ORIGINAL ARTICLE

Serum obestatin and omentin levels in patients with diabetic nephropathy

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Abstract

Introduction: Diabetic nephropathy is the leading cause of chronic kidney disease and accounts for almost 45% of all new patients requiring renal replacement therapy. Omentin and obestatin, two novel proteins were suggested to be associated with insulin resistance, type 2 diabetes and cardiovascular risk factors. Thus, we postulated that they may also have an association with diabetic nephropathy which is known to be an independent cardiovascular risk factor. In order to investigate such an association we compared serum omentin and obestatin levels in type 2 diabetic patients with normoalbuminuria (NA) and macroalbuminuria (MA).

Materials and Methods: A total of 81 type 2 diabetic patients were separated into two groups according to their proteinuria status; patients with NA (n = 39) and patients with MA (n = 42). Two groups were compared in terms of serum omentin and obestatin levels.

Results: While serum omentin levels did not differ among two groups (P = 0.407), serum obestatin levels were significantly higher in MA group (P = 0.001).

Conclusion: The results of this study showed that higher serum levels of obestatin were associated with macro albuminuria suggesting that obestatin may have a role in underlying pathogenic mechanisms that leads to diabetic nephropathy.

Key words: Diabetes mellitus type 2, diabetic nephropathy, obestatin, omentin

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Introduction

Diabetic nephropathy is the leading cause of chronic kidney disease (CKD) and accounts for almost 45% of all new patients requiring renal replacement therapy.[1,2] Diabetic nephropathy develops in about 20–40% of type 2 diabetes patients, and it is not known why it is not seen in all of the patients with diabetes mellitus type 2. Many mechanisms were suspected to contribute to the emergence of diabetic nephropathy and its clinical course including atherosclerotic and inflammatory processes.[3] It is now believed that adipose tissue actively participates in neuroendocrine, cardiovascular and immune systems by secreting proteins and other products (called adipokines), as well as responding to neural, hormonal, and nutritional signals.[4]

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Omentin is an adipokine preferentially produced by visceral adipose tissue with insulin-sensitizing effects and its expression was shown to be reduced in obesity, insulin resistance (IR) and type 2 diabetes. Omentin was also found to be positively related with adiponectin, high-density lipoprotein levels and negatively related with body mass index (BMI), waist circumference, IR, triglyceride (TG) and leptin levels. Lower plasma omentin levels was suspected to contribute to the pathogenesis of IR, type 2 diabetes and cardiovascular diseases in obese or overweight patients.[5-8]

Obestatin, a recently discovered 23 amino acid peptide hormone, is derived by posttranslational cleavage of the same peptide precursor (preproghrelin) as ghrelin, which is a peptide mainly released from the stomach.[9] In several studies in adult humans, decreasing concentrations of obestatin were associated with diabetes and impaired glucose regulation and the insulin-sensitivity surrogate homeostasis model assessment (HOMA) of IR indicating an important role for obestatin in body weight regulation.[10-12] Obestatin has been reported to have important effects on endothelial cells such as decreasing vascular cell adhesion molecule-1 expression and increasing oxidized low-density lipoprotein binding to macrophages.[13] Therefore, it was suggested that obestatin may also have a potential function in the regulation of blood pressure.[14]

Because these two proteins, omentin and obestatin were reported to be associated with diabetes, IR and cardiovascular risk factors, we hypothesized that they may also play a role in underlying pathogenic mechanisms which leads to progression of albuminuria in type 2 diabetic patients. The aims of the present study were to measure fasting serum omentin and obestatin concentrations in type 2 diabetic patients with normoalbuminuria (NA) and macroalbuminuria (MA).

Materials and Methods

Study population

This study was designed as a prospective, cross-sectional, case–control study. A total of 81 patients with type 2 diabetes presented to internal medicine outpatient clinic of Bezmialem Vakif University Faculty of Medicine between March and August 2015 were included into this study. All individuals provided written informed consent prior to inclusion in the study. The study protocol was approved by the Ethics Committee at the Bezmialem Vakif University Faculty of Medicine. Two age and sex-matched groups were formed: Type 2 diabetic patients with MA (n = 42; 23 women and 19 men) and patients with NA (n = 39; 21 women and 18 men).

Patients with malignancy, chronic pulmonary diseases, chronic liver diseases, chronic renal diseases, coronary, cerebrovascular and peripheral arterial diseases, urinary tract infection during proteinuria test and abnormal thyroid function tests were excluded from the study.

All volunteers underwent a thorough physical examination and their height, weight and waist circumferences were recorded. Weight and height were measured to the nearest kilogram and centimeter, respectively and BMI was calculated from the formula (BMI = weight/[height] ^{2}).

Blood assay

Venous blood samples were collected from all patients in the morning (8:00–9:00) after an at least 12 h overnight fast and laboratory analysis of fasting glucose, urea, creatinine, glycated hemoglobin (HbA1c), total cholesterol (total-C), TGs, high-density lipoprotein cholesterol (HDL-C), low-density lipoprotein cholesterol (LDL-C), sodium (Na), potassium (K), calcium (Ca), phosphate (P), total protein, albumin, aspartate aminotranspherase (AST), alanine aminotranspherase (ALT), total protein, albumin, alkaline phosphatase (ALP), lactate dehydrogenase (LDH), creatine kinase (CK), serum iron, total iron binding capacity (TIBC), ferritin, complete blood count (CBC), thyroid stimulating hormone (TSH), parathormone (PTH) were performed with standard methods.

Serum samples of volunteers were transferred into separate eppendorf tubes and frozen at–80°C for later determination of omentin and obestatin levels. Serum obestatin levels were measured using a commercial enzyme immunoassay kit (Sunredbio, Baoshan District, Shanghai) and serum omentin levels were measured using a commercial enzyme immunoassay kit (Aviscera Bioscience, Santaclara, USA) according to the manufacturers' instructions with an analyzer (Thermo Scientific Multiskan FC, USA). Samples were measured in duplicate and the average was used in the data analysis.

Measurement of albumin in urine samples

Urine samples were taken for biochemical analyses after an overnight fast of 12 h. Urinary albumin was determined in an early morning spot urine sample. The urine albumin concentration was estimated by a using a commercial kit (Abbott Architect) via the immunoturbidimetric method on a biochemical analyzer (Abbott Architect, C16.000, USA).

The state of albuminuria was defined as NA (urinary albumin-to-creatinine ratio [UACR] <30 mg/g), microalbuminuria (UACR = 30–299 mg/g), or MA (UACR UACRalbumi) by using first morning urine specimen.[15]

Statistical analysis

Statistical Package for Social Sciences (SPSS) for Windows 20.0 software (IBM Corporation, Armonk, NY, USA) was used to perform the statistical analysis of the data. The

continuous variables were expressed as mean ± standard deviation. Continuous variables were compared between the two groups using Mann–Whitney U-test. Student's *t*-test was used to compare parametric variables between the patient and control groups. Bivariate correlation analyses were done by Spearman's test.

Results

Two groups (MA and NA) did not differ in terms of age, sex, BMI, waist circumference, systolic and diastolic blood pressure readings, creatinine, total-C, HDL-C, LDL-C, Ca, P, AST, ALT, ALP, LDH, HbA1c, PTH, CK, serum iron, TIBC, ferritin, CBC parameters, TSH. Diabetes duration, serum levels of fasting glucose and TGs were significantly higher in MA group ($P = 0.043$, $P = 0,014$, $P = 0,008$; respectively). Serum albumin levels were significantly lower in MA group ($P < 0,001$). Serum omentin levels did not differ amongst two groups ($P = 0.124$) while serum obestatin levels were significantly higher in MA group ($P = 0,002$). Table 1 summarizes some of these parameters compared.

Results of this study showed that serum omentin levels correlated positively with diabetes duration, fasting glucose

Table 1: The comparison of antropometric and biochemical parameters between macroalbuminuria and normoalbuminuria groups

	Mean±SD		*P*
	Macroalbuminuria (*n*=42)	Normoalbuminuria (*n*=39)	
Female/male	23/19	21/18	
Age (years)	56.67±9.87	55.87±7.11	0.681
Diabetes duration (years)	12.69±6.22	10.03±5.37	0.043*
BMI (kg/m^2)	32.38±6.09	30.41±4.68	0.109
Waist circumference (cm)	101.43±9.28	99.62±8.76	0.370
SBP (mmHg)	133.45±11.81	129.23±8.47	0.070
DBP (mmHg)	84.29±6.58	81.92±6.02	0.097
Obestatin (ng/mL)	4.048±1.78	3.024±0.90	0.002*
Omentin (ng/mL)	1.619±0.62	1.43±0.43	0.124
Fasting glucose (mg/dL)	191.62±100.57	146.72±49.89	0.014*
HbA1c (%)	8.04±2.00	7.38±1.07	0.072
Creatinine (mg/dl)	1.09±1.31	0.80±0.12	0.174
Total cholesterol (mg/dL)	215.8±45.60	207.00±36.21	0.362
Triglycerides (mg/dL)	229.66±137.38	161.49±76.82	0.008*
LDL-C (mg/dL)	130.71±36.65	122.56±28.34	0.271
HDL-C (mg/dL)	46.49±9.14	46.21±9.79	0.896
Albumin (g/dL)	4.19±0.27	4.35±0.23	0.007*
ALT (U/L)	21.62±8.67	22.23±16.33	0.832
Calcium (mg/dL)	9.88±0.47	9.84±0.35	0.693
Phosphate (mg/dL)	3.57±0.55	3.64±0.56	0.562
PTH (pg/ml)	66.82±34.44	62.58±26.37	0.538
Albuminuria (mg/L)	915.93±647.74	14.82±8.80	<0.001*

*Statistically significant. SD=Standard deviation; BMI=Body mass index; SBP=Systolic blood pressure; DBP=Diastolic blood pressure; HbA1c=Glycated hemoglobin; LDL-C=Low-density lipoprotein cholesterol; HDL-C=High-densitylipoprotein cholesterol; ALT=Alanine aminotranspherase; TSH=Thyroid stimulating hormone; PTH=Parathormone

Table 2: The correlation of serum omentin levels with anthropometric and biochemical parameters in all study population

	r	*P*
Age (years)	−0.010	0.932
Diabetes duration (years)	0.59	0.603
BMI (kg/m^2)	−0.14	0.905
Fasting glucose (mg/dL)	0.007	0.953
Obestatin (ng/mL)	−0.50	0.659
Creatinine (mg/dl)	−0.006	0.960
Total cholesterol (mg/dL)	−0.32	0.791
Triglycerides (mg/dL)	−0.124	0.276
LDL-C (mg/dL)	0.064	0.573
HDL-C (mg/dL)	0.110	0.353
HbA1c (%)	0.107	0.344
Calcium (mg/dL)	0.112	0.322
Phosphate (mg/dL)	−0.019	0.868
PTH (pg/ml)	−0.103	0.365
Albuminuria (mg/L)	0.094	0.407

BMI=Body mass index; LDL-C=Low-density lipoprotein cholesterol; HDL-C=High-density lipoprotein cholesterol; HbA1c=Glycated hemoglobin; PTH=Parathormone

Table 3: The correlation of serum obestatin levels with anthropometric and biochemical parameters in all study population

	r	*P*
Age (years)	0.37	0.740
Diabetes duration (years)	0.013	0.910
BMI (kg/m^2)	0.024	0.835
Fasting glucose (mg/dL)	0.011	0.925
Omentin (ng/mL)	−0.50	0.659
Creatinine (mg/dl)	−0.029	0.796
Total cholesterol (mg/dL)	−0.121	0.311
Triglycerides (mg/dL)	0.030	0.794
LDL-C (mg/dL)	−0.050	0.662
HDL-C (mg/dL)	−0.094	0.421
HbA1c (%)	−0.092	0.416
Calcium (mg/dL)	−0.72	0.524
Phosphate (mg/dL)	−0.171	0.126
PTH (pg/ml)	−0.043	0.700
Albuminuria (mg/L)	0.349	0.001*

*Statistically significant. BMI=Body mass index; LDL-C=Low-density lipoprotein cholesterol; HDL-C=High-density lipoprotein cholesterol; HbA1c=Glycated hemoglobin; PTH=Parathormone

levels, LDL-C, HDL-C, HbA1c, Ca and albuminuria and negatively with age, BMI, obestatin, total-C, TGs, P, PTH, but these correlations did not reach statistical significance [Table 2].

Serum obestatin levels correlated positively with age, diabetes duration, BMI, fasting glucose levels, TGs, and albuminuria and negatively correlated with serum omentin, creatinine, total-C, LDL-C, HDL-C, HbA1c, Ca, P, PTH. Of these, only positive correlation with albuminuria reached statistical significance ($P = 0.001$, $r = 0.349$) [Table 3].

Discussion

In this study, we sought to determine the relationship between circulating omentin-1 and obestatin levels and MA in patients with type 2 diabetes. This study has two main findings: (1) Serum Omentin-1 levels did not differ between patients with NA and MA. (2) Serum obestatin levels were significantly higher in patients with MA. The common early signs of diabetic nephropathy are microalbuminuria and overt proteinuria.[15] Microalbuminuria is a strong and independent indicator of increased cardiovascular risk among individuals with and without diabetes.[16]

In recent years, visceral adipose tissues and adipokines have been implicated to play a crucial role in the pathogenesis of atherosclerosis and coronary artery disease. Omentin is a novel adipokine mainly expressed in visceral adipose tissue shown to be associated with chronic inflammatory diseases, IR, obesity and carotid atherosclerosis and has been suggested as a biomarker of metabolic disorders.[17] Several studies have shown that serum omentin levels were negatively correlated with metabolic risk factors and seemed to have anti-inflammatory and insulin-sensitizing effects.[8,17,18] Recent studies have shown omentin as a modulator of vascular function via endothelium-dependent vasodilation and may play a protective role in the cardiovascular system.[19,20] Omentin plays a role in vascular inflammation as it suppresses cytokine-stimulated expression of adhesion molecules in endothelial cells so it was suggested that omentin may be involved in the pathogenesis of atherosclerosis.[21] Recently, in a meta-analysis Agasthi *et al.* found that serum omentin level is independently and negatively associated with coronary artery disease. They concluded that further studies were needed to define the role of omentin in the pathogenesis of coronary artery disease and its potential to serve as a novel biomarker.[22] Moreover, there is now convincing data demonstrating that common pathogenic mechanisms such as inflammation, oxidative stress and altered levels of adipocytokines are related to both microvascular and macrovascular complications.[23]

Only very few papers analyzed serum omentin levels in patients with type 2 diabetes.[24-26] Similarly, until recently, a few studies have reported associations between omentin and subclinical atherosclerosis (e.g., carotid atherosclerosis) but not in diabetic patients.[27,28] To the best of our knowledge there are two studies investigating the relationship between serum omentin levels and diabetic microvascular complications. Jung *et al.* recently evaluated 97 patients with type 2 diabetes and reported that there was no association between serum omentin levels and diabetic microvascular complications such as nephropathy, retinopathy and peripheral neuropathy.[25] Similarly in this study, we found that there was no difference in serum omentin levels amongst two groups of diabetic patients with or without MA. Tekce *et al.* analyzed 64 patients with CKD with or without type 2 diabetes and 27 healthy controls. Serum omentin levels were significantly lower in the diabetic CKD subgroup compared to the healthy control group and nondiabetic CKD subgroup. However, no significant differences were found between nondiabetic CKD and control groups.[26] Because both patients in two groups in our study were diabetic and we found no difference between NA and MA groups in serum omentin levels it may be suggested that omentin plays a role in pathophysiological pathways resulting in diabetes rather than MA. On the contrary of majority of the studies investigating serum omentin levels in healthy subjects or patients with metabolic syndrome or obesity, significant associations of glycemic parameters or BMI, TGs, HDL-C with serum omentin levels were not detected in our present study.[5,17,18] Consistent with our results, Hossein-Nezhad *et al.* and more recently Jung *et al.* reported that no significant relationship between serum omentin levels and glucose metabolism was found.[25,29] Similarly, Kilic *et al.* reported that plasma omentin levels did not differ between metabolic syndrome patients and control subjects, and in all subjects, omentin was positively correlated with TG levels and negatively correlated with HDL-C levels.[30] It can be argued that this discrepancy is likely due to differences in study designs, measurement methods and population demographics and further prospective studies with larger number of patients are needed to clarify these conflicting results.

Obestatin is a 23 amino acid amidated peptide, member of the preproghrelin gene-derived peptides. Initially, obestatin was reported to exert opposite effects to those of ghrelin on food intake and body weight gain, through interaction with GPR39.[31] However, these findings are still strongly debated and biological role of obestatin remains largely unknown.[32] Despite being a controversial peptide, recent findings have clearly indicated that obestatin is indeed a multifunctional peptide, exerting a variety of effects, such as stimulation of cell proliferation, survival and differentiation, influence on glucose and lipid metabolism, as well as anti-inflammatory and cardioprotective actions.[33-36] Its positive effects on glucose and lipid metabolism candidate this peptide as a potential therapeutic tool in pathological conditions such as IR and diabetes. Studies in humans have

shown that blood obestatin levels are significantly lower in obese subjects and correlate negatively with BMI, insulin, glucose and the HOMA-IR.[11,12] Contrary to these positive findings, our results suggested a rise in serum obestatin levels in type 2 diabetes patients with MA compared with type 2 diabetes patients with NA. Albumuniria was reported to reflect a local (renal) endothelial dysfunction and low-grade inflammation.[37,38] So, it may be expected a decrease in serum obestatin levels in patients with MA. We also found that serum obestatin levels positively correlated with albumin levels in urine samples. Thus, it may be contemplated that there is an association between albumin and obestatin in terms of pathophysiological pathways. Moreover, Ma *et al*. recently reported that plasma ghrelin concentrations were negatively correlated with UACR in newly diagnosed type 2 diabetes.[39] Vicennati *et al*. and Zhang *et al*. reported lower ghrelin and oppositely higher obestatin levels in obese patients.[40,41] So, these two peptides may be working opposite each other as reported initially and a decrease in ghrelin levels may result in an increase in obestatin levels in patients with IR, low grade inflammation or T2DM.

The strengths of the present study are that it is one of the few studies investigating association of serum omentin levels and to our best knowledge, the only study evaluating serum obestatin levels with microvascular complications of T2DM. Nevertheless, this study has several limitations. This was a cross-sectional study, which therefore could not determine causal relationships between omentin and obestatin levels and diabetic nephropathy. In addition, we chose patients with MA, tha later stage of diabetic nephropathy omitting patients with microalbuminuria expecting more pronounced results. Finally, we did not investigate serum ghrelin levels which might have given more insight for our obestatin results.

Conclusion

The results of the present study suggest that higher serum levels of obestatin were associated with MA suggesting that obestatin may have a role in underlying pathogenic mechanisms that leads to diabetic nephropathy.

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Conflicts of interest
There are no conflicts of interest.

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