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Original Article

Correlation of leptin, adiponectin, and C-reactive protein with body composition in Taiwanese patients undergoing maintenance hemodialysis

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Abstract: Purpose: Few studies have reported the relationship of body composition with adipocytokines and inflammatory markers in Asian patients undergoing hemodialysis. The present study aimed to investigate these relationships in Taiwanese hemodialysis patients. Materials and methods: A total of 186 hemodialysis patients were enrolled in this cross-sectional study from 2010 to 2011. Pearson's correlation test and multivariate regression model analyses were used to examine the correlation between body mass index (BMI), waist circumference (WC), circulating adipocytokines, and inflammatory cytokines. Results: BMI and WC showed a significant positive correlation with C-reactive protein (CRP) and leptin, as well as a negative correlation with adiponectin. Triceps skinfold thickness showed a significant positive correlation with leptin. According to adjusted model regression analysis, ln[CRP] increased 0.1 mg/L per BMI 1 kg/m^2 (adjusted R-squared 0.137, root mean square error (RMSE) 1.083, p<0.001), with BMI as a reference. ln[CRP] increased 0.040 mg/L per WC 1 cm (adjusted R-squared 0.136, RMSE 1.113, p<0.001), with WC as a reference. ln[leptin] increased 0.197 pg/mL per BMI 1 kg/m^2 (adjusted R-squared 0.475, RMSE 0.996, p<0.001) and ln[adiponectin] reduced 0.061 ug/mL per BMI 1 kg/m^2 (adjusted R-squared 0.191, RMSE 0.625, p<0.001), with BMI as a reference. ln[leptin] increased 0.069 pg/mL per WC 1 cm (adjusted R-squared 0.520, RMSE 0.952, p<0.001) and ln[adiponectin] reduced 0.023 ug/mL per WC 1 cm (adjusted R-squared 0.222, RMSE 0.612, p<0.001), with WC as a reference. Conclusion: Present results indicate that lean/fat mass (represented by BMI) and visceral fat (represent by WC) have a positive association with CRP and leptin levels in Taiwanese hemodialysis patients.

Keywords: Body mass index, waist circumference, leptin, adiponectin, C-reactive protein, hemodialysis

Introduction

Excess body fat has been associated with adverse clinical outcomes in the general population and in patients with chronic illnesses [1-3]. Notably, abdominal or visceral fat has been considered the more metabolically active component, contributing to chronic inflammation [4]. Body fat can be quantified by dual-energy X-ray absorptiometry (DXA), computed tomography scans, and magnetic resonance imaging. However, these techniques are expensive and are not feasible for routine clinical assessment and frequent follow-ups.

Body mass index (BMI) is the most widely used anthropometric measure of body composition and fat. Excessive body fat, associated with a high BMI (i.e., overweight/obese), has been used to predict unfavorable health outcomes [5]. Waist circumference (WC) is another frequently used measure used to assess abdominal fat. Both methods are easily obtained and reproducible, making them ideal for routine clinical practice.

Adipose tissue is an active endocrine organ that regulates energy homeostasis in the body [6]. Various adipocytokines and cytokines are

secreted from adipose tissue, including interleukin-6 (IL-6), tumor necrosis factor-α (TNF-α), leptin, and resistin. Prior studies have reported the correlation of these adipocytokines and cytokines with clinical outcomes in patients with chronic kidney disease [7, 8]. In dialysis patients, Delgado *et al.* found that body fat was associated with markers of inflammation and adipokines in overweight and obese American hemodialysis (HD) patients, predominantly black or white [9]. Previous studies have demonstrated significant relationships between adipocytokines and proinflammatory cytokines in peritoneal dialysis (PD) patients [10]. Unfavorable outcomes and protein-energy wasting have been associated with adipocytokines in dialysis patients [11]. However, there have been few reports fully examining relationships between body composition, adipocytokines, and inflammatory markers in Asian HD patients.

The current study aimed to examine the association between body composition parameters (BMI and WC), circulating proinflammatory markers, and adipocytokines in HD patients. It was hypothesized that HD patients with higher BMI and WC would have heightened inflammatory states and adipocytokine profiles. This study also examined clinical parameters affecting intricate relationships between BMI, WC, adipocytokines, and cytokines in the HD population.

Methods and materials

Participants

Prevalent HD patients were enrolled from Kaohsiung Chang Gung Memorial Hospital in Taiwan, from 2010 to 2011. Inclusion criteria included patients over 20 years of age undergoing regular 4-hour HD sessions, three times per week, for at least 3 months. Exclusion criteria included those with concurrent active medical diseases, including malignancies, acute pulmonary edema, infections, cardiovascular diseases, and hospitalization within 3 months before enrollment.

Laboratory measurements

For each participant, medical histories were reviewed and relevant information, including HD vintage and diabetes mellitus (DM), was recorded. Blood samples were collected to measure cytokine and adipocytokine levels and for routine biochemistry panels. Blood sampling was performed at mid-week, after overnight fasting, at the pre-dialysis stage. Kt/V urea was calculated using the following equation: $Kt/V\ urea = -Ln(R - 0.008 \times t) + [4 - (3.5 \times R)] \times UF/W$, where R is the ratio of post-dialysis and pre-dialysis serum urea nitrogen content, t is the duration of dialysis (h), UF is the ultra-filtrate amount (L), and W is the post-dialysis body weight (kg). Albumin levels were measured using the bromocresol green (BCG) method. WCs were measured by the same experienced nurse. BMIs were calculated using body weight and body height. Triceps skinfold thickness (TSFT) was measured by a Lange skinfold caliper (Beta Technology, Santa Cruz, CA, USA). Immunoassay kits for leptin, total adiponectin, CRP, IL-6 and TNF-α were obtained from R&D Systems (Minneapolis, MN, USA). All measurements were performed twice. This study was approved by the Institutional Review Board and Ethics Committee of Chang Gung Memorial Hospital (IRB No. 201600677B0, 98-2685B). Experiments were conducted according to the Declaration of Helsinki. Informed consent was obtained from all participants.

Statistical methods

SPSS version 24.0 (IBM Corporation, Armonk, NY, USA) was employed for all analyses. Participant characteristics are expressed as mean ± standard deviation or frequencies (percentages). Inflammatory markers and adipocytokines (CRP, IL-6, TNF-α, adiponectin, and leptin) were transformed into natural log (ln) values to reduce highly skewed distribution among included measurements. Correlation between participant characteristics and markers of nutrition, inflammation, and adipose hormones was estimated using Pearson's correlation test. Association of inflammatory markers with body composition parameters was divided into two-model analysis using different parameters. Model 1 included BMI, age, sex, and diabetes as covariates, while Model 2 included WC, TSFT, age, sex, and diabetes as covariates. Association of adipose hormones (leptin and adiponectin) with body composition parameters was also divided into two-model analysis using different adipose hormones. Model 1 included BMI, age, sex, and diabetes as covariates, while Model 2 included WC, age, sex, and

Table 1. Participant Characteristics (N = 186)

Characteristics	Mean ± SD
Sex (male:female) (n,%)	78 (41.9%):108 (58.1%)
Age (years)	59.4 ± 10.5
Diabetes (n,%)	47 (25.3%)
Dialysis vintage (years)*	5.0 (3-9)
Total CV	84 (44.7%)
Kt/V-urea	1.7 ± 0.3
Ca (mg/dl)	9.3 ± 0.8
P (mg/dl)	4.9 ± 1.4
Glucose (mg/dl))	145.7 ± 70.8
Cr (mg/dl)	10.9 ± 2.1
Urea (mg/dl)	42.4 ± 10.0
Body composition parameters	
BMI (kg/m^2)	22.9 ± 4.0
WC (cm)	85.1 ± 12.5
TSFT (mm)	15.9 ± 6.4
Markers of nutrition and inflammation	
Albumin (g/dL)	3.9 ± 0.2
ln(IL-6 in pg/mL)*	1.0 (0.4-1.5)
ln(CRP in mg/L)*	1.1 (0.3-1.9)
ln(TNF-α in pg/mL)*	1.9 (1.4-2.4)
Adipose hormones	
ln(Leptin in ng/mL)*	9.6 (8.7-10.6)
ln(Adiponectin in μg/mL)*	9.5 (8.9-9.9)

Abbreviations: BMI, body mass index; WC, waist circumference; TSFT, triceps skinfold thickness; IL, interleukin; CRP, C-reactive protein; TNF, tumor necrosis factor; Ca, serum calcium; P, serum phosphorus; Cr, serum creatinine; Urea, urea nitrogen; *: median (interquartile range).

diabetes as covariates. Model analysis with WC and TSFT was performed to delineate differential relationships between these two components of adipose tissue and cytokines. WC was used to indicate visceral fat and TSFT was used to indicate subcutaneous fat. Mean variance inflation factors (VIF) for each model were computed to check the collinearity of included covariates in each model. R-square, adjusted R-square statistic, RMSE (Root mean square error) values, and Prob > F were computed to interpret model performance. Results are considered significant if *p*-values are less than 0.05.

Results

Demographics and baseline characteristics

Table 1 shows the demographic and clinical features of the 186 regular HD patients included in this study. The mean age of the patients was 59.4 years, while the mean HD vintage was 6.2 years. The patients had reached the substantial target of dialysis adequacy (mean Kt/V-urea 1.7) and serum albumin levels (mean serum albumin 3.9 g/dL). Forty-seven patients (25.3%) had comorbidity with diabetes.

Body composition

Mean values of BMI, WC, and TSFT in the participants were 22.9 kg/m^2, 85.1 cm, and 15.9 mm, respectively (**Table 1**). Eleven (5.9%) patients had low BMI (<18 kg/m^2) and sixty-two (33.3%) had high BMI (> 24 kg/m^2). Overall, 99 patients (men and women, 53%) had WCs above standard reference levels (80 cm for women and 90 cm for men). Standard reference levels of BMI and WC were determined using the National Nutrition and Health Survey in Taiwan [12]. Of the 62 patients with BMIs greater than 24 kg/m^2, 61 also had higher WCs. Of those with BMIs between 18 and 24 kg/m^2, 38 (34%) had higher WCs. All 11 patients with low BMIs also had WCs below reference levels (data not shown).

Correlation of body composition, inflammation, and adipocytokines

According to Pearson's correlation testing, sex showed a significant negative correlation with leptin (r -0.39, p<0.001) and adiponectin (r -0.29, *p*<0.001). Age showed a significant negative correlation with albumin (r -0.21, *p*<0.01) and a positive correlation with IL-6 (r 0.33, *p*<0.001). Diabetes showed a significant positive correlation with CRP (r 0.16, *p*<0.05). Kt/V urea showed a significant positive correlation with adiponectin (0.31, *p*<0.001) and a negative correlation with IL-6 (r -0.15, *p*<0.05) and CRP (r -0.29, *p*<0.001). BMI and WC showed a significant positive correlation with CRP (r 0.36, *p*<0.001; r 0.39, *p*<0.001, respectively) and leptin (r 0.52, *p*<0.001; r 0.49, *p*<0.001, respectively) and a negative correlation with adiponectin (r -0.37, *p*<0.001; r -0.44, *p*<0.001, respectively). TSFT was positively correlated with leptin (r 0.54, *p*<0.001) (**Table 2**). Additionally, male patients had a higher BMI

Table 2. Correlation between baseline characteristic and markers of nutrition and inflammation, adipose hormones

	Markers of nutrition and inflammation				Adipose hormones	
	Albumin (g/dL)	ln (IL-6 in pg/mL)	ln (CRP in mg/L)	ln (TNF-α in pg/mL)	ln (Leptin in ng/mL)	ln (Adiponectin in μg/mL)
Sex (male vs. female)	0.05	-0.03	0.14	0.03	-0.39***	-0.29***
Age (years)	-0.21**	0.33***	0.09	0.00	-0.02	0.04
Diabetes (yes vs. no)	-0.09	-0.01	0.16*	0.01	0.13	-0.03
Dialysis vintage (years)	0.06	-0.01	0.07	-0.05	-0.05	-0.06
Kt/V-urea	-0.02	-0.15*	-0.29***	-0.05	0.02	0.31***
BMI (kg/m^2)	0.11	0.05	0.36***	0.02	0.52***	-0.37***
WC (cm)	0.11	0.05	0.39***	0.03	0.49***	-0.44***
TSFT (mm)	0.11	-0.03	0.09	0.04	0.54***	-0.04

*P<0.05, **P<0.01, ***P<0.001. P-value is estimated using Pearson's correlation test. The present values were the correlation coefficient (r) estimated using Pearson's correlation test.

Table 3. Association of body composition parameters with inflammatory markers by two-model analysis

	ln (CRP in mg/L)	P	ln (IL-6 in pg/mL)	P	ln (TNF-α in pg/mL)	P
Model 1						
BMI, per 1 kg/m^2	0.100 (0.060 to 0.141)	<0.001	0.019 (-0.015 to 0.052)	0.272	0.005 (-0.027 to 0.036)	0.773
Mean VIF	1.04		1.04		1.05	
Prob > F	<0.0001		0.0001		0.995	
R-squared	0.156		0.120		0.001	
Adj R-squared	0.137		0.100		-0.021	
Root MSE	1.083		0.887		0.839	
Model 2						
WC, per 1 cm	0.040 (0.022 to 0.580)	<0.001	0.005 (-0.010 to 0.020)	0.490	0.004 (-0.010 to 0.017)	0.593
TSFT, per 1 mm	-0.005 (-0.039 to 0.029)	0.781	-0.007 (-0.035 to 0.021)	0.624	0.005 (-0.210 to 0.032)	0.689
Mean VIF	1.38		1.38		1.38	
Prob > F	<0.0001		0.001		0.943	
R-squared	0.163		0.119		0.008	
Adj R-squared	0.136		0.091		-0.024	
Root MSE	1.113		0.911		0.853	

Both model 1 and 2 adjusted for age, sex, and diabetes. VIF, variance inflation factors. A-R-squared, adjusted R-squared. Root mean square error, RMSE.

than their female counterparts (23.4 ± 4.4 vs. 22.5 ± 3.6 kg/m^2, p = 0.103) (data not shown in Table). DM patients had a significantly higher BMI than non-DM patients (24.4 ± 4.1 vs. 22.3 ± 3.8 kg/m^2, p = 0.001) (data not shown in Table).

Table 3 shows the association of body composition parameters with inflammatory markers, according to two-model regression analysis adjusting for age, sex, and diabetes. In model 1 with BMI as a reference, ln[CRP] increased 0.1 mg/L per BMI 1 kg/m^2 (adjusted R-squared 0.137, RMSE 1.083, p<0.001). In Model 2 with WC and TSFT as a reference, respectively, ln[CRP] increased 0.040 mg/L per WC 1 cm (adjusted R-squared 0.136, RMSE 1.113, p< 0.001). There was no significant association with TSFT and lnIL-6 and lnTNF-α.

Table 4 shows the association of body composition parameters with adipose hormones, according to two-model analysis adjusting for age, sex, and diabetes. In model 1 with BMI as a reference, ln[leptin] increased 0.197 pg/mL per BMI 1 kg/m^2 (adjusted R-squared 0.475, RMSE 0.996, p<0.001). ln[adiponectin] reduced 0.061 ug/mL per BMI 1 kg/m^2 (adjusted R-squared 0.191, RMSE 0.625, p<0.001). In model 2 with WC as a reference, ln[leptin]

Table 4. Association of body composition parameters with adipose hormones (leptin and adiponectin) by two-model analysis

	ln (Leptin in pg/mL)	*P*	ln (Adiponectin in μg/mL)	*P*
Model 1				
BMI, per 1 kg/m^2	0.197 (0.159 to 0.234)	<0.001	-0.061 (-0.084 to -0.037)	<0.001
Mean VIF	1.04		1.04	
Prob > F	<0.0001		<0.0001	
R-squared	0.486		0.208	
Adj R-squared	0.475		0.191	
Root MSE	0.996		0.625	
Model 2				
WC, per 1 cm	0.069 (0.058 to 0.081)	<0.001	-0.023 (-0.03 to -0.015)	<0.001
Mean VIF	1.09		1.09	
Prob > F	<0.0001		<0.0001	
R-squared	0.531		0.239	
A-R-squared	0.520		0.222	
Root MSE	0.952		0.612	

Both model 1 and 2 adjusted for age, sex, and diabetes.

increased 0.069 pg/mL per WC 1 cm (adjusted R-squared 0.520, RMSE 0.952, $p<0.001$). ln[adiponectin] reduced 0.023 ug/mL per WC 1 cm (adjusted R-squared 0.222, RMSE 0.612, $p<0.001$).

Discussion

The current study examined the association between body composition, adipocytokines, and proinflammatory cytokines in Taiwanese HD patients. The main findings were that BMI and WC had a significant association with circulating CRP and adipocytokines levels. Increased BMI and WC were positively associated with CRP and leptin. Conversely, increased BMI and WC were negatively associated with adiponectin. Results revealed that, in Taiwanese HD patients, visceral fat appeared to be associated with inflammatory status and altered adipocytokine secretion.

Very few studies have fully examined the relationship between BMI, WC, adipocytokines, and inflammatory markers in Asian patients with chronic kidney disease. A report from Singapore described the association between elevated levels of leptin and adiponectin and chronic kidney disease [13]. Two small studies from Taiwan explored leptin and adiponectin, separately, in patients undergoing PD. Fang *et al.* reported a direct correlation between BMI, WC, and leptin in 40 PD patients [14]. Tzao *et al.* described an inverse correlation between BMI, waist-to-hip ratio, and adiponectin in 60 non-diabetic PD patients [15]. Previous studies, involving 147 PD patients, also found that those with higher BMIs (> 23 kg/m^2) had significantly higher CRP and leptin, with lower adiponectin [10]. Another report from Turkey described the association between BMI and leptin in 65 non-obese (BMI<25 kg/m^2) HD patients [16]. Results of the current study are compatible with abovementioned studies, in that body composition proxies (BMI and WC) are positively associated with leptin and inversely associated with adiponectin.

Chronic kidney disease is a chronic inflammatory condition which predisposes patients to metabolic derangements, multiple organ dysfunction, and poor clinical outcomes, including infections, malnutrition, and cardiovascular events [17-21]. CRP is one of the common clinical proxies of inflammation. The relationship between body composition and inflammation has been explored in several recent US and European population studies. In a study involving 45 Spanish HD patients, those with a high conicity index (indicator of central obesity) demonstrated higher CRP levels [22]. Miyamoto T. *et al.* divided their Swedish HD patients into two groups using gender-specific median WC, finding significantly higher CRP levels in the high WC group [23]. Similarly, Delgado C. *et al.* analyzed the US Renal Data System and found a

direct association between WC, BMI and CRP levels [9]. Present analysis also showed an association between WC, BMI and CRP levels. Although the findings seem similar, several major differences in patient characteristics may have important implications. Swedish and American patients had higher BMIs (mean 24 and 28 kg/m^2, respectively) and WCs (100 cm), compared to present patients (22.9 kg/m^2 and 85 cm). In addition, 43% of the participants in the American study, 22.5% in the Swedish study, and 25.3% in the present study had DM. Patients in the current study had been on HD much longer (median dialysis vintage 5.0 years vs. mean 2.3~2.8 years). However, even though most present patients had "normal" ethnicity-specific BMIs (18-24 kg/m^2), a direct association between BMI and CRP still exists. The current investigation focused on Taiwanese HD patients and incorporated different important proinflammatory markers. CRP was the predominant significant inflammatory marker with body composition. An exact explanation concerning the non-association between other proinflammatory markers and body composition in HD patients cannot be drawn from the current study. Further studies are warranted to examine the relationship between proinflammatory markers and body composition.

Leptin is a pleiotropic hormone, exclusively produced in adipocytes, that regulates energy expenditure and food intake [24]. Circulating leptin levels are elevated in patients with renal failure [25] and correlated with weight changes in dialysis patients [26-29]. Moreover, loss of lean body mass has been found to be correlated with increased serum leptin levels in some observational studies [26, 27]. Adiponectin, another adipocytokines produced by visceral fat, can increase insulin sensitivity and decrease glucose intolerance and diabetes [30, 31]. Plasma adiponectin levels have been found to have a negative correlation with BMI and waist-to-hip ratio in overweight/obese Asian subjects without chronic kidney disease [32]. In dialysis patients, data has consistently demonstrated that plasma adiponectin levels are inversely associated with visceral fat, total body fat, and lean body mass [9, 33, 34]. Delgado *et al.* stratified BMIs into 6 groups with 5 kg/m^2 increments (from <20 to > 40 kg/m^2) [9]. The groups with higher BMIs had higher leptin and lower adiponectin levels than the reference group (20-25 kg/m^2). When WC was stratified into 5 groups with 10 cm increments (from <90 [reference] to > 120 cm), higher WC groups also had higher leptin and lower adiponectin levels. Present findings also provide evidence of a positive association between BMI, WC, and adipocytokines in Taiwanese HD patients. Furthermore, when WC and TSFT (indicator of subcutaneous fat) were modeled together, it was found that WC, but not TSFT, remained associated with CRP. This suggests that visceral fat is the main fat component linked to inflammation.

The current study had several limitations, however, that require consideration. This study was cross-sectional. It could only establish associations between variables, not causality. Present analysis adjusted for numerous potential confounding variables, but residual confounding from unmeasured variables could have been present. The sample size was relatively small. Statistical power may have been obviated by the small sample size. Patients in this study were from a single dialysis center. Results may not be generalizable to other populations. Finally, this study used BMI and WC as indicators of total body fat and visceral fat, respectively. More precise measurements could have been obtained using bioimpedance spectroscopy and DXA. However, BMI and WC are easy to perform and follow-up in routine practice. The strength of this study was the examination of body composition with proinflammatory markers and adipocytokines in HD patients that received longer HD vintage. In addition, the current study is one of the few studies to report this relationship in long-term HD patients in Taiwan. A qualified study design with adequate sample size and observational period is warranted to further prove the roles of adipocytokines and proinflammatory cytokines in determining body composition in Asian HD populations.

Conclusion

Body composition proxies (BMI and WC) had a significant correlation with circulating CRP and adipocytokine levels in Taiwanese HD patients. Visceral fat (represented by WC), but not subcutaneous fat, was associated with inflammation. Measures to reduce visceral fat may potentially reduce inflammation. Further investigations

are warranted to clarify the roles of CRP and adipocytokines at various levels of BMI and WC. Assessment of the alterations of inflammatory markers and adipocytokines, with respect to body composition changes, may offer an opportunity for risk modification for important clinical outcomes.

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Disclosure of conflict of interest

None.

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