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Original Article

Hypoadiponectinemia is associated with metabolic syndrome in hemodialysis patients

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ABSTRACT

Objective: The serum adiponectin level decreases in patients with metabolic syndrome (MetS) and is an inverse predictor of cardiovascular outcomes in hemodialysis (HD) patients. The aim of this study was to investigate the relationship of adiponectin and MetS among HD patients.
Materials and Methods: Fasting blood samples were obtained from 101 HD patients. MetS and its components were defined using diagnostic criteria from the International Diabetes Federation.
Results: Forty-eight of the 101 HD patients (47.5%) had MetS. Adiponectin levels negatively correlated with MetS among HD patients ($p = 0.001$). Univariate linear regression analysis showed that the pre-HD body weight ($p < 0.001$); waist circumference ($p = 0.001$); body mass index (BMI; $p < 0.001$); hemoglobin ($p = 0.038$); triglyceride level ($p < 0.001$); insulin level ($p = 0.005$); and homeostasis model assessment of insulin resistance ($p = 0.001$) correlated negatively with the fasting serum adiponectin levels, whereas the high-density-lipoprotein cholesterol (HDL-C; $p < 0.001$) level correlated positively with the fasting serum adiponectin levels in the HD patients. Multivariate forward stepwise linear regression analysis of the significant variables showed that the HDL-C level (R^2 change = 0.142, $p = 0.001$) and BMI (R^2 change = 0.078, $p = 0.002$) were independent predictors of fasting serum adiponectin levels in HD patients.
Conclusion: The serum adiponectin concentration correlates inversely with MetS in HD patients. For these patients, the HDL-C level and BMI are independent predictors of the serum adiponectin value.

1. Introduction

Metabolic syndrome (MetS), a constellation of physical and laboratory abnormalities, including hypertension, hyperglycemia, dyslipidemia, and central obesity, affects about 47 million people in the United States and places them at about a threefold increase in risk for coronary artery disease and stroke [1–5]. MetS is associated with chronic kidney disease (CKD) and increases cardiovascular mortality [1,5].

Adiponectin is a 247-amino acid protein that is produced largely by white adipose tissue and has a wide range of effects in the immune and inflammatory components of pathogenesis, such as those in cardiovascular disease (CVD), Type 2 diabetes mellitus (DM), and MetS [6,7]. Although the adiponectin level is generally elevated in dialysis patients, it has been observed that dialysis patients with relatively lower adiponectin levels have an increased mortality rate [8–10].

Although hypoadiponectinemia has been found to be an independent risk marker for MetS in Type 2 DM, in obese children and adolescents and in middle and elderly populations, few studies have examined the characteristics of adiponectin in maintenance hemodialysis (HD) patients [11–13]. This study is intended to investigate the adiponectin distribution and relationships with MetS and the components of MetS in HD patients.

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2. Materials and methods

2.1. Patients

One hundred one HD patients, including 55 men and 46 women with the same high-flux polysulfone disposable artificial kidney (FX class dialyzer; Fresenius Medical Care, Bad Homburg, Germany), were enrolled in June 2009 at Dalin Tzu Chi General Hospital, Chiayi, Taiwan. Patients from our HD program were invited to participate in the study if they were older than 20 years, were receiving standard 4-hour three-time weekly dialysis using standard bicarbonate dialysate, and had been on dialysis for at least 12 months. Patients were excluded if they had any acute infection, a life expectancy of less than 3 months, malignancy, or refusal or inability to provide informed consent for the study. The Protection of Human Subjects Institutional Review Board at Tzu Chi Hospital approved the study. The Kt/*V* and urea reduction ratio (URR) were measured before dialysis and immediately after dialysis using a formal, single-compartment dialysis urea kinetic model.

2.2. Anthropometric analysis

Body weight (BW) was measured to the nearest half kilogram with the patient in light clothing without shoes. Height was measured to the nearest half centimeter. Waist circumference was measured in a horizontal plane, midway between the inferior margin of the ribs and the superior border of the iliac crest. Body mass index (BMI) was calculated as weight (kilograms) divided by height squared (meters) [14].

2.3. Biochemical investigations

Fasting blood samples of approximately 0.5 mL were drawn to measure the complete blood count (Sysmex K-1000; Sysmex, Bohemia, NY, USA) and other factors, and were immediately centrifuged at 3000 *g* for 10 minutes. Serum samples were stored at 4°C and used for biochemical analyses within 1 hour of collection. Serum levels of BUN, creatinine, fasting glucose, total cholesterol, triglycerides (TGs), high-density-lipoprotein cholesterol (HDL-C), albumin, and C-reactive protein (CRP) were measured using a commercial kit (COBAS Integra 800; Roche Diagnostics, Basel, Switzerland). The serum intact parathyroid hormone levels were measured using a commercially available enzyme-linked immunosorbent assay (Diagnostic Systems Laboratories, Webster, TX, USA) [14]. Patients were classified as having secondary hyperparathyroidism if the intact parathyroid hormone level was greater than 300 pg/mL. Serum adiponectin (SPI- BIO, Montigny le Bretonneux, France) concentrations were determined using a commercially available enzyme immunoassay [14]. The limit of detection, calculated as the concentration of human adiponectin corresponding to the blank average minus 3 standard deviations, was 0.7 μg/mL. The inter- and intra-assay coefficients of variation for adiponectin were 7.3% and 6.4%, respectively. The serum insulin levels were measured using the microparticle enzyme immunosorbent assay method by an autoanalyzer (Abbott Laboratories, Abbott Park, IL, USA). Insulin resistance was evaluated using a homeostasis model assessment of insulin resistance (HOMA-IR) as follows: HOMA-IR = glucose (mg/dL) × insulin (μU/mL)/405 [15].

2.4. MetS and its components

The presence of MetS was established using the International Diabetes Federation definition [3]. Patients were diagnosed as having MetS if they had central (abdominal) obesity with a waist circumference greater than or equal to 90 cm (Chinese males) or greater than or equal to 80 cm (Chinese females), plus two or more of the following: (1) fasting serum glucose values of 110 mg/dL or greater; (2) TG values of 150 mg/dL or greater; (3) HDL-C concentrations less than 40 mg/dL for males or less than 50 mg/dL for females; or (4) blood pressure measurements of 130/85 mmHg or higher or use of antihypertensive agents. The presence of Type 2 DM was established according to World Health Organization criteria [4]. An individual was considered diabetic if the fasting plasma glucose was 126 mg/dL or greater, 2-hour glucose during an oral glucose tolerance test was 200 mg/dL or greater, or if antidiabetic therapy (oral agent or insulin) was required.

2.5. Statistical analysis

Data were expressed as mean ± standard deviation. Categorical variables were analyzed by the Chi-square test. Comparisons between patients were performed using Student independent *t* test (two-tailed) for parametric data or the Mann-Whitney *U* test for parameters presenting with nonparametric distributions (TG, fasting glucose, CRP, insulin, and HOMA-IR). Correlations of clinical variables with serum adiponectin concentrations were evaluated by univariate linear regression analysis. Variables significantly associated with adiponectin in HD patients were tested for independence by multivariate stepwise linear regression analysis. Data were analyzed using SPSS for Windows (version 13.0; SPSS Inc., Chicago, IL, USA). A *p* value less than 0.05 was considered statistically significant.

3. Results

Biochemical and clinical characteristics of the 101 HD patients are presented in Table 1. The causes of uremia included DM ($n = 28$; 27.7%); hypertensive nephrosclerosis ($n = 37$; 36.6%); glomerulonephritis ($n = 19$; 18.8%); and others ($n = 17$; 16.9%).

Table 1
Clinical and analytical characteristics of 101 hemodialysis patients

	Parameter	
Anthropometric data	Height (cm)	154.43 ± 8.16
	Pre-HD body weight (kg)	60.88 ± 13.39
	Body mass index (kg/m^2)	25.73 ± 6.25
	Systolic pressure (mmHg)	145.37 ± 22.36
	Waist circumference (cm)	88.02 ± 10.75
	Age (y)	62.00 ± 13.62
	HD duration (mo)	71.51 ± 45.47
	Diastolic pressure (mmHg)	78.00 ± 14.26
Biochemical data	White blood count (×1000/uL)	6.58 ± 3.09
	Albumin (g/dL)	3.97 ± 0.41
	Triglyceride (mg/dL)	136.99 ± 92.00
	Fasting glucose (mg/dL)	143.83 ± 65.57
	Blood urea nitrogen (mg/dL)	60.95 ± 15.47
	C-reactive protein (mg/dL)	0.85 ± 1.97
	Kt/*V* (Gotch)	1.46 ± 0.20
	Adiponectin (μg/mL)	23.55 ± 16.62
	Hemoglobin (g/dL)	10.56 ± 1.38
	Total cholesterol (mg/dL)	160.05 ± 39.56
	High-density-lipoprotein cholesterol (mg/dL)	43.54 ± 16.81
	Creatinine (mg/dL)	9.11 ± 2.09
	Intact parathyroid hormone (pg/mL)	239.23 ± 226.01
	Urea reduction ratio	0.76 ± 0.05
	Insulin (μU/dL)	23.54 ± 33.60
	Homeostasis model assessment of insulin resistance	7.92 ± 10.24
Causes of uremia	Diabetes	28 (27.7)
	Glomerulonephritis	19 (18.8)
	Hypertension	37 (36.6)
	others	17 (16.9)

Data are expressed as means ± standard deviations or *n* (%).
HD = hemodialysis.

The baseline characteristics of these 101 HD patients are presented in Table 2. Forty-eight patients (47.5%) were diagnosed as having MetS. HD patients with MetS had a significantly higher pre-HD BW ($p < 0.001$), waist circumference ($p < 0.001$), BMI ($p < 0.001$), TG level ($p = 0.001$), insulin level ($p < 0.001$), and HOMA-IR ($p < 0.001$), but a significantly lower HDL-C level ($p = 0.002$), URR ($p = 0.004$), and Kt/V ($p = 0.047$) than those without MetS. No statistically significant differences were found between HD patients with and without MetS in terms of gender, age, HD duration, DM, hypertension, hyperparathyroidism, systolic blood pressure, or diastolic blood pressure.

Clinical characteristics and fasting serum adiponectin values for the 101 HD patients are presented in Table 3. The fasting serum adiponectin level negatively correlated with MetS among HD patients ($p = 0.001$). No statistically significant differences in adiponectin values were found as a function of gender; presence of DM, hypertension, or hyperparathyroidism; or use of angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, β-blockers, calcium channel blockers, or statins.

Univariate linear analysis of fasting serum adiponectin concentrations with clinical variables in HD patients is presented in Table 4. The pre-HD BW ($r = -0.374$, $p < 0.001$); waist circumference ($r = -0.328$, $p = 0.001$); BMI ($r = -0.363$, $p < 0.001$); hemoglobin ($r = -0.207$, $p = 0.038$); TG level ($r = -0.353$, $p < 0.001$); insulin level ($r = -0.273$, $p = 0.005$); and HOMA-IR ($r = -0.317$, $p = 0.001$) correlated negatively with fasting serum adiponectin values, whereas the HDL-C level ($r = 0.377$, $p < 0.001$) correlated positively with the fasting serum adiponectin level in HD patients.

Analysis using multivariate stepwise linear regression of the variables (pre-HD BW, BMI, hemoglobin, TG, insulin, HOMA-IR, and HDL-C) significantly associated with fasting serum adiponectin in HD patients revealed that the HDL-C level ($R^2 = 0.142$, $p = 0.001$) and BMI ($R^2 = 0.078$, $p = 0.002$) were independent predictors associated with serum adiponectin in HD patients (Table 5).

Table 2
Comparison of individuals with and without metabolic syndrome

Items	No metabolic syndrome ($n = 53$)	Metabolic syndrome ($n = 48$)	p
Gender (male)	31 (58.5)	24 (50.0)	0.392
Diabetes mellitus	13 (24.5)	17 (35.4)	0.232
Hypertension	27 (50.9)	30 (62.5)	0.242
Hyperparathyroidism	14 (26.4)	9 (18.8)	0.359
Age (y)	61.45 ± 13.51	62.60 ± 13.84	0.673
Hemodialysis duration (mo)	78.51 ± 50.72	63.77 ± 37.90	0.104
Height (cm)	154.85 ± 9.54	153.96 ± 6.39	0.587
Pre-hemodialysis body weight (kg)	55.20 ± 11.25	67.15 ± 12.84	<0.001*
Waist circumference (cm)	81.01 ± 7.53	95.76 ± 8.15	<0.001*
Body mass index (kg/m^2)	22.56 ± 5.21	27.49 ± 5.78	<0.001*
White blood count (×1000/uL)	6.51 ± 3.74	6.65 ± 2.18	0.829
Hemoglobin (g/dL)	10.40 ± 1.48	10.74 ± 1.25	0.214
Albumin (g/dL)	3.98 ± 0.36	3.97 ± 0.47	0.899
Total cholesterol (mg/dL)	161.17 ± 37.87	158.81 ± 41.70	0.767
Triglyceride (mg/dL)	115.58 ± 84.86	160.63 ± 94.61	0.001*
High-density-lipoprotein cholesterol (mg/dL)	48.36 ± 15.82	38.23 ± 16.41	0.002*
Fasting glucose (mg/dL)	154.36 ± 79.50	142.15 ± 46.35	0.324
Blood urea nitrogen (mg/dL)	59.32 ± 15.86	62.75 ± 14.99	0.268
Creatinine (mg/dL)	8.89 ± 1.99	9.36 ± 2.19	0.264
C-reactive protein (mg/dL)	0.95 ± 2.32	0.72 ± 1.51	0.747
Systolic blood pressure (mmHg)	145.87 ± 22.37	144.81 ± 22.57	0.814
Diastolic blood pressure (mmHg)	76.42 ± 13.30	79.75 ± 15.20	0.243
Intact parathyroid hormone (pg/mL)	259.03 ± 244.81	217.36 ± 203.57	0.403
Insulin (μU/dL)	16.10 ± 32.49	31.75 ± 33.21	<0.001*
Homeostasis model assessment of insulin resistance	5.29 ± 8.86	10.82 ± 10.96	<0.001*
Urea reduction ratio	0.78 ± 0.05	0.75 ± 0.004	0.004*
Kt/V (Gotch)	1.50 ± 0.22	1.42 ± 0.16	0.047*

Data are expressed as means ± standard deviations or n (%).
*$p < 0.05$ versus other group.

Table 3
Clinical characteristics and fasting serum adiponectin levels of the 101 hemodialysis patients

Characteristic	n (%)	Adiponectin level (μg/mL)	p
Gender			
Male	55 (54.5)	23.09 ± 16.11	0.765
Female	46 (45.5)	24.09 ± 17.34	
Diabetes			
No	71 (70.3)	25.63 ± 17.44	0.052
Yes	30 (29.7)	18.62 ± 13.49	
Hypertension			
No	44 (43.6)	24.52 ± 20.00	0.607
Yes	57 (56.4)	22.80 ± 13.59	
Hyperparathyroidism			
No	78 (77.2)	22.67 ± 16.68	0.328
Yes	23 (22.8)	26.54 ± 16.41	
Metabolic syndrome			
No	53 (52.5)	28.81 ± 18.65	0.001*
Yes	48 (47.5)	17.75 ± 11.71	
Angiotensin-converting enzyme inhibitor			
No	88 (87.1)	23.73 ± 17.15	0.774
Yes	13 (12.9)	22.31 ± 12.96	
Angiotensin receptor blocker			
No	68 (67.3)	21.59 ± 15.42	0.088
Yes	33 (32.7)	27.60 ± 18.44	
β-Blocker			
No	71 (70.3)	23.56 ± 17.56	0.992
Yes	30 (29.7)	23.52 ± 14.41	
Calcium channel blocker			
No	56 (55.4)	23.13 ± 14.37	0.779
Yes	45 (44.6)	24.07 ± 19.21	
Statin			
No	96 (95.0)	23.71 ± 16.93	0.665
Yes	5 (5.0)	20.39 ± 9.03	

*$p < 0.05$ was considered statistically significant after the Student t test.

Table 4
Correlation of fasting serum adiponectin levels and clinical variables by univariate linear regression analyses among the 101 hemodialysis patients

Items	Beta	p
Age (y)	−0.084	0.402
Hemodialysis duration (mo)	0.182	0.068
Height (cm)	0.040	0.689
Pre-hemodialysis body weight (kg)	−0.374	<0.001*
Waist circumference (cm)	−0.328	0.001*
Body mass index (kg/m^2)	−0.363	<0.001*
White blood count (×1000/uL)	−0.179	0.073
Hemoglobin (g/dL)	−0.207	0.038*
Albumin (g/dL)	−0.066	0.515
Total cholesterol (mg/dL)	−0.043	0.672
Triglyceride (mg/dL)	−0.353	<0.001*
High-density-lipoprotein cholesterol (mg/dL)	0.377	<0.001*
Fasting glucose (mg/dL)	−0.141	0.159
Blood urea nitrogen (mg/dL)	−0.039	0.702
Creatinine (mg/dL)	−0.096	0.340
C-reactive protein (mg/dL)	−0.128	0.200
Systolic blood pressure (mmHg)	0.009	0.928
Diastolic blood pressure (mmHg)	−0.094	0.348
Intact parathyroid hormone (pg/mL)	0.050	0.617
Insulin (μU/dL)	−0.273	0.005*
Homeostasis model assessment of insulin resistance	−0.317	0.001*
Urea reduction ratio	0.140	0.162
Kt/V (Gotch)	0.132	0.188

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

Table 5
Multivariate stepwise linear regression analysis of body weight, waist circumference, body mass index, hemoglobin, triglyceride, insulin, homeostasis model assessment of insulin resistance, and HDL-C: correlation with fasting serum adiponectin level among 101 hemodialysis patients

Items	Beta	R^2	R^2 change	p
HDL-C (mg/dL)	0.306	0.142	0.142	0.001*
Body mass index (kg/m^2)	−0.288	0.078	0.078	0.002*

*$p < 0.05$ is considered statistically significant in the multivariate stepwise linear regression analysis.
HDL-C = high-density-lipoprotein cholesterol.

4. Discussion

Results of this study showed that the fasting adiponectin level was inversely associated with MetS in HD patients. HDL-C and BMI were independent predictors associated with the serum adiponectin in HD patients.

MetS has been postulated to be associated with insulin resistance, hyperinsulinemia, and glucose intolerance, and has been associated with potentially atherogenic lipoprotein profiles, including hypertriglyceridemia, elevated apolipoprotein B, and decreased HDL-C concentrations [2,3]. It causes major health problems in Western populations and is estimated to affect at least 20% of the adult population and approximately 40% of adults older than 60 years [2]. Previous studies revealed that MetS is associated with reduced kidney function, is a significant risk factor for CVD and mortality in uremic patients, and predicts hospitalization in HD patients [1,5,9,16,17]. According to International Diabetes Federation criteria, MetS occurs in about 62.4% of HD patients in the United States, which is higher than that in the general population [18]. The prevalence of MetS in our study was 47.5%, and patients with MetS had a significantly higher pre-HD BW; waist circumference; BMI; and TG, insulin, and HOMA-IR levels, but a significantly lower HDL-C level, URR, and Kt/*V* than those without MetS.

Adiponectin, a unique insulin sensitizer adipocyte-derived substance, plays an important role in regulating glucose and lipid metabolism and in controlling energy homeostasis in insulin-sensitive tissues [7]. A decrease in the circulating level of adiponectin has been linked to insulin resistance, Type 2 DM, atherosclerosis, and MetS [6,11–13]. Our previous study found that the fasting adiponectin level was inversely associated with MetS in peritoneal dialysis patients [19]. In this study, adiponectin was also significantly lower in HD patients with MetS.

Adiponectin levels correlate inversely with the HOMA-IR, TG level, BMI, waist circumference, and insulin level, and correlate positively with HDL-C levels in patients with CKD, DM, and HD [11,16,20]. Serum adiponectin concentrations are increased in CKD, HD, and peritoneal dialysis patients [8,9,19,21]. Adiponectin levels were also found to be inversely correlated with BMI, HOMA-IR, and TG level, but had no relationship with CRP in HD patients [8,21]. Our study found that the pre-HD BW; waist circumference; hemoglobin; TG and insulin levels; and HOMA-IR correlated negatively with the fasting serum adiponectin levels, whereas the HDL-C level correlated positively with the fasting serum adiponectin levels in HD patients.

Previous studies noted that β-blockers worsen insulin sensitivity, and the use of angiotensin-converting enzyme inhibitors was associated with an increase in plasma adiponectin in hypertensive and DM patients [22–24]. There were no relationships between therapeutic regimens and serum adiponectin in our HD patients. Further studies are required to elucidate the relationship between medication and adiponectin in HD patients.

There were some limitations of our study. First, this was a cross-sectional study, which restricted the ability to compare causal relationships between adiponectin levels and the variables investigated. Second, this study was performed in one hospital. The number of patients was small, and more patients are needed for further analysis. Third, the adiponectin levels were checked only once, and we could not monitor intraindividual trends during long-term HD. Another limitation was that the adiponectin enzyme immunoassay kit used in the present study measures total serum adiponectin but does not discriminate between low- and high-molecular-weight (HMW) forms of the adipokine. Certain pharmacological interventions may influence serum adiponectin concentrations in humans. The HMW form of adiponectin possesses bioactivity, whereas the low-molecular-weight form does not; the function of the latter remains to be determined [25]. Plasma HMW adiponectin levels have been negatively associated with visceral fat area and positively associated with treatment with blockade of the renin-angiotensin system and calcium channel blockers in HD patients [26]. Additional studies will be required to ascertain whether the concentration of HMW adiponectin in the serum of HD patients is inversely associated with the presence of MetS and whether drugs influence serum HMW adiponectin concentrations in HD patients.

In conclusion, we found an inverse association between circulating fasting adiponectin and MetS in HD patients. The HDL-C level and BMI were independent predictors associated with the adiponectin level in HD patients.

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