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Fasting Serum Adiponectin Level Inversely Correlates with Metabolic Syndrome in Peritoneal Dialysis Patients

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Key Words
Adiponectin · Peritoneal dialysis · Metabolic syndrome

Abstract
Background: Metabolic syndrome is a significant risk factor for cardiovascular disease and predicts hospitalization in peritoneal dialysis (PD) patients. An inverse association between circulating adiponectin and metabolic syndrome has been observed in humans. However, no data are available on the relationship between metabolic syndrome and serum adiponectin levels in PD patients. ***Method:*** Fasting blood samples were obtained from 47 PD patients and 47 subjects in an outpatient department were enrolled as a control group. Metabolic syndrome and its components were defined using diagnostic criteria from the International Diabetes Federation. Adiponectin levels were measured using a commercial enzyme immunoassay kit. ***Results:*** Twenty-seven of 47 PD patients (57.5%) had metabolic syndrome. PD patients had lower serum albumin ($p < 0.001$) and higher serum adiponectin levels ($p = 0.016$), high-sensitivity C-reactive protein ($p = 0.008$), creatinine ($p < 0.001$) and metabolic syndrome ($p < 0.001$) than controls. The fasting adiponectin level inversely correlated with the metabolic syndrome in these PD patients ($p = 0.006$). Univariate linear regression analysis showed that the waist circumference ($r = -0.304$; $p = 0.038$), body mass index ($r = -0.347$; $p = 0.017$), body fat mass ($r = -0.305$; $p = 0.037$), white blood count ($r = -0.631$; $p < 0.001$), triglyceride (TG; $r = -0.526$; $p < 0.001$), and fasting glucose ($r = -0.394$; $p = 0.006$) were negatively correlated with the fasting serum adiponectin levels, while high-density lipoprotein-cholesterol ($r = 0.443$; $p = 0.002$) was positively correlated with the fasting serum adiponectin levels among the PD patients. Multivariate forward stepwise linear regression analysis of the significant variables showed that white blood count (R^2 change = 0.398, $p < 0.001$), and TG (R^2 change = 0.118, $p = 0.002$) were the independent predictors of fasting serum adiponectin levels and explained 51.6% of variance. ***Conclusions:*** We observed that PD patients had higher metabolic syndrome than the general population and an inverse association was found between the circulating fasting adiponectin level and metabolic syndrome in PD patients. White blood count and TG were independent predictors of the serum adiponectin level among PD patients.

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Introduction

Adiponectin is a novel collagen-like protein synthesized by white adipose tissue and is an important adipokine because of its beneficial effects on glucose and lipid metabolism [1]. Adiponectin plays an important role in the inhibition of inflammatory response and possesses anti-atherogenic properties [2]. Plasma adiponectin levels have been inversely correlated with obesity, coronary artery disease and diabetes [3–6]. Moreover, plasma adiponectin levels are an inverse predictor of cardiovascular outcomes among hemodialysis patients [7, 8] and peritoneal dialysis (PD) patients [9, 10].

Metabolic syndrome is a significant risk factor for cardiovascular disease, mortality and chronic kidney disease in the general population [11, 12]. Metabolic syndrome also predicts hospitalization in uremic patients [13]. Cardiovascular disease is the leading cause of mortality among PD patients [14]. Recent studies showed an inverse association between circulating adiponectin and metabolic syndrome in humans [15–17]. The association between serum adiponectin and metabolic syndrome in peritoneal hemodialysis patients has not been examined. The aim of this study was to investigate the relationships of fasting serum adiponectin level and the metabolic syndrome among PD patients.

Patients and Methods

In June 2008, sixty PD patients who had received regular PD for more than 3 months at a medical center in Hualien, eastern Taiwan, were recruited. Patients were excluded if they had any acute infection at the time of blood sampling, such as peritonitis (1 patient) and peritoneal catheter exit-site infection (2 patients), or refusal to provide informed consent for the study (10 patients). Patients were included if they agreed to this study and provided informed consent. A total of 47 PD patients agreed to this study and serum samples were collected. The mean duration of PD treatment was 38.00 ± 31.33 months. As controls 47 age-matched patients with normal renal function were enrolled at the same time from the cardiac outpatient department of the same hospital. The Protection of Human Subjects Institutional Review Board of Tzu-Chi University and Hospital approved this study. Thirty-four patients had been on continuous ambulatory peritoneal dialysis (CAPD; Dianeal, Baxter Health Care, Taiwan) with 3–5 dialysate exchanges/day. The other 13 patients performed 4–5 dialysate exchanges each night with an automated peritoneal device.

Anthropometric Analysis

Body weight was measured in light clothing and without shoes and without the presence of dialysate in the abdominal cavity in the PD patients to the nearest 0.5 kg. Height was measured to the nearest 0.5 cm. Waist circumference was measured to the nearest 0.5 cm at the shortest point below the lower rib margin and the iliac crest without the presence of dialysate in the abdominal cavity in the PD patients. Body mass index (BMI) was calculated as weight (kilograms) divided by height (meters) squared. Subjects with BMIs of ≥27 were considered obese by Asian population standards [18]. Bioimpedance measurements of fat mass were performed at the bedside according to the standard, tetrapolar, whole body (hand-foot) technique, using a single-frequency (50-kHz) analyzer (Biodynamic-450, Biodynamics Corp., Seattle, Wash., USA). Measurements were carried out by the same operator without dialysate in the abdominal cavity of the PD patients; fat mass data were collected and analyzed by specific formulae offered by the manufacturer [19].

Biochemical Investigations

Dialysis exchange was not performed before blood sampling in the morning. Fasting blood samples taken from each subject were immediately centrifuged for biochemical study. To measure hemoglobin (Sysmex K-1000, Sysmed, Chicago, Ill., USA), blood samples of approximately 0.5 ml were immediately centrifuged at 3,000 *g* for 10 min. The serum was stored at 4°C for biochemical examination within 1 h after collection. Serum levels of blood urea nitrogen, creatinine (Cre), fasting glucose, total cholesterol (TCH), triglyceride (TG), high-density lipoprotein-cholesterol (HDL-C), albumin, glutamic oxaloacetic transaminase, glutamic pyruvic transaminase, uric acid, and high-sensitivity C-reactive protein (hs-CRP) were measured using an autoanalyzer (COBAS Integra 800, Roche Diagnostics, Basel, Switzerland). Serum intact parathyroid hormone (Diagnostic Systems Laboratories, Webster, Tex., USA) levels and adiponectin (SPI-BIO, Montigny le Bretonneux, France) levels were measured using a commercially available enzyme immunoassay [19]. The limit of detection calculated as the concentration of human adiponectin corresponding to the blank average minus three standard deviations was 0.7 μg/ml. The inter- and intra-assay coefficients of variation for adiponectin were 7.3 and 6.4%. Patients were classified as secondary hyperparathyroidism if serum intact parathyroid hormone greater than 300 pg/ml.

Metabolic Syndrome and Its Components

The prevalence of the metabolic syndrome and its components were defined using the International Diabetes Federation definition [20]. People were classified as having metabolic syndrome if they had central (abdominal) obesity with a waist circumference of ≥90 (men) or ≥80 cm (women; Chinese criteria), plus two or more of the following: fasting serum glucose of 110 mg/dl or more, TGs of 150 mg/dl or higher, HDL-C level of <40 mg/dl in men or <50 mg/dl in women, or blood pressure of 130/85 mm Hg or higher. The use of antihypertensive medication was included as high blood pressure in this analysis. Type 2 diabetes was determined according to World Health Organization criteria [21]. A person was regarded as diabetic if their fasting plasma glucose was 126 mg/dl or more, if the 2-hour glucose during an oral glucose tolerance test was 200 mg/dl or more, or if he/she was using diabetes medication (oral or insulin).

Cumulative Glucose Load

The total exposure to glucose was calculated from the dialysis regime reported the day before blood sampling. The product of the volume and the glucose concentration for each exchange was

calculated. For example, for an individual who was using 4 × 2-liter exchanges (2 × 1.36%, 1 × 2.27%, and 1 × 3.86%), there would be 54.4 + 45.4 + 77.2 = 176.8 g of glucose/day, as described by Davies et al. [22].

Statistical Analysis

Data are expressed as means ± standard deviations (SDs). Categorical variables were analyzed by χ^2 test. Comparisons between patients were performed using Student's independent t test (two-tailed) for normally distributed data or Mann-Whitney U test for parameters presented with non-normal distribution (fasting glucose, hs-CRP). Clinical variables correlated with serum adiponectin levels in PD patients were evaluated by univariate linear analyses. Variables significantly associated with adiponectin in PD patients were tested for independence in multivariate forward stepwise analysis. Data were analyzed using SPSS for Windows (version 11.0; SPSS Inc., Chicago, Ill., USA). A p value of <0.05 was considered statistically significant.

Results

The clinical and laboratory characteristics of the PD patients and controls are presented in tables 1 and 2. PD patients had lower serum albumin ($p < 0.001$) and higher serum adiponectin levels ($p = 0.016$), hs-CRP ($p = 0.008$),

Table 1. Baseline characteristics of peritoneal dialysis patients and control group

Characteristic	PD	Control	p value
Gender			
Male	17 (36.1)	24 (51.1)	0.212
Female	30 (63.9)	23 (48.9)	
Age			
<65 years	34 (72.3)	31 (66.0)	0.656
≥65 years	13 (27.7)	14 (34.0)	
Diabetes			
No	31 (65.9)	29 (61.7)	0.830
Yes	16 (34.1)	18 (38.3)	
Hypertension			
No	24 (51.1)	16 (34.1)	0.144
Yes	23 (48.9)	31 (65.9)	
Obesity			
No	40 (85.1)	38 (80.9)	0.785
Yes	7 (14.9)	9 (19.1)	
Metabolic syndrome			
No	20 (42.5)	36 (76.6)	<0.001*
Yes	27 (57.5)	11 (23.4)	

Data are expressed as the number of patients (%) and analysis was made by χ^2 test.

* $p < 0.05$ was considered statistically significant.

Table 2. Clinical variables of peritoneal dialysis patients and control group

Variable	PD (n = 47)	Control (n = 47)	p value
Age, year	56.00 ± 14.80	59.04 ± 11.37	0.267
Height, cm	157.57 ± 8.48	160.19 ± 9.26	0.155
Body weight, kg	58.24 ± 11.23	61.97 ± 10.50	0.100
Waist circumference, cm	87.92 ± 12.20	86.15 ± 13.51	0.506
BMI	23.51 ± 3.89	24.19 ± 3.96	0.345
Body fat mass, %	27.09 ± 10.25	29.89 ± 7.71	0.137
Albumin, g/dl	3.62 ± 0.58	4.33 ± 0.40	<0.001*
Total cholesterol, mg/dl	192.57 ± 46.33	179.32 ± 36.43	0.121
Triglyceride, mg/dl	189.26 ± 111.20	174.91 ± 135.55	0.567
HDL-C, mg/dl	48.70 ± 18.89	45.21 ± 12.15	0.291
Fasting glucose, mg/dl	124.04 ± 57.87	114.43 ± 34.25	0.329
Creatinine, mg/dl	10.18 ± 3.76	0.85 ± 0.27	<0.001*
Uric acid, mg/dl	6.79 ± 1.24	6.70 ± 2.00	0.800
hs-CRP, mg/dl	1.12 ± 1.81	0.38 ± 0.46	0.008*
Adiponectin, μg/ml	24.61 ± 9.14	12.90 ± 13.88	<0.001*

Data are expressed as means ± SD. HDL-C = High-density lipoprotein-cholesterol; hs-CRP = high-sensitivity C-reactive protein.

* $p < 0.05$ was considered statistically significant according to Student's t test or Mann-Whitney U test (fasting glucose, hs-CRP).

Table 3. Clinical characteristics and fasting serum adiponectin levels of the 47 peritoneal dialysis patients

Characteristic	Number	Adiponectin level, pg/ml	p value
Gender			
Male	17 (36.2)	25.59 ± 8.51	0.586
Female	30 (63.8)	24.14 ± 9.62	
Age			
<65 years	34 (72.3)	25.02 ± 9.55	0.625
≥65 years	13 (27.7)	23.54 ± 8.24	
Diabetes			
No	31 (65.9)	25.16 ± 8.71	0.578
Yes	16 (44.1)	23.56 ± 10.14	
Hypertension			
No	24 (51.1)	24.13 ± 8.78	0.718
Yes	23 (48.9)	25.11 ± 9.68	
Hyperparathyroidism			
No	29 (61.7)	24.69 ± 9.96	0.943
Yes	18 (38.3)	24.49 ± 7.94	
Metabolic syndrome			
No	20 (42.5)	28.73 ± 7.41	0.006*
Yes	27 (57.5)	21.56 ± 9.22	
PD model			
CAPD	34 (72.3)	23.94 ± 9.05	0.417
APD	13 (27.7)	26.38 ± 9.52	
Extraneal used			
No	29 (61.7)	25.36 ± 8.09	0.485
Yes	18 (38.3)	23.42 ± 10.78	
Thiazolidinediones			
No	43 (91.5)	23.97 ± 9.09	0.118
Yes	4 (8.5)	31.48 ± 7.57	
ACE inhibitor or ARB			
No	28 (59.6)	22.57 ± 9.75	0.063
Yes	19 (40.4)	27.62 ± 7.42	
Statin			
No	34 (72.3)	25.55 ± 9.75	0.259
Yes	13 (27.7)	27.15 ± 7.09	

DM = Diabetes mellitus; PD = peritoneal dialysis; APD = automated peritoneal dialysis; CAPD = continuous ambulatory peritoneal dialysis; ACE = angiotensin-converting enzyme; ARB = angiotensin receptor blocker. Data are expressed as the number of patients (%) or mean ± SD.

* $p < 0.05$ was considered statistically significant according to Student's t test.

Table 4. Correlation of fasting serum adiponectin levels and clinical variables by univariate linear analyses among the 47 peritoneal dialysis patients

Items	β	p value
Age, years	–0.180	0.227
Peritoneal dialysis duration, months	–0.066	0.660
Height, cm	0.085	0.572
Body weight, kg	–0.244	0.098
Waist circumference, cm	–0.304	0.038*
BMI	–0.347	0.017*
Body fat mass, %	–0.305	0.037*
White blood count, ×1,000/μl	–0.631	<0.001*
Hemoglobulin, g/dl	0.003	0.983
Platelet count, ×1,000/μl	–0.170	0.254
Albumin, g/dl	–0.287	0.051
GOT, IU/l	0.090	0.547
GPT, IU/l	0.045	0.766
Total cholesterol, mg/dl	–0.163	0.275
Triglyceride, mg/dl	–0.526	<0.001*
HDL-C, mg/dl	0.443	0.002*
Fasting glucose, mg/dl	–0.394	0.006*
Creatinine, mg/dl	0.125	0.402
Intact parathyroid hormone, pg/ml	–0.080	0.592
hs-CRP, mg/dl	–0.277	0.059
Weekly Kt/V	0.055	0.713
nPNA, g/kg/day	0.029	0.848
Cumulative glucose load, g/day	0.017	0.909

HDL-C = High-density lipoprotein-cholesterol; Kt/V = fractional clearance index for urea; nPNA = normalized protein nitrogen appearance; hs-CRP = high-sensitivity C-reactive protein.

* $p < 0.05$ was considered statistically significant after univariate linear analyses.

Cre ($p < 0.001$) and metabolic syndrome ($p < 0.001$) than controls. There was no significant difference by gender distribution, age, diabetes, hypertension, obesity, height, body weight, waist circumference, BMI, body fat mass, TCH, TG, HDL-C, fasting glucose, or uric acid between PD patients and controls.

The clinical characteristics and fasting serum adiponectin levels of the 47 PD patients are presented in table 3. Twenty-seven patients (57.5%) had metabolic syndrome, whereas 20 patients (42.5%) did not. PD patients who had metabolic syndrome had lower serum fasting adiponectin levels than those without metabolic syndrome ($p = 0.006$). Adiponectin levels did not differ statistically by gender distribution, age, diabetes, hypertension, coronary artery disease, secondary hyperparathyroidism, PD model, extraneal, thiazolidinediones, angiotensin-converting enzyme inhibitors, or angiotensin receptor-blocker drugs used.

Univariate linear analysis of fasting serum adiponectin levels in PD patients are presented in table 4. Waist circumference ($r = –0.304$; $p = 0.038$), BMI ($r = –0.347$;

Table 5. Multivariate stepwise linear regression analysis of waist circumference, body mass index, body fat mass, white blood count, triglyceride, fasting glucose and high-density lipoprotein-cholesterol: correlation to fasting serum adiponectin level among 47 peritoneal dialysis patients

Items	β	R^2	R^2 change	p value
White blood count, ×1,000/μl	−0.516	0.398	0.398	<0.001*
Triglyceride, mg/dl	−0.362	0.516	0.118	0.002*

* $p < 0.05$ is considered statistically significant in the multivariate stepwise linear regression analyses.

p = 0.017), body fat mass (r = −0.305; p = 0.037), white blood count (r = −0.631; p < 0.001), TG (r = −0.526; p < 0.001), and fasting glucose (r = −0.394; p = 0.006) were negatively correlated with the fasting serum adiponectin levels, while HDL-C (r = 0.443; p = 0.002) was positively correlated with the fasting serum adiponectin levels among the PD patients. Age (r = −0.180; p = 0.227), duration of PD (r = −0.066; p = 0.660), height (r = 0.085; p = 0.572), body weight (r = −0.244; p = 0.098), systolic blood pressure (r = 0.268; p = 0.069), hemoglobulin (r = 0.003; p = 0.983), platelet (r = −0.170; p = 0.254), albumin (r = −0.287; p = 0.051), glutamic oxaloacetic transaminase (r = 0.090; p = 0.547), glutamic pyruvic transaminase (r = 0.045; p = 0.766), TCH (r = −0.163; p = 0.275), Cre (r = 0.125; p = 0.402), intact parathyroid hormone (r = −0.080; p = 0.592), hs-CRP (r = −0.277; p = 0.059), weekly Kt/V (r = 0.055; p = 0.713), cumulative glucose load (r = 0.017; p = 0.909) and nPNA (r = 0.029; p = 0.848) were not associated with fasting serum adiponectin levels among the PD patients.

Multivariate forward stepwise linear regression analysis of the variables was significantly associated with fasting serum adiponectin level among patients on PD, showing that white blood count (R^2 change = 0.398, p < 0.001) and TG (R^2 change = 0.118, p = 0.002) are independent predictors of fasting serum adiponectin levels and explained 51.6% of variance (table 5).

Discussion

The results of our study showed a high prevalence of metabolic syndrome and higher serum adiponectin levels in PD patients than controls. The fasting adiponectin level was inversely associated with metabolic syndrome in PD patients. White blood count and TG were an independent predictor of the adiponectin level among PD patients.

Metabolic syndrome is a constellation of physical and laboratory abnormalities including hypertension, hyperglycemia, hyperlipidemia and abdominal obesity [20]. It constitutes a major health problem in the West and is estimated to affect at least 20% of the adult population [23]. Recent studies also demonstrated that metabolic syndrome is a significant risk factor for cardiovascular disease, mortality and chronic kidney disease in the general population [11, 12]. PD patients have an increased metabolic syndrome prevalence ranging from 22.1% at baseline to 69.2% during PD [24]. The prevalence of metabolic syndrome in our study was 57.5%, which is almost the same as that reported by other studies in PD patients [25, 26]. Our study also noted that metabolic syndrome in PD patients is higher than in the general population. Previous studies have demonstrated that CRP is independently associated with mortality and cardiovascular death in PD patients [10, 27]. Cardiovascular disease is the leading cause of mortality among PD patients [28]. Our study showed that PD patients had a higher serum hs-CRP level than the general population. Infections, malnutrition, bioincompatible dialysis solution, and cardiovascular disease all cause higher CRP in PD patients [28].

Adiponectin, an adipokine secreted by the white adipose tissue, plays an important role in regulating glucose and lipid metabolism and controlling energy homeostasis in insulin-sensitive tissues [1]. A decrease in the circulating level of adiponectin has been linked to insulin resistance, type 2 diabetes, atherosclerosis, and metabolic syndrome [29]. Serum adiponectin concentrations were reported to be increased in chronic kidney disease patients before dialysis and in patients on maintenance dialysis [7, 9, 30]. Our study noted higher serum adiponectin levels in PD patients than controls.

Serum adiponectin levels were positively correlated with HDL-C [5, 6] and negatively correlated with TG and

waist circumference in patients with type 2 diabetes [5, 31]. Recent studies also noted that serum adiponectin levels were positively correlated with HDL-C and negatively correlated with TG in PD patients [9, 30]. The administration of adiponectin enhances insulin sensitivity and reduces glucose levels in animal models, in part through mechanisms involving the hexosamine signaling pathway [32]. Human studies have shown a correlation between plasma adiponectin levels and insulin sensitivity [33]. Adiponectin may play a protective role against atherosclerosis [34]. Our study also found that waist circumference, TG and fasting glucose were negatively correlated with fasting serum adiponectin levels, while HDL-C was positively correlated with the fasting serum adiponectin levels of PD patients. Recent studies showed an inverse association between circulating adiponectin and metabolic syndrome in humans [15–17]. Our study also showed that the fasting serum adiponectin levels were inversely associated with metabolic syndrome in PD patients.

Adiponectin plasma levels correlate negatively with BMI in PD patients [9]. We also found that fasting adiponectin was negatively correlated with BMI among our PD patients. Serum adiponectin is inversely correlated with body fat mass in obesity [3]. Our results also noted that body fat mass is inversely correlated with the fasting adiponectin level in PD patients. Some studies have shown a negative correlation between serum adiponectin levels and CRP among PD patients [9], but ours did not. Other studies noted negative associations of the serum adiponectin level with white blood count in obesity [35]. Our study also demonstrated inverse associations between the serum adiponectin level and white blood count.

A previous study showed that the administration of thiazolidinediones increases the serum adiponectin concentration in diabetic patients [36]. Use of an angiotensin-converting enzyme inhibitor was associated with an increase in plasma adiponectin in patients with essential hypertension and those with diabetes [37–39]. Furthermore, candesartan was reported to increase the plasma adiponectin level in association with a reduction in oxidative stress in PD patients [40]. Treatment with ramipril given alone or in combination with simvastatin has also been reported to be associated with an increased adiponectin concentration in patients with type 2 diabetes [39]. Our results did not show a relationship between drug medication and serum adiponectin among PD patients. Further studies are required to elucidate the relationship between drug medication and adiponectin in PD patients.

In our study, waist circumference, BMI, body fat mass, white blood count, TG, and fasting glucose were inversely correlated, and serum HDL-C was positively correlated with serum adiponectin levels among PD patients. After multivariate forward stepwise linear regression analysis, white blood count and TG were independent predictors of fasting adiponectin among PD patients; these independent variables explained 51.6% of the variance in the adiponectin level among the patients.

Our study has some limitations. First, the number of patients enrolled was too small and more patients are needed for further analysis. Second, this study is cross-sectional in design. Therefore our findings should be investigated in long-term prospective studies before a causal relationship between serum adiponectin and metabolic syndrome in PD patients can be established. Another limitation to the interpretation of results is the lack of a clear definition for metabolic syndrome in PD patients, since these patients are quite peculiar in terms of body composition and glucose exposure. Further studies are needed to show the association of metabolic syndrome and serum adiponectin levels in PD patients.

Conclusions

We found an inverse association between circulating fasting adiponectin and metabolic syndrome among our PD patients. White blood count and TG were independent predictors of the serum adiponectin level in PD patients.

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