8.6)
Abdominal fat thickness (mm)	10.8 (7.8-16.1)	13.2 (8.7-16.5)
Subcutaneous fat thickness (mm)	43.8 (28.4-62.9)	57.4 (39.5-72.7)
Plasma resistin levels *(ng/ml)*	8.5 (4.7-38.1)	10.8 (0.7-26.4)
Plasma visfatin levels *(ng/ml)*	55.5 (5.1-209.5)	78.2 (4.7-228.0)
TSH *(mIU/ml)*	1.7 (0.6-4.6)	1.6 (0.7-6.3)
Data are shown as median(min-max).		

Table 1: Baseline characteristics.

Correlates of epicardial fat thickness

Linear regression analysis with inclusion of obesity type, HOMA, CIMT, plasma resistin and visfatin levels in the regression model revealed that being morbidly obese was the only variable that showed significant correlation to epicardial fat thickness which likely to increase epicardial fat thickness by 4.33 mm (p=0.004) compared with obesity (Table 2).

	Epicardial fat thickness				Subcutaneous fat thickness				Abdominal fat thickness			
	B	SEM	P	95% CI	B	SEM	P	95% CI	B	SEM	P	95% CI
Morbid obesity	4.33	1.32	**0.004**	2.61; 7.56	1.36	5.29	0.800	-9.75; 12.47	0.61	1.31	0.645	-2.14; 3.36
HOMA	0.24	0.14	0.099	-0.11; 0.41	-1.16	0.39	**0.009**	-1.99; -.033	0.15	0.11	0.219	-0.09; 0.39
Plasma resistin levels	0.11	0.07	0.138	-0.07; 0.25	-0.12	0.24	0.621	-0.63; 0.39	-0.06	0.06	0.352	-0.18; 0.07
Plasma visfatin levels	-0.02	0.01	0.192	-0.03; 0.02	0.03	0.04	0.476	-0.05; 0.10	0.00	0.01	0.879	-0.02; 0.02
CIMT	-1.21	0.58	0.052	-2.44; 0.01	-0.34	2.06	0.872	-4.66; 3.99	0.96	0.46	0.052	-0.01; 1.92
B: regression coefficient, CI: confidence interval, P: significance level, SEM: standart error of mean												

Table 2: Linear regression analysis for the correlates of visceral and subcutaneous fat thickness.

Correlates of subcutaneous fat thickness

Linear regression analysis with inclusion of obesity type, HOMA, CIMT, plasma resistin and visfatin levels in the regression model revealed that for each 1 unit increase in HOMA levels, subcutaneous fat thickness was likely to decrease by 1.16 mm (p=0.009), while none of the other variables showed a significant correlation to subcutaneous fat thickness (Table 2).

Correlates of abdominal fat thickness

Linear regression analysis with inclusion of obesity type, HOMA, CIMT, plasma resistin and visfatin levels in the regression model revealed that no significant association between abdominal fat thickness and the analyzed variables (Table 2).

Discussion

Our findings in obese and morbidly obese non-diabetic females revealed that morbid obesity had a positive linear correlation with epicardial fat thickness, while insulin resistance had a negative linear correlation with subcutaneous fat thickness. No significant correlation of visceral and subcutaneous fat thickness was noted to plasma levels for resistin and visfatin and also to CIMT.

Epicardial fat thickness has been reported to be significantly correlated with the severity of coronary artery stenosis in patients with CAD[20] and suggested to be significantly related to CIMT with prediction of CIMT better than other correlates of atherosclerosis[21]. Obesity, primarily abdominal obesity, was shown as a significant risk factor for atherosclerosis which increases the risk of clinical atherosclerotic diseases, and accelerates the progression of preclinical atherosclerosis[22].

In this regard, while not correlated directly with CIMT, positive linear correlation between morbid obesity and epicardial fat thickness in our study population with a likely increase in epicardial fat thickness by 0.004 mm in case of morbid obesity seems notable given the statement that visceral fat was strongly associated with obesity-related complications like Type 2 diabetes and CAD[5,23,24].

The presence of insulin resistance has been suggested to have an impact on response and association among inflammatory and subclinical markers of atherosclerosis, i.e. contributed to positive correlation between CIMT and visceral/subcutaneous fat ratio in obese adolescents submitted to an interdisciplinary intervention[5].

In this context, negative correlation between HOMA-IR and subcutaneous fat thickness in our study population seems in agreement with the significant reduction of visceral/subcutaneous fat ratio in non-insulin resistant than insulin resistant group reported in obese adolescents after one year of interdisciplinary hypoglycemic therapy[5]. Likewise, in a past study concerning the investigation of the relationship between the hypoglycemic effects of rosiglitazone and the alteration in body fat distribution in type 2 diabetic patients, it was reported that the more the body weight or subcutaneous fat thickness was increased, the better the hypoglycemic effect of rosiglitazone treatment[25]. This may suggests that the improvement in dyslipidemia or insulin resistance under hypoglycemic treatment in diabetic patients may be partly related to the increase in subcutaneous fat mass, alike to hypoglycemic effect[25].

In our study population neither plasma visfatin levels nor plasma resistin levels were noted to correlate with visceral or subcutaneous fat thickness. In fact, data from past studies on the role of these adipokines in insulin sensitivity and obesity yielded inconsistent results[18,19,26-28].

Our findings related to lack of significant correlation of plasma visfatin levels to visceral and subcutaneous fat thickness seem in line with the results of a past study indicated that circulating visfatin levels were not significantly related to cardiovascular risk variables such as obesity, blood pressure, lipid profile, and insulin resistance and were not different in comparisons between patients with coronary heart disease (CHD) and control subjects[27].

Our results are compatible with the recent observations based on investigation of a community-based sample which suggested that circulating visfatin may not be a useful clinical biomarker for metabolic traits[19]. Furthermore, no difference was reported in circulating visfatin levels between subjects with CHD and control subjects in a past study, although a recent study reported increased expression of visfatin in macrophages of human unstable carotid and coronary atherosclerosis[29].

Median value for epicardial fat thickness (8.8 mm) in our patients was comparable to previously reported amounts in morbidly obese patients that ranged between 5.2 and 9.4 mm (median 6.3)[2].

Notably, with regard to a past study indicating that plasma visfatin levels were significantly higher in morbidly obese than in lean controls (27.5 (9.8) vs. 13.0(4.3) ng/mL)[2], our findings revealed plasma much higher levels for visfatin both in obese (55.5 (5.1-209.5) ng/mL) and morbidly obese (78.2 (4.7-228) ng/mL) non-diabetic patients.

Likewise, given the similar levels for plasma resistin in the general population (4.3 (2.4) ng/mL) compared to obese patients (4.3 (0.15) ng/ml) reported in the literature[26], our findings revealed much higher levels for resistin both in obese (8.5 (4.7-38.1) ng/mL) and morbidly obese (10.8 (0.7-26.4) ng/mL) non-diabetic patients.

Hence much higher levels for both plasma visfatin and resistin, while similar levels for epicardial fat thickness in our study population with respect to previously reported ranges in obese patients might be attributed to the lack of obesity related comorbidities such as hypertension, diabetes mellitus or insulin-resistance and dyslipidemia[2] and seems notable given the statement that the role of epicardial fat in enhancing cardiovascular risk in obese was only sustained by the higher levels of pro-inflammatory proteins and adipocytokines in patients with greater epicardial fat thickness[2].

Additionally, lack of a relation of visfatin levels to visceral and subcutaneous fat thickness in our study population despite the high levels of plasma visfatin seems in agreement with the previously reported correlation of visceral visfatin mRNA expression and visfatin plasma concentration with measures of obesity, i.e. BMI and percent body fat, but not with visceral fat mass along with no differences between visfatin mRNA expression in visceral and subcutaneous fat reported in the past studies[11,30,31].

Despite the statement that visceral fat was correlated closer to CVD than subcutaneous body fat[32], our findings revealed no correlation of CIMT to visceral or subcutaneous fat thickness and failed to support that the measurement of adipocytokines could provide a reliable marker of visceral adiposity and inflammation and an indicator of cardiovascular risk[2].

Given the reported gender influence on the relation of adipocytokines to insulin resistance, dyslipidemia and CHD with demonstration of significant associations between plasma levels of adipocytokines such as resistin and both metabolic and anthropometric parameters in females but not males[26, 33, 34], failure to show significant associations between these parameters in our study population composed solely of females seems a rather unanticipated finding.

Nonetheless, use of different assay methods and differences in the study populations along with the low number of patients enrolled in the different studies has been stated likely to account for the discrepancies in the literature considering association among obesity, visceral fat, adipocytokines, insulin resistance and subclinical atherosclerosis[2, 26].

In this regard, relatively low sample size in the present study might prevent us to achieve the statistical significance concerning the correlates of visceral and subcutaneous fat thickness as well as to project results of the present regression models to the entire population.

The present study has a number of limitations. First, relatively low sample size might prevent us to achieve the statistical significance concerning the correlation of visceral and subcutaneous fat thickness to resistin, visfatin, insulin resistance and CIMT as well as to project results of the present regression models to the entire population. Secondly, the cross-sectional design made it impossible to establish any cause and effect relationships.

In conclusion, our finding revealed that neither plasma levels for resistin and visfatin nor CIMT correlated with visceral or subcutaneous fat thickness in non-diabetic obese females, while increase in subcutaneous and epicardial fat thickness values were noted with decrease in HOMA-IR and the presence of morbid obesity, respectively. Further larger scale mechanistic studies are required to better comprehension of mechanisms involved in the interaction between obesity, insulin resistance and subclinical atherosclerosis along with regulatory role of adipocytokines.

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