SERUM OMENTIN-1 LEVELS AND ENDOTHELIAL DYSFUNCTION IN OBESITY

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Abstract

Introduction. Our aim was to investigate the relationship between serum omentin-1 levels and endothelial dysfunction in obese patients.

Material and Methods. We evaluated 50 obese patients, and age/gender matched 45 healthy non-obese subjects as controls. Oral glucose tolerance test, lipid parameters, uric acid levels, homeostatic model assessment-insulin resistance (HOMA-IR) index, serum omentin-1 levels and flow mediated dilatation (FMD) % were measured in all subjects. Body compositions were analyzed with bioelectrical impedance method using a Tanita Body Composition Analyzer and ViScan.

Results. Serum omentin-1 levels were found significantly lower in obese population compared to the control subjects. FMD response was significantly decreased in obese population. There was a significant positive correlation between serum omentin-1 levels and FMD response ($r=0.359$, $p<0.001$). Serum omentin-1 levels were negatively correlated with body mass index (BMI), waist circumference, total fat percentage, visceral fat, fasting insulin and HOMA-IR index.

Conclusion. Lower serum omentin-1 levels and decreased FMD response may be an early marker of endothelial dysfunction in obese patients.

Key words: Omentin-1, Obesity, Endothelial Dysfunction, Flow Mediated Dilatation.

INTRODUCTION

Obesity is a complex, multifactorial disease and characterized with excess fat accumulation (1). Obesity raises the risk of morbidity from hypertension, dyslipidemia, type 2 diabetes mellitus, coronary heart disease and stroke (2, 3). Obesity causes adipose tissue dysregulation especially in visceral adipose tissue. This is reflected by alterations in circulating adipokines. Since adipokines play role in inflammation and mediate cross talk between insulin sensitive tissues, the alteration

of adipokines may link obesity to inflammation, insulin resistance and cardiovascular disease (4).

Omentin-1 is a 38 kDa adipokine, secreted and produced by stromal vascular cells in visceral adipose tissue rather than subcutaneous adipose tissue (5). Circulating levels and adipose tissue gene expression of omentin-1 is reduced in obese patients (6). Omentin-1 is also found in endothelial cells and may play role in endothelial function. Besides, several clinical studies showed an association between low omentin levels and coronary heart disease, increased arterial stiffness and carotid atherosclerosis (7, 8).

Endothelial dysfunction is an important and very early step in atherogenesis and is likely to play a central role in the development of vascular diseases (9). Flow mediated dilatation (FMD) is a non-invasive method for determination of vascular endothelial dysfunction and it has been shown to be an independent predictor of atherosclerosis (10).

The aim of this study was to evaluate association between endothelial dysfunction determined by flow mediated dilatation method and serum omentin-1 levels in obese population.

MATERIAL AND METHODS

Subjects

We enrolled 50 obese patients and 45 healthy non-obese age and gender matched healthy subjects as the control group. Obese patients of either sex and age older than 18 years were eligible for inclusion in the study if they had a body mass index (BMI) ≥ 30 kg/m². Subjects who smoked any amount of cigarettes and subjects with diagnosed cardiovascular disease (coronary artery disease, arrhythmia, heart failure) and other organic heart diseases, cerebrovascular disease, peripheral vascular disease, familial and/or severe dyslipidemia, stable hypertension treated by drugs, chronic renal failure, chronic hepatic failure and with

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known diabetes mellitus were not included in the study. The study protocol was approved by the local ethics board of Gazi University and written informed consent was obtained from all participants. All patients underwent an initial screening assessment that included the collection of medical history, physical examination, vital signs, a 12-lead electrocardiogram and 24-hour ambulatory blood pressure measurement (ABPM).

Anthropometric, body composition, and FMD measurements

Body mass index was calculated by the researchers as weight in kilograms divided by the square of height in meters. Waist circumference (WC) was measured midway between the lateral lower rib margin and the iliac crest. 24-hour ABPM were obtained from each patient using an ABPM device (Microlife WatchBP O3 24-hr ABPM) with a cuff of appropriate size.

Bioelectrical impedance analysis (BIA) was performed in all subjects in the early morning after an overnight fast of at least 12 h. A Tanita BC-418 MA Segmental Body Composition Analyzer (Tanita Corp., Tokyo, Japan) was used. This device provided further data on weight and, total body fat.

Abdominal BIA was performed with the use of a bioelectrical abdominal fat analyzer (AB-140 ViScan) (Tanita Corporation, Tokyo, Japan). The ViScan consists of a rigid electrode belt that is placed on the bare midriff of the subject. The belt has two pairs of injecting and sensing electrodes placed directly on the skin at the umbilicus in the sagittal plane and uses dual frequency BIA technology (6.25 and 50 kHz) to take bioelectrical measurements. The following abdominal body composition values are derived from extrapolation of impedance measures using inbuilt software: trunk fat percentage on a scale of 5.0–75.0 % (0.1 % graduation); visceral fat level on a scale of 1–59 arbitrary units (0.5 graduation). The method has a high reproducibility and required less than 1 min for data acquisition (11).

FMD was measured at the right brachial artery, by the same researcher, both before and after reactive hyperemia, and FMD % was calculated via the formula as described earlier (12).

Biochemical measurements

All subjects underwent a 75-gr oral glucose tolerance test (OGTT). Based on the results of OGTT subjects were diagnosed as impaired fasting glucose (IFG), impaired glucose tolerance (IGT), Diabetes Mellitus (DM) and normal glucose tolerance (NGT).

Venous blood samples were obtained at baseline and 2 h after glucose load. Plasma glucose (mg/dL) was measured by the glucose-oxidase method. Total cholesterol (mg/dL), triglycerides (mg/dL), high density lipoprotein (HDL)-cholesterol (mg/dL), and uric acid (mg/dL) levels were measured with enzymatic-spectrophotometric standard laboratory methods using an autoanalyzer (Beckman, Olympus AU2700plus model).

Low-density lipoprotein (LDL) cholesterol (mg/dL) was calculated using the Friedewald method. Glycosylated hemoglobin (HbA1c) (%) were determined using Agilent Technologies 1200 Series analyzer with commercially available kits by HPLC method (Chromsystems Instruments and Chemicals GmbH, München, Germany). Fasting insulin (mU/L) was measured with chemiluminescence method using an autoanalyzer (Abbott, Architect I2000). Homeostatic model assessment insulin resistance (HOMA-IR) was calculated using the “[fasting plasma glucose level (mg/dL) x fasting plasma insulin (μU/mL)] /405” formula (13). Serum omentin-1 levels (ng/mL) were determined using an omentin-1 Enzyme Linked Immuno Sorbent Assay (ELISA; Bio-Vendor Laboratorni medicina, Brno, Czech Republic). Blood samples for the biochemical evaluations were taken from all the participants following a 12 h fasting period between 08:00 and 10:00 am. Blood samples were centrifuged and stored at -80°C for no more than 3 months.

Statistical Analysis

Statistical analyses were performed using the SPSS software version 16. Continuous data were presented as mean ± standard deviation or median (minimum-maximum) as appropriate. The level of significance was determined using the t test for normally distributed values and the Mann-Whitney U test was used for non-normally distributed values. The relationships between variables were analyzed by simple bivariate correlation (Spearman's r) and multiple regression analysis. p value of <0.05 was considered statistically significant.

RESULTS

Anthropometric and biochemical measurements of study subjects were shown in Table 1. Patient and control groups were similar for age and gender (Table 1). As expected, we observed a significantly higher BMI and WC in obese patients compared with

Table 1. Anthropometric and biochemical parameters of study subjects

	Obese Subjects (n=50)	Control (n=45)	p
Age (years) †	37±5.9	35±6.4	0.140
Female (n/%)	22 (44)	14 (31)	0.823
BMI (kg/m ²) ‡	35.6 (33.2- 40.8)	22 (20.4- 24.3)	<0.001
BMI >35 kg/m ² (n/%)	25 (50)		
Waist Circumference (cm)	120 (111- 128)	90 (85-96)	<0.001
Systolic BP (mmHg)	115.2±9.7	115.3±10.4	0.265
Diastolic BP (mmHg)	72.5±8.0	71.5±7.4	0.523
Total Body Fat (%)†	40.7 ±8	23.7±6	<0.001
ViScan Visceral Fat ‡	17.5 (14- 24)	6 (5-9.5)	<0.001
ViScan Truncal Fat (%)	49 (45- 53)	30 (24-35)	<0.001
FMD(%)‡	8.9 (6-11.2)	20.5 (18.6-26.5)	<0.001
FPG (mg/dL) †	102±10.6	90±7.9	<0.001
FPI (μU/mL) ‡	15.1 (10-21.8)	5.8 (4.5-7.9)	<0.001
HbA1c (%)‡	5.5 (5.3-5.7)	5.2 (5.1-5.4)	<0.001
HOMA-IR‡	3.5 (2.5-5.5)	1.2 (0.8-1.5)	<0.001
Triglyceride (mg/dL) ‡	139.5 (92.7-175)	82 (60.5-122.5)	<0.001
HDL-C (mg/dL) †	44.7 ±9.4	54.6 ±13.3	<0.001
LDL-C (mg/dL) †	117.7 ±31	116±36.5	0.877
T Cholesterol (mg/dL) †	192±33.6	192±42	0.978
Uric Acid (mg/dL) †	5±1.5	4±1.3	<0.001
Omentin-1 (ng/mL) †	457.7±172	622±213	<0.001

† Data are means±SD;‡ Data are median (interquartile ranges); BMI=Body mass index, BP=Blood pressure, FMD= Flow-mediated dilation, FPG= Fasting plasma glucose, FPI= Fasting plasma insulin, HOMA-IR= Homeostatic model assessment-insulin resistance.

Figure 1. (A) Correlation between Omentin-1 and FMD ($r=0.359$, $p<0.001$), (B) Correlation between Omentin-1 and HOMA-IR score ($r=-0.304$, $p=0.005$).

controls. Among obese subjects 25 (50 %) had a BMI >35 kg/m². Obese patients and controls were similar in terms of systolic and diastolic blood pressure. Total body fat, visceral fat and truncal fat was significantly higher in obese subjects compared with controls. Fasting plasma glucose (FPG), fasting plasma insulin (FPI) and HOMA score were also higher in obese subjects. In obese group, 21 subjects had IFG, 6 had IGT, 3 had combined IGT and IFG and 2 patients diagnosed DM with OGTT. The control group has normal glucose tolerance. Obese subjects were more likely to have higher triglyceride and lower HDL-C levels compared to non-obese subjects, whereas total cholesterol and

LDL-C levels were similar between patient and control groups. Uric acid levels were significantly higher in obese subjects compared with non obese subjects.

Omentin-1 levels and FMD response were significantly lower in obese patients compared with controls (Table 1).

There was a positive correlation between FMD rate and Omentin-1 levels and negative correlations between omentin 1 and WC; BMI; visceral fat; truncal fat; serum insulin levels; HOMA-IR and triglyceride in the whole study population. We also observed a positive correlation between omentin-1 and HDL-C (Figs 1A and 1B).

Table 2. Flow-mediated dilation and omentin-1 levels according to glucose tolerance status in obese patients

	IGT(n=32)	NGT(n=18)	p
FMD (%)	7.9±4.1	10.6±3.8	0.027
Omentin-1 (ng/mL)	450.1±181.3	470.5±158.3	0.696

† Data are means±SD IGT:impaired glucose tolerance; NGT: normal glucose tolerance. FMD= Flow-mediated dilation, IGT= Impaired glucose tolerance, NGT= Normal glucose tolerance.

Figure 2. (A) Correlation between FMD and BMI ($r=-0.678$, $p<0.001$); (B) Correlation between FMD and HOMA-IR score ($r=-0.648$, $p<0.001$); (C) Correlation between FMD and ViScan Visceral Fat ($r=-0.677$, $p<0.001$).

FMD= Flow mediated dilatation. BMI= Body mass index. HOMA-IR= homeostatic model assessment-insulin resistance.

There were negative correlations between FMD and BMI; WC; total body fat; visceral body fat; triglyceride; FPG; uric acid; HOMA-IR in the whole study population (Figs 2A, 2B and 2C).

Omentin-1 level was similar between obese patients with NGT and IGT, however FMD rate was significantly higher in NGT obese patients (Table 2). There were positive correlations between omentin-1 and HDL-C; omentin 1 and triglyceride in the obese subjects (Table 3).

The results of the multivariate linear regression analysis revealed that omentin-1 levels and BMI were independently associated with FMD (Table 4).

DISCUSSION

In our study, obese patients have lower omentin-1 concentrations and lower FMD compared to control subjects and there is a positive correlation between FMD and omentin-1. Omentin-1 and BMI were independent predictors of FMD.

Increased visceral fat tissue reduces omentin-1 gene expression and thus, serum omentin-1 level and visceral adiposity are negatively correlated (6). Adipokine changes, leading to endothelial dysfunction, causes atherosclerosis in obesity. There is good evidence from experimental and clinical studies regarding the effect of omentin-1 on vascular reactivity and atherogenesis. Experimental studies showed that Omentin-1 induces vasodilation in rat isolated blood vessels by increasing endothelial nitric oxide synthase and stimulates ischemia-induced revascularization in mice (14). Omentin modulates endothelial cell function and revascularization processes. Maruyama S. *et al.* showed that omentin-1 stimulates Akt-eNOS signaling pathway and promotes endothelial function in response to ischemia *in vivo* and *in vitro* (15). Several clinical studies also showed an association between low omentin-1 levels and carotid intima media thickness (16), carotid plaque (8) and coronary artery disease (7). In these studies omentin-1 levels had a negative correlation with atherosclerotic parameters. Saremi A. *et al.* showed that aerobic training increases serum omentin-1 levels and cardiovascular risk factors in overweight and obese men (17). Urbanová M. *et al.* reported that laparoscopic sleeve gastrectomy increases serum omentin levels in non-diabetic obese women (18). In our cross sectional study we evaluated vascular health with FMD and atherosclerotic markers in obese patients and lean controls. We found that serum omentin-1 level is an independent predictor of

Table 3. Correlation analysis between omentin-1 and anthropometric and biochemical parameters in obese and control groups

	Obese Subjects (n=50)		Control (n=45)	
	r	p	r	p
BMI (kg/m ²)	0.185	0.204	0.117	0.448
Waist Circumference (cm)	0.126	0.383	0.098	0.527
ViScan Truncal Fat (%)	0.073	0.624	-0.056	0.724
ViScan Visceral Fat	-0.180	0.226	0.126	0.427
Insulin	-0.079	0.619	0.182	0.250
Triglyceride (mg/dL)	-0.355	0.011	-0.030	0.848
HDL-C	0.317	0.025	0.107	0.488
FMD (%)	0.177	0.219	0.092	0.559

† Data are means±SD;‡ Data are median (interquartile ranges); BMI=Body mass index, BP=Blood pressure, FMD= Flow-mediated dilation, FPG= Fasting plasma glucose, FPI= Fasting plasma insulin, HOMA-IR= Homeostatic model assessment insulin resistance.

Table 4. Univariate and Multiple Regression analysis of the relation between flow-mediated dilation and variables

	r	p	β	p
Age (years)	-0.133	0.203		
Gender	0.602	0.759		
Systolic BP (mmHg)	-0.067	0.523		
Diastolic BP (mmHg)	-0.116	0.265		
BMI (kg/m ²)	-0.678	<0.001	-0.343	0.037
Waist Circumference (cm)	-0.643	<0.001		
Total Body Fat (%)	-0.471	<0.001	-0.123	0.278
ViScan Visceral Fat	-0.677	<0.001		
FPG (mg/dL)	-0.394	<0.001	-0.017	0.827
T Cholesterol (mg/dL)	-0.065	0.535		
LDL-C (mg/dL)	-0.080	0.444		
Triglyceride (mg/dL)	-0.411	<0.001	-0.009	0.427
Uric acid (mg/dL)	-0.377	<0.001		
HDL-C	0.361	<0.001	0.006	0.924
HOMA IR	-0.648	<0.001	-0.509	0.217
Omentin-1 (ng/mL)	0.359	<0.001	0.008	0.025

BP=Blood pressure, BMI=Body mass index, FPG= Fasting plasma glucose, LDL-C= Low density lipoprotein cholesterol , HDL-C= High density lipoprotein cholesterol , HOMA-IR= Homeostatic model assessment insulin resistance.

FMD. Although we assessed endothelial function with a different technique, our results confirm the study by Moreno-Navarrete *et al.* who showed that omentin-1 was correlated with endothelium-dependent and independent vasodilation measured from brachial artery (19). Taken together with our present data lower levels of omentin-1 may be an earlier marker of endothelial dysfunction and may link obesity to cardiovascular diseases in obese patients.

We found a negative correlation between omentin-1 levels and serum fasting insulin levels and HOMA-IR score. Lower omentin-1 concentrations are associated with insulin resistant states such as impaired glucose tolerance, type 2 diabetes and overweight PCOS (polycystic ovary syndrome) women (20, 21). The precise mechanism between omentin-1 and insulin sensitivity remains obscure. *In vitro* studies showed that omentin-1 has direct insulin-sensitizing effects through enhancing insulin-mediated Akt-phosphorylation and glucose uptake in adiposits and

also binds to the iron-binding protein lactoferrin (22, 23), which has been linked with insulin resistance and altered glucose tolerance (24). There is a need for more detailed studies demonstrating molecular mechanism of omentin action.

The major limitations of our study are its cross sectional design and small sample size. We found that lower omentin-1 levels are associated with lower FMD response but we could not assess whether weight loss has an impact on the relationship between omentin-1 levels and endothelial dysfunction. Longitudinal intervention studies are warranted to understand the effect of weight loss on omentin-1 levels and endothelial dysfunction.

In conclusion, our data suggest that lower omentin-1 levels, correlated with lower FMD response, may be an early marker of endothelial dysfunction in obese patients. Further studies are needed to investigate the role of omentin receptors and its molecular and cellular dynamics in endothelial dysfunction and insulin resistance.

Conflict of interest

The authors declare that they have no conflict of interest concerning this article.

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