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Original Article

Fasting serum resistin level positively correlates with metabolic syndrome in patients on peritoneal dialysis

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Abstract: Resistin is an adipocyte-derived polypeptide that provides a link between obesity and insulin resistance. The aim of this study was to explore the relationship between fasting serum resistin levels and the metabolic syndrome (MetS) among patients on peritoneal dialysis (PD). Fasting blood samples were obtained from 51 patients on PD. According to the diagnostic criteria of the International Diabetes Federation, 28 (54.9%) patients had MetS. Fasting resistin levels positively correlated with MetS among patients on PD (P = 0.001). On multivariate logistic regression analysis, resistin remained a significant independent predictor of MetS (odds ratio [OR]: 1.103, 95% confidence interval: 1.011-1.203, P = 0.027). Univariate linear analysis showed that waist circumference (P = 0.015), body mass index (BMI; P = 0.001), body fat mass (P = 0.001), triglycerides (P = 0.003), logarithmically transformed insulin (log-insulin; P = 0.003), and logarithmically transformed homeostasis model assessment of insulin resistance (P = 0.003) were positively correlated and high-density lipoprotein-cholesterol (P = 0.021) was negatively correlated with fasting serum resistin levels. Multivariate forward stepwise linear regression analysis of significant variables showed that body fat mass (β = 0.454, adjusted R^2 change = 0.190, P = 0.001) was an independent predictor of fasting serum resistin levels in patients on PD. Resistin levels are significantly increased in patients on PD with MetS. Body fat mass is an independent predictor of serum resistin levels in such patients.

Keywords: Resistin, metabolic syndrome, peritoneal dialysis, body fat mass

Introduction

Resistin is an adipocyte-derived polypeptide linked to obesity and insulin resistance [1]. In humans, resistin is produced in macrophages and is involved in inflammation [2]. Other tissues, including pancreatic islets, spleen, and bone marrow cells, and ovarian granulosa cells, can produce this molecule [1, 2].

Serum resistin is markedly elevated in end-stage renal disease because of decreased renal clearance and chronic inflammation [3]. Resistin initiates an immune response, induces proinflammatory cytokines, and affects immune function [2, 4]. High serum resistin levels are independently associated with major cardiovascular events and all-cause mortality in patients with type 2 diabetes and coronary artery disease [5], a finding also reported in patients with end-stage renal disease [6].

Metabolic syndrome (MetS) shares many of the risk factors for chronic kidney disease and has a high prevalence in patients on peritoneal dialysis (PD) [7, 8]. When renal function deteriorates, glucose and insulin homeostasis is altered by a number of factors including anemia, dyslipidemia, uremic toxins, hyperparathyroidism, metabolic acidosis, elevated plasma free fatty acids, and proinflammatory cytokines [7, 9]. However, there are additional considerations unique to patients on PD. Serum glucose levels may fluctuate because of the glucose contained in the dialysate. Also, assessing that the abdomen is empty of fluid for accurate measurement of abdominal circumference is difficult [8, 10]. The prevalence of MetS in these patients is substantially higher than that in the general population, even when considering only those on PD without diabetes [8]. In Taiwan, more than half of patients on PD reportedly have MetS [11]. Among individuals with MetS,

Table 1. Clinical characteristic of patients on peritoneal dialysis with or without metabolic syndrome

Variables	All participants (*n* = 51)	No metabolic syndrome (*n* = 23)	Metabolic syndrome (*n* = 28)	*P* value
Age (years)	52.71 ± 13.25	51.83 ± 15.28	53.43 ± 11.56	0.672
PD duration (months)	42.35 ± 37.50	49.17 ± 42.10	36.75 ± 32.98	0.243
Height (cm)	159.07 ± 8.40	160.28 ± 9.01	158.07 ± 7.89	0.355
Body weight (kg)	61.89 ± 13.67	57.37 ± 13.21	65.61 ± 13.13	0.031*
Waist circumference (cm)	89.50 ± 10.11	83.46 ± 9.66	94.46 ± 7.53	< 0.001*
Body mass index (kg/m^2)	24.30± 4.15	22.12 ± 3.44	26.09 ± 3.87	< 0.001*
Body fat mass (%)	29.74 ± 7.47	24.97 ± 5.75	33.66 ± 6.40	< 0.001*
SBP (mmHg)	133.69 ± 24.10	138.65 ± 26.01	129.61 ± 22.05	0.185
DBP (mmHg)	77.27 ± 16.00	81.57 ± 15.39	73.75 ± 15.90	0.083
Albumin (g/dL)	3.83 ± 0.45	3.81 ± 0.39	3.84 ± 0.49	0.794
Globulin (g/dL)	2.95 ± 0.55	2.85 ± 0.52	3.03 ± 0.56	0.234
Fasting glucose (mg/dL)	111.00 (95.00-167.00)	101.00 (91.00-113.00)	150.00 (103.25-191.00)	0.002*
Total cholesterol (mg/dL)	195.27 ± 51.90	195.91 ± 56.31	194.75 ± 49.04	0.937
Triglycerides (mg/dL)	210.39 ± 135.11	153.91 ± 120.61	256.79 ± 130.41	0.006*
HDL-C (mg/dL)	44.14 ± 13.81	50.22 ± 16.91	39.14 ± 7.91	0.003*
Creatinine (mg/dL)	10.23 ± 3.05	10.21 ± 3.40	10.24 ± 2.84	0.979
Total calcium (mg/dL)	9.68 ± 0.65	9.78 ± 0.67	9.59 ± 0.63	0.306
Phosphorus (mg/dL)	5.27 ± 1.22	5.14 ± 1.36	5.37 ± 1.10	0.511
iPTH (pg/mL)	284.70 (152.30-618.60)	298.70 (149.60-658.50)	245.05 (157.53-537.16)	0.590
Resistin (ng/mL)	23.25 ± 10.95	17.79 ± 6.66	27.74 ± 11.81	0.001*
Insulin (μU/dL)	10.10 (6.70-23.20)	8.00 (4.60-15.90)	15.15 (8.78-30.20)	0.003*
HOMA-IR	3.21 (1.54-7.47)	1.91 (1.10-4.27)	6.11 (2.76-12.65)	< 0.001*
Cumulative glucose load (g/day)	141.61 ± 40.05	149.32 ± 39.59	135.28 ± 40.03	0.216
Hypertension (*n*, %)	32 (62.7)	11 (47.8)	21 (75.0)	0.046*
Diabetes (*n*, %)	19 (37.3)	5 (21.7)	14 (50.0)	0.038*

Continuous variables are reported as mean ± standard deviation or median and interquartile range and compared by a *t*-test or Mann-Whitney U test, as appropriate. Categorical variables are reported as number (%) compared by the chi-square test. PD, peritoneal dialysis; SBP, systolic blood pressure; DBP, diastolic blood pressure; HDL-C, high-density lipoprotein-cholesterol; iPTH, intact parathyroid hormone; HOMA-IR, homeostasis model assessment of insulin resistance. *$P < 0.05$ was considered statistically significant.

those on PD have higher serum levels of inflammatory markers and visfatin than those not on PD [12]. However, in a small cohort of 18 patients on PD, an association between serum resistin levels and PD was not found [12]. Debate continues about the role of resistin in insulin resistance, and limited data is available on resistin's connection with MetS and PD. Therefore, this study aimed to examine the relationship between fasting serum resistin levels and MetS in patients on PD.

Material and methods

Patients

Fifty-one patients on PD in eastern Taiwan were enrolled. The Protection of the Human Subjects Institutional Review Board of Tzu-Chi University and Hospital approved this study. Forty-two patients had been on continuous ambulatory peritoneal dialysis (CAPD; Dianeal, Baxter Health Care, Taiwan) with three to five dialysate exchanges per day. The other 9 patients were on automated peritoneal dialysis (APD), performing four to five dialysate exchanges each night with an automated device (Dianeal, Baxter Health Care). Patients were excluded if they had any acute infection at the time of blood sampling, such as peritonitis or peritoneal catheter exit-site infection; acute myocardial infarction; pulmonary edema; liver cirrhosis; thyroid disease at the time of blood sampling; or if they refused informed consent for the study.

Anthropometric analysis

All anthropometric variables were measured in the morning with patients fasting and without the presence of dialysate in the abdominal cavity. Weight was measured in light clothing and

Table 2. Clinical characteristics and fasting serum resistin levels of 51 patients on peritoneal dialysis

Characteristic		Number (%)	Resistin level (ng/mL)	*P* value
Gender	Male	19 (37.3)	20.63 ± 10.24	0.190
	Female	32 (62.7)	24.81 ± 11.21	
DM	No	32 (62.7)	21.91 ± 11.21	0.258
	Yes	19 (37.3)	25.52 ± 11.53	
Hypertension	No	19 (37.3)	22.45 ± 11.58	0.688
	Yes	32 (62.7)	23.74 ± 10.71	
PD type	CAPD	42 (82.4)	23.37 ± 9.34	0.873
	APD	9 (17.6)	22.72 ± 17.35	
Thiazolidinedione	No	46 (91.0)	22.75 ± 10.97	0.327
	Yes	5 (9.0)	27.86 ± 10.68	
Sulfonylurea	No	41 (80.4)	22.08 ± 10.99	0.123
	Yes	10 (19.6)	28.05 ± 9.82	
Insulin	No	42 (82.4)	24.13 ± 11.15	0.222
	Yes	9 (17.6)	19.18 ± 9.45	
ACE inhibitor or ARB	No	28 (54.9)	23.98 ± 11.74	0.605
	Yes	23 (45.1)	22.37 ± 10.09	
Statin	No	33 (64.7)	22.48 ± 11.99	0.498
	Yes	18 (35.3)	24.68 ± 8.85	

DM, diabetes mellitus; PD, peritoneal dialysis; CAPD, continuous ambulatory peritoneal dialysis; APD, automated peritoneal dialysis, ACE, angiotensin-converting enzyme; ARB, angiotensin receptor blocker. *$P < 0.05$ was considered statistically significant. Data were compared by a *t*-test.

without shoes to the nearest half-kilogram. Height was measured to the nearest half centimeter. Waist circumference was measured around the waist at a point between the lowest ribs and the hip bones with the patient's hands on the hips. Body mass index (BMI) was calculated as weight in kilograms divided by height in meters. Bioimpedance measurements of fat mass were performed at the bedside with the standard, tetrapolar, whole body (hand-foot) technique using a single-frequency (50-kHz) analyzer (Biodynamic-450, Biodynamics Corporation, Seattle, WA, USA). Measurements were carried out by the same operator. The fat mass data was analyzed by specific formulas provided by the manufacturer [13, 14].

Biochemical investigations

Blood sampling was performed in the morning before patients had a dialysis exchange. Fasting blood samples of approximately 5 mL were tested within 1 h after collection. Serum levels of creatinine, glucose, total cholesterol, triglycerides, high-density lipoprotein-cholesterol (HDL-C), albumin, globulin, total calcium, and phosphorus were measured using an autoanalyzer (COBAS Integra 800, Roche Diagnostics, Basel, Switzerland). Serum intact parathyroid hormone (iPTH) (Diagnostic Systems Laboratories, Texas, USA) levels and serum resistin (SPI-Bio, Montigny le Bretonneux, France) concentrations were determined using a commercially available enzyme immunoassay [15, 16]. The limit of detection, calculated as the concentration of human resistin corresponding to the blank average minus three standard deviations, was 0.1 ng/mL. Inter- and intra-assay coefficients of variation for resistin measurements were 5.1% and 2.8%, respectively. Serum insulin levels were measured using the microparticle enzyme immunosorbent assay method with an autoanalyzer (Abbott Laboratories, Abbott Park, IL, USA) [13]. Insulin resistance was evaluated using a homeostasis model assessment of insulin resistance (HOMA-IR) as follows: HOMA-IR = fasting plasma glucose (mg/dL) × fasting serum insulin (μU/mL)/405 [13].

Cumulative glucose load

The total exposure to glucose was calculated based on the dialysis regimen reported the day before blood sampling. The product of the volume and the glucose concentration for each exchange was calculated as described by Davies et al [14, 17].

Metabolic syndrome and its components

MetS was defined using the International Diabetes Federation definition [18], that is, central (abdominal) obesity with a waist circumference ≥ 90 cm for men or ≥ 80 cm for women (Chinese criteria) plus two or more of the following criteria: fasting serum glucose ≥ 100 mg/dL, triglycerides ≥ 150 mg/dL or higher, HDL-C level < 40 mg/dL in men or < 50 mg/dL in women, and blood pressure ≥ 130/85 mmHg. If patients were taking antihypertensive medications, they were considered to have high blood pressure for this analysis. Type 2 diabetes was defined according to World Health Organization criteria [19], that is, a fasting plasma glucose ≥ 126 mg/dL or a 2-h glucose dur-

Table 3. Correlation of fasting serum resistin levels and clinical variables by univariate linear analyses among 51 patients on peritoneal dialysis

Variables	Resistin level (ng/mL)				
	Univariate		Multivariate		
	r	*P* value	Beta	Adjusted R^2 change	*P* value
Age (years)	-0.045	0.750	-	-	-
PD duration (months)	0.076	0.595	-	-	-
Height (cm)	-0.145	0.309	-	-	-
Body weight (kg)	0.258	0.068	-	-	-
Waist circumference (cm)	0.339	0.015*	-	-	-
Body mass index (BMI; kg/m^2)	0.442	0.001*	-	-	-
Body fat mass (%)	0.454	0.001*	0.454	0.190	0.001*
Systolic blood pressure (mmHg)	0.014	0.925	-	-	-
Diastolic blood pressure (mmHg)	-0.033	0.817	-	-	-
Albumin (g/dL)	0.083	0.563	-	-	-
Globulin (g/dL)	0.216	0.128	-	-	-
Log-glucose (mg/dL)	0.210	0.139	-	-	-
Total cholesterol (mg/dL)	0.207	0.145	-	-	-
Triglyceride (mg/dL)	0.402	0.003*	-	-	-
HDL-C (mg/dL)	-0.321	0.021*	-	-	-
Creatinine (mg/dL)	0.175	0.218	-	-	-
Total Calcium (mg/dL)	0.092	0.519	-	-	-
Phosphorus (mg/dL)	0.208	0.144	-	-	-
Log-iPTH (pg/mL)	0.096	0.503	-	-	-
Log-insulin (uIU/ml)	0.403	0.003*	-	-	-
Log-HOMA-IR	0.403	0.003*	-	-	-
Cumulative glucose load (g/day)	0.046	0.749	-	-	-

Data on glucose, iPTH, insulin, and HOMA-IR levels had skewed distributions and therefore were log-transformed before analysis. Analysis was done using univariate linear regression analysis or multivariate stepwise linear regression analysis (adopted factors: waist circumference, body mass index, body fat mass, triglyceride, insulin, HOMA-IR, and HDL-C). PD, peritoneal dialysis; HDL-C, high-density lipoprotein-cholesterol; iPTH, intact parathyroid hormone; HOMA-IR, homeostasis model assessment of insulin resistance. *Values of *P* < 0.05 were considered statistically significant.

ing an oral glucose tolerance test ≥ 200 mg/dL or if the individual was on diabetes medication (oral or insulin).

Statistical analysis

Comparisons were made between patients with or without MetS. Data were tested for normal distribution using the Kolmogorov-Smirnov test. Non-normally distributed data were expressed as median and interquartile range and compared using the Mann-Whitney U test (fasting glucose, iPTH, insulin, and HOMA-IR). Normally distributed data were expressed as mean ± standard deviation, and comparisons were performed using a two-tailed independent t-test. Clinical variables were evaluated for correlation with serum resistin levels by univariate linear regression analyses. Variables that were significant on univariate analysis were tested for independency with multivariate forward stepwise regression analysis. Resistin levels were tested for an independent association with MetS using multivariate logistic regression analysis. Data were analyzed using SPSS for Windows (version 19.0; SPSS Inc., Chicago, IL, USA). *P* value < 0.05 was considered significant.

Results

The clinical and laboratory characteristics of the 51 patients with PD, of whom 28 (54.9%) had MetS, are presented in **Table 1**. Those with MetS had significantly higher body weight (*P* = 0.031), waist circumference (*P* < 0.001), BMI (*P* < 0.001), body fat mass (*P* < 0.001), fasting glucose levels (*P* = 0.002), triglyceride concentrations (*P* = 0.006), resistin levels (*P* = 0.001), insulin levels (*P* = 0.003), and HOMA-IR (*P* < 0.001); they also had significantly lower HDL-C concentrations (*P* = 0.003). Comorbid conditions, including diabetes (n = 19 [37.3%]) and hypertension (n = 32 [62.7%]) were significantly more frequent in those with MetS than those without.

The fasting serum resistin levels according to various clinical characteristic are presented in **Table 2**. Medications in use included thiazolidinediones (n = 5 [9.0%]), sulfonylureas (n = 10 [19.6%]), insulin (n = 9 [17.6%]), angiotensin receptor blockers (ARB) or angiotensin-converting enzyme inhibitor (ACEI) (n = 23 [45.1%]), and statins (n = 18 [35.3%]). Resistin levels did

Table 4. Odds ratios for metabolic syndrome by multivariate logistic regression analysis of serum resistin levels among 51 patients on peritoneal dialysis

Resistin (ng/mL)	Unadjusted		Model 1		Model 2	
	OR (95% CI)	*P* value	OR (95% CI)	*P* value	OR (95% CI)	*P* value
Per 1 ng/mL resistin increase	1.154 (1.055-1.262)	0.002*	1.153 (1.054-1.260)	0.002*	1.103 (1.011-1.203)	0.027*

Model 1 is adjusted for age and gender. Model 2 is adjusted for the Model 1 variables and for serum insulin levels and homeostasis model assessment of insulin resistance. *Values of $P < 0.05$ were considered statistically significant. OR, odds ratio; CI, confidence interval.

not differ statistically by gender, comorbidities, type of PD, or any of the medications.

On univariate linear analysis, waist circumference ($r = 0.339$; $P = 0.015$), BMI ($r = 0.442$; $P = 0.001$), body fat mass ($r = 0.454$; $P = 0.001$), triglyceride concentrations ($r = 0.402$; $P = 0.003$), logarithmically transformed insulin levels (log-insulin; $r = 0.329$; $P = 0.003$), and log-HOMA-IR ($r = 0.329$; $P = 0.003$) were all positively correlated with fasting serum resistin levels, while HDL-C concentrations ($r = -0.321$; $P = 0.021$) were negatively correlated (**Table 3**). Multivariate forward stepwise linear regression analysis of those significant variables showed that body fat mass ($\beta = 0.454$, adjusted R^2 change = 0.190, $P = 0.001$) was a significant independent predictor of fasting serum resistin levels.

Unadjusted and multivariate logistic regression analysis of an association between MetS and serum resistin levels is presented in **Table 4**. Unadjusted analysis indicated that a 1 ng/mL increase in resistin increased the risk of having MetS by 15.4% (odds ratio [OR]: 1.154, 95% confidence interval [CI]: 1.055-1.262, $P = 0.002$)]. Multivariate logistic regression analysis adjusted for age and gender revealed a 15.3% increase in the risk of MetS (adjusted OR 1.153, 95% CI: 1.054-1.260, $P = 0.002$) for every 1 ng/mL increase in resistin (Model 1). Adding serum insulin level and HOMA-IR (Model 2) revealed a 10.3% increased risk of MetS (adjusted OR 1.103, 95% CI: 1.011-1.203, $P = 0.027$) for every 1 ng/mL increase in resistin (Model 2). Each of these analyses confirmed a positive association of serum resistin levels with MetS in patients on PD.

Discussion

Our study demonstrated a high prevalence of MetS in patients on PD. Serum resistin levels were positively associated with MetS in these patients. Body fat mass was positively associated with serum resistin levels.

The global prevalence of MetS ranges from 20% to 40% in patients on PD, depending on the definition used and the varying characteristics of the populations studied, such as gender, age, and ethnicity [8]. One study in Taiwan indicated that 52.9% of patients on PD had MetS [11]. In our study, the prevalence of MetS in individuals on PD was 54.9%. MetS is a cluster of metabolic abnormalities consisting of dyslipidemia, hypertension, obesity, and insulin resistance [18]. In our study, weight, waist circumference, BMI, body fat mass, insulin levels, HOMA-IR, and proportions of hypertension and diabetes differed significantly between patients with and without MetS.

Resistin is a cytokine derived from adipocytes and peripheral blood mononuclear cells. It has been implicated in energy modulation, insulin action, and glucose and lipid homeostasis [20]. Circulating resistin levels have been positively associated with central obesity as well as with insulin resistance in human studies [2, 21]. In a follow-up assessment of 2356 people in the Framingham Offspring Study, there was a significant positive association between resistin levels and insulin resistance [22]. This has also been demonstrated in individuals with type 2 diabetes [23]. Our results indicated that waist circumference, BMI, body fat mass, insulin level, and HOMA-IR were all positively correlated with the serum resistin level. In patients on PD, inflammation is recognized as one of the nontraditional risk factors associated with cardiovascular deaths [24]. Obesity-associated inflammation is characterized by an increased abundance of macrophages and enhanced production of proinflammatory cytokines in adipose tissue [25]. Resistin upregulates expression of proinflammatory cytokines via the nuclear factor-κB (NF-κB) pathway, playing a major regulatory role in the inflammatory response and acting as a messenger between inflammation and insulin homeostasis [2]. As a molecular link between energy, insulin action, glucose and lipid homeostasis, and inflamma-

tion, resistin appears to play a significant role in contributing to the risk of MetS [20]. We noted that serum triglyceride levels were positively correlated and HDL-C levels negatively correlated with serum resistin levels. Multivariate analysis of our data indicated that serum resistin levels were positively associated with MetS in patients on PD.

Increased lipid accumulation in adipocytes has been noted in obese subjects, triggering cellular stress and activation of the JNK and NF-κB pathways and leading to inflammation in the adipocyte [26]. Obesity affects synthesis of resistin, primarily in subcutaneous adipose tissue [27]. Serum resistin levels are reported to be positively associated with body fat mass in healthy young subjects [28]. Serum resistin levels were correlated with visceral, intrathoracic, and pericardial fat depots in the Framingham Heart Study [29]. We also found body fat mass to be positively correlated with serum resistin levels in our patients on PD. After adjustment for a variety of confounders, body fat mass remained an independent predictor of serum resistin levels in these patients.

Our study has several limitations. First, the fact that markers of inflammation were not assessed restricts our analysis of the role of inflammation in the link between resistin and MetS. Second, high or low peritoneal transport is another factor that may affect insulin homeostasis. Finally, the small sample size and cross-sectional study design means that the possibility of bias cannot be excluded. Further studies are required to confirm an association between serum resistin levels and MetS in individuals on PD.

To summarize, we found that the serum resistin level is positively associated with MetS in patients on PD. Body fat mass is an independent predictor of serum resistin levels in these patients.

Disclosure of conflict of interest

None.

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