Association of plasma omentin-1 level with insulin resistance in chronic kidney disease patients

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Introduction
The early prediction and prevention of cardiovascular disease risk factors is highly important in chronic kidney disease (CKD) patients. The plasma level of omentin was found to be associated with different disorders such as insulin resistance, diabetes mellitus, obesity, endothelial dysfunction, and atherosclerosis. The aim of the study was to clarify the influence of changes in levels of circulating omentin-1 on insulin resistance in CKD patients with and without type 2 diabetes mellitus.

Participants and methods
Seventy-eight patients were enrolled in this cross-sectional study: 23 patients with CKD on conservative treatment, 35 patients on maintenance hemodialysis, and 20 healthy volunteers. Serum concentrations of omentin-1 were determined with an enzyme-linked immunosorbent assay kit.

Results
Significant difference in plasma omentin-1 level was noticed between diabetic patients and nondiabetic patients in both the predialysis group and the hemodialysis (HD) group. There was also a significant difference in plasma omentin-1 level between nondiabetic patients in the predialysis group and the HD group and between diabetic patients in the predialysis group and hemodialysis group. There were significant negative correlation between plasma Omentin-1 level (ng/ml), fasting insulin level (mIU/ml), HOMA-IR and eGFR (ml/min/1.73m^2) while significant positive correlation with IL-6 (pg/ml) and hsCRP (mg/l).

Conclusion
Plasma omentin-1 concentration was higher in CKD patients. In addition, there was an association between omentin-1 and insulin resistance in hemodialysis patients, which may be considered a cardiovascular risk factor in CKD patients.

Keywords:
chronic kidney disease, homeostasis model assessment of insulin resistance, insulin, omentin

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Introduction

The most important cause of morbidity and mortality in end-stage renal disease patients, especially in those on hemodialysis, is cardiovascular disease, and the main pathophysiologic mechanisms underlying the high mortality are atherosclerosis and chronic inflammation [1]. Early prediction and prevention of cardiovascular disease risk factors is essential in chronic kidney disease (CKD) patients [2]. All components of the metabolic syndrome are cardiovascular risk factors and predispose to atherosclerosis. Adipose tissue, mainly visceral obesity, has been increasingly recognized to be an endocrine organ more than heat insulator and stock of energy. Adipokines, the secretory products of adipose tissue, represent a novel and causative association between obesity and atherosclerosis [3]. Omentin is a novel fat depot-specific secretory factor that was recognized from a cDNA library from human omental adipose tissue. In addition, it is known that it is completely secreted from stromal vascular cells of visceral adipose tissue [4]. There are two highly homologous isoforms of omentin: omentin-1 and omentin-2. The former is the main circulating form in human blood [5]. The plasma level of omentin (also named intelectin-1, intestinal lactoferrin receptor, endothelial lectin HL-1, or galactofuranose-binding lectin) was found to be associated with different disorders such as insulin resistance, diabetes mellitus, obesity, endothelial dysfunction, and atherosclerosis. However, there are limited studies investigating the relationship between omentin level and insulin resistance in CKD patients [6]. Therefore, in this study we aimed to clarify the influence of changes in levels of circulating omentin-1 on insulin resistance in CKD patients with and without type 2 diabetes mellitus. Furthermore, we detected whether baseline circulating

omentin-1 levels could change with progression of renal failure.

Participants and methods

Seventy-eight individuals were included in this cross-sectional study: 20 apparently healthy individuals constituting the control group; 23 patients with CKD on conservative treatment (the predialysis group) (14 men and nine women); and 35 chronic renal failure patients (the hemodialysis group) (20 men and 15 women). The patient groups were subdivided into diabetic and nondiabetic patients. Diabetes mellitus was defined according to the criteria of the American Diabetes Association – 2014 [7]. All patients were undergoing regular treatment at the Internal Medicine Department, Nephrology Unit, Zagazig University Hospital, during the period from December 2013 to December 2014. All patients were clinically stable and free of active infections, autoimmune diseases or thrombotic complications, hepatic diseases, acute or chronic inflammatory diseases, cancer, thyroid dysfunction, acute or chronic infection, and alcohol or drug abuse at the time of the study. Female patients taking hormonal replacement therapy were also excluded. Patients included in the study gave written informed consent. The study was conducted in accordance with the guidelines approved by the local research ethics committee. Each participant was subjected to the following.

Clinical assessment

This included history taking and physical examination, calculation of BMI [calculated as weight/height^2 (kg/m^2)], and waist circumference (measured at the midpoint between the lower border of the rib cage and the iliac crest).

Routine laboratory investigations

These included fasting and postprandial blood glucose, lipid profile (triglycerides, total cholesterol, high-density lipoprotein-cholesterol, and low-density lipoprotein-cholesterol), kidney and liver function tests, and highly sensitive C-reactive protein (hsCRP) (assayed using the immunonephelometric method). These parameters were determined on a Cobas 6000, automated analyzer (Roche Diagnostics GmbH, SandhoferStrasse 116, D-68305 Mannheim). Low-density lipoprotein-cholesterol concentration was calculated using the Friedewald formula [8,9].

Special laboratory investigations

These included evaluation of omentin-1, interleukin-6 (IL-6), and insulin levels. Plasma omentin-1 and serum IL-6 levels were measured using an enzyme-linked immunosorbent assay in accordance with the manufacturer's instructions (Glory Science Co. Ltd and AviBion, Orgenium, Vantaa, Finland, respectively). Insulin levels were measured using an electrochemiluminescence immunoassay on a Cobas 411 analyzer (Roche Diagnostics GmbH). Insulin resistance was calculated using the homeostasis model assessment of insulin resistance (HOMA-IR) index, which was calculated using the following equation: HOMA-IR = fasting insulin (μU/ml) ×FBG (mg/dl)/405 [10]. Estimated glomerular filtration rate (eGFR) was calculated according to the Modification of Diet in Renal Disease formula [11]. Blood samples were collected from all participants by means of venous puncture into vacutainer tubes and centrifuged at 2500*g* for 15 min. Blood samples from renal failure patients were taken directly from the arteriovenous fistula immediately before the beginning of a routine 4-h HD session. For omentin-1, IL-6, and insulin determination, plasma or serum samples were stored at −20°C until analysis according to the manufacturer's instructions. Some patient results were taken from the patient files after obtaining the permission of their doctors.

Statistical analysis

Data were checked, entered, and analyzed using the SPSS 18 software package (SPSS Inc., Chicago, Illinois, USA). The normally distributed data were expressed as mean ± SD. Multiple group comparisons were performed by one-way analysis of variance. Univariate correlations between study variables were calculated with Spearman's rank correlation coefficients (r). P-values less than 0.05 were considered significant and those less than 0.001 were considered highly significant.

Results

There was significant difference between the control group, the predialysis group, and the hemodialysis group in all clinical parameters except BMI (P > 0.05) (Table 1). Plasma omentin-1 level, insulin resistance, levels of hsCRP, lipid profile, creatinine, and blood glucose were significantly increased in the patient groups compared with the control group (Table 2). Significant decrease in plasma omentin-1 levels (ng/ml) was noticed in diabetic patients compared with nondiabetic patients in both the predialysis group and the hemodialysis group, whereas there were increased insulin levels, HOMA-IR, IL-6, and hsCRP levels in diabetic patients in both the predialysis group and the

hemodialysis group (Table 3). There was significant positive correlation between plasma omentin-1 level (ng/ml) and fasting insulin level (mIU/ml), HOMA-IR, IL-6 (pg/ml), and hsCRP (mg/l), whereas there was a significant negative correlation with eGFR (ml/min/1.73 m^2) (Table 4, Figs. 1 and 2).

Discussion

Cardiovascular disease has become a major health disorder worldwide with increasing incidence in CKD patients. The common pathological features of cardiovascular complications in CKD are systemic inflammation and accelerated atherosclerosis. In the present study, we determined the level of omentin-1 in CKD patients (predialysis and on hemodialysis) and clarified the relationship between serum omentin-1 and insulin resistance in these groups. In the present study the omentin-1 levels in CKD patients were higher than those in the control group; serum levels of IL-6, insulin, and HOMA-IR were found to be markedly higher in CKD patients than in the control group. These results were supported by the findings of Alcelik *et al.* [6], who found significantly higher omentin levels in hemodialysis patients than in healthy individuals. Increased levels of omentin might be related to impaired renal clearance of this molecule. Thus, omentin levels may be found to be higher in end-stage renal disease patients because of defective degradation and elimination. Besides, omentin is a relatively large protein, 40 kDa, which during hemodialysis may not be significantly cleared from plasma [12]. Common pathogenic features of CKD are systemic inflammation, accelerated atherosclerosis, and insulin resistance. Alcelik *et al.* [6] suggested that

Table 1 Demographic and clinical assessments of all studied groups

Parameters	Predialysis (*n* = 23)	Hemodialysis (*n* = 35)	Control (*n* = 20)	*F*	*P*
Age (years)	48.09 ± 8.08	51.94 ± 9.31	43.35 ± 7.9	6.38	0.003
SBP (mmHg)	138.13 ± 19.77	146.6 ± 27.15	122.3 ± 7.21	8.13	0.001
DBP (mmHg)	89.9 ± 11.48	90.74 ± 16.07	78.2 ± 6.1	6.74	0.002
BMI (kg/m^2)	26.65 ± 4.4	25.62 ± 3.27	25.04 ± 3.03	1.14	0.3
Waist circumference (cm)	95.91 ± 8.33	98.89 ± 9.79	89.95 ± 10.31	5.6	0.005

DBP, diastolic blood pressure; SBP, systolic blood pressure.

Table 2 Laboratory finding of all studied groups

Parameters	Predialysis (*n* = 23)	Hemodialysis (*n* = 35)	Control (*n* = 20)	*F*	*P*
Serum creatinine (mg/dl)	3.87 ± 1.53	8.64 ± 2.5	0.68 ± 0.21	117.77	0.001
eGFR (ml/min/1.73 m^2)	38.49 ± 10.43	8.21 ± 2.46	100.1 ± 11.7	772.7	0.001
TG (mg/dl)	187.76 ± 57.19	141.48 ± 38.85	126.3 ± 32.7	12.13	0.001
TC (mg/dl)	205.68 ± 41.13	219.87 ± 53.39	192.34 ± 23.71	2.57	0.05
HDL-C (mg/dl)	55.93 ± 10 76	44.87 ± 10.59	55.98 ± 8.42	7.84	0.001
LDL-C (mg/dl)	112.18 ± 52.1	146.71 ± 46.24	111.1 ± 21.13	6.3	0.003
Hb (g/dl)	11.13 ± 1.4	10.37 ± 1.56	13.24 ± 1.45	23.75	0.001
hsCRP (mg/l)	0.41 ± 0.12	0.63 ± 0.26	0.16 ± 0.03	48.07	0.001
FBG (mg/dl)	111.65 ± 15.33	124.8 ± 24.79	98.05 ± 7.28	12.87	0.001
Insulin (μU/ml)	19.48 ± 4.59	25.06 ± 6.66	12.275 ± 2.37	37.79	0.001
HOMA-IR	5.43 ± 1.78	7.96 ± 3.23	2.96 ± 0.58	28.36	0.001
IL-6 (pg/ml)	10.74 ± 1.45	13.3 ± 1.36	6.92 ± 1.25	139.6	0.001
Plasma omentin-1 (ng/ml)	309.22 ± 26.29	485.09 ± 24.13	303.55 ± 24.01	502	0.001

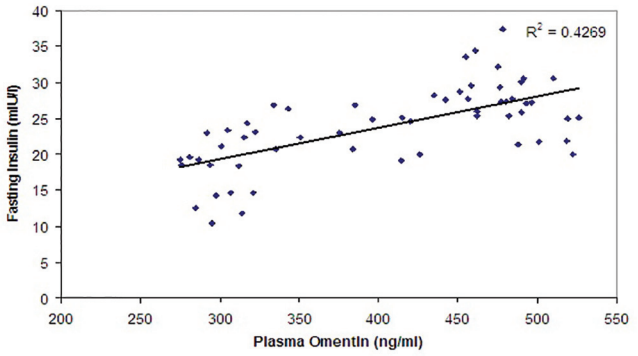
eGFR, estimated glomerular filtration rate; HDL-C, high-density lipoprotein-cholesterol; HOMA-IR, homeostasis model assessment of insulin resistance; hsCRP, highly sensitive C-reactive protein; IL-6, interleukin-6; LDL-C, low-density lipoprotein-cholesterol; TC, total cholesterol; TG, triglycerides; FBG, fasting blood glucose.

Table 3 Laboratory finding in nondiabetic and diabetic groups

Parameters	Predialysis group (*n* = 23)		Hemodialysis group (*n* = 35)		P_1	P_2	P_3	P_4
	Nondiabetic patients (*n* = 23)	Diabetic patients (*n* = 13)	Nondiabetic patients (*n* = 17)	Diabetic patients (*n* = 18)				
Insulin (μU/ml)	18.8 ± 4.2	26.4 ± 0.4	21.2 ± 6.5	28.7 ± 4.5	0.001	0.003	0.3	0.07
HOMA-IR	5.1 ± 1.4	9.1 ± 1.3	5.4 ± 1.7	10.4 ± 2.3	0.001	0.001	0.6	0.07
IL-6	10.7 ± 1.5	11.5 ± 1.6	12.8 ± 1.4	13.7 ± 1.1	0.2	0.04	0.001	0.001
Omentin-1 (ng/ml)	317.73 ± 19	301 ± 11.87	505.12 ± 14	455.17 ± 14	0.01	0.001	0.001	0.001

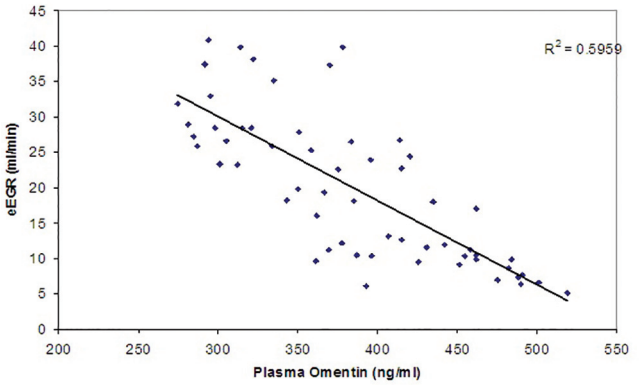
P_1, no diabetes versus diabetes (predialysis group); P_2, no diabetes versus diabetes (hemodialysis group); P_3, no diabetes (predialysis group) versus no diabetes (hemodialysis group); P_4, diabetes (predialysis group) versus diabetes (hemodialysis group); HOMA-IR, homeostasis model assessment of insulin resistance; IL-6, interleukin-6.

Figure 1



Correlation between insulin and omentin-1 levels in predialysis and hemodialysis patients.

Figure 2



Correlation between estimated glomerular filtration rate (eGFR) and plasma omentin-1 levels in predialysis and hemodialysis patients.

Table 4 Correlation between plasma omentin level (ng/ml) and some laboratory parameters

Parameters	*r*	*P*
Insulin	−0.556	0.001
HOMA	−0.429	0.001
eGFR	−0.595	0.001
hsCRP	0.6	0.001
IL-6	0.696	0.001

eGFR, estimated glomerular filtration rate; HOMA, homeostasis model assessment; hsCRP, highly sensitive C-reactive protein.

decrease in omentin levels in CKD patients may be mainly due to inflammation, insulin resistance, and atherosclerosis [13–15]. In this study omentin-1 levels in diabetic CKD patients were found to be lower than in nondiabetic CKD patients; in addition, there was an increase in inflammatory markers such as hsCRP and IL-6 as well as increased insulin resistance. These results are supported by those of Pan *et al.* [16], who suggested that omentin-1 expression and production are decreased with elevated inflammatory adipokines, such as tumor necrosis factor-a and IL-6, in patients with impaired glucose intolerance and newly diagnosed type 2 diabetes mellitus. Yang *et al.* [17] reported that omentin is a secreted factor that improves the effect of insulin on glucose metabolism by increase glucose uptake in human adipocytes and may regulate insulin sensitivity. Yoo *et al.* [18] suggested that omentin-1 levels were significantly decreased in type 2 diabetes patients compared with healthy controls and was further reduced in type 2 diabetes patients with atherosclerosis compared with those without atherosclerosis. In patients with metabolic syndrome omentin levels were found to be low. This state may be related to the accelerated atherosclerosis in metabolic syndrome [19]. Sengul *et al.* [20] reported increased omentin-1 levels and IL-6 in nondiabetic CKD patients compared with healthy individuals. In the current study there were significant positive correlations between plasma omentin-1 level, insulin resistance, IL-6, and hsCRP, and negative correlations with GFR. Omentin-1 has an anti-inflammatory action as illustrated by its ability to reduce the induction of migration, angiogenesis, and activation of nuclear factor k-B) and p38 by proinflammatory factors in endothelial cells and smooth muscle cells, which have a role in the pathogenesis of atherosclerosis [21,22]. Yamawaki *et al.* [23] and Yamawaki *et al.* [24] reported that omentin-1 modulates vascular function and attenuates cyclooxygenase-2 expression and c-jun N-terminal kinase activation in cytokine-stimulated endothelial cells. These studies suggest that high levels of omentin-1 may improve insulin resistance and decrease the progression of atherosclerosis through vascular inflammation suppression. De Souza Batista *et al.* [5] demonstrated that decrease in omentin-1 levels was caused by hyperglycemia. They found that omentin-1 levels were negatively correlated with waist circumference, BMI, leptin, fasting insulin, and HOMA-IR and positively with adiponectin and high-density lipoprotein-cholesterol. Tan *et al.* [25] reported that two major factors affecting the level of circulating omentin-1 are insulin and glucose. They demonstrated a significant decrease in the level of omentin-1 caused by prolonged insulin and glucose infusions. Omentin is a protein expressed and secreted from visceral but not subcutaneous adipose tissue that increases insulin sensitivity in human adipocytes [5]. There are some restrictions in this study, such as small sample size.

Conclusion

From the present study we can conclude that there is an association between omentin-1 and insulin resistance in CKD patients (predialysis or hemodialysis), which may be considered a cardiovascular risk factor in CKD patients.

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Nil.

Conflicts of interest
There are no conflicts of interest.

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