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LEPTIN/ADIPONECTIN RATIO IS AN INDEPENDENT PREDICTOR OF MORTALITY IN NONDIABETIC PERITONEAL DIALYSIS PATIENTS

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♦ ***Background:*** **The leptin/adiponectin (L/A) ratio has been suggested to be an atherosclerotic index for diabetic patients and a useful marker of insulin resistance in patients with and without diabetes. Even though end-stage renal disease (ESRD) patients on peritoneal dialysis (PD) are well characterized by abnormal adipocytokine metabolism, the significance of alterations in the L/A ratio is largely unexplored in these patients. In this prospective study, we investigated the associations of leptin, adiponectin, and the L/A ratio with clinical outcomes in nondiabetic PD patients.**

♦ ***Methods:*** **The study included 131 stable nondiabetic ESRD patients who had been on PD for more than 3 months. Serum leptin and adiponectin levels were determined at baseline. Mortality was evaluated over a 5-year follow-up period.**

♦ ***Results:*** **During the follow-up period, 22 patients died (16.8%), including 10 (45.5%) as a result of cardiovascular disease. The L/A ratio showed a significant positive correlation with body mass index [BMI ($r = 0.47$, $p < 0.001$)], high-sensitivity C-reactive protein ($r = 0.32$, $p < 0.001$), and triglycerides ($r = 0.43$, $p < 0.001$). In addition, we observed significant inverse correlations between the L/A ratio and percentage lean body mass ($r = -0.30$, $p = 0.001$) and high-density lipoprotein cholesterol ($r = -0.31$, $p = 0.001$). In contrast to individual leptin and adiponectin levels, the L/A ratio was found to be independently associated with an increased mortality risk (relative risk: 1.15; 95% confidence interval: 1.05 to 1.27; $p = 0.003$) even after adjustments for age and BMI.**

♦ ***Conclusions:*** **The L/A ratio might be better related to patient outcomes than adipocytokines are individually in nondiabetic patients undergoing PD.**

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Patients with chronic kidney disease are characterized by metabolic disturbances. Insulin resistance is more prevalent as renal function deteriorates (1). In addition, the levels of several adipokines are increased because of decreased renal clearance (2). Those features are reinforced in end-stage renal disease (ESRD) patients on peritoneal dialysis (PD), partially because of continuous absorption of glucose from dialysate (3,4).

In the general population, leptin and adiponectin, the two major adipokines, play a central role in cardiovascular and metabolic homeostasis. Plasma leptin levels, which are strongly correlated with fat mass, are independently linked with increased risks for myocardial infarction and stroke (5). In addition, higher concentrations of plasma leptin are associated with the development and prognosis of malignancies (6). In contrast, lower plasma adiponectin levels have been found to predict the development of type 2 diabetes, coronary artery disease, and various types of cancers (6–8). Those findings associate both hyperleptinemia and hypoadiponectinemia with a worse outcome. In line with that view, the ratio of leptin to adiponectin (L/A) has recently been proposed for the evaluation of patient outcomes in the general population. That proposal has been supported by findings that patients with a higher plasma L/A ratio are susceptible to cardiovascular events and the development of type 2 diabetes (9,10).

However, the effects of those adipokines on clinical outcome in patients with chronic kidney disease are confounding. Lower plasma leptin and higher plasma adiponectin have been shown to be independent predictors of mortality in patients on hemodialysis (HD) compared with a nonuremic population (11,12). Moreover, previous studies failed to demonstrate relevant associations between plasma adipokines and cardiovascular diseases in

ESRD patients (13,14). As already mentioned, alterations in adipokine metabolism are known to be remarkable in PD patients. Compared with ESRD patients on HD and the general population, PD patients show higher L/A ratios because of extraordinarily high levels of plasma leptin and a moderate degree of hyperadiponectinemia. To date, however, investigations into the consequences for patients of those abnormal adipokine levels are limited. Therefore, in this prospective study, we investigated whether plasma leptin and adiponectin or the balance of those adipokines is associated with clinical outcomes in nondiabetic PD patients.

METHODS

PATIENT POPULATION

This prospective observational study included 131 prevalent nondiabetic ESRD patients on PD who were being followed at Yonsei University Health System, Seoul, Korea. We recruited patients who were more than 18 years of age, who had maintained PD for more than 3 months, who had experienced no overt infections during the 3 months before the start of the study, and who had no history of malignancy or another chronic inflammatory disease (for example, rheumatoid arthritis or systemic lupus erythematosus). To reduce the confounding effects of glucose and lipid metabolism, we excluded patients with diabetes. All participants gave informed consent before participation in the study.

A senior nursing clinician obtained demographic data through an interview. Body mass index (BMI) was calculated as weight in kilograms divided by height in meters squared. Baseline comorbid conditions were expressed as a Charlson comorbidity index (CCI) score, which was determined according to the International Classification of Diseases 10 and encompassed the period starting 6 months before study enrollment, as described by Jassal *et al.* (15). To simulate actual dialysis conditions, all patients had a full abdomen at the time of sampling. Blood samples for laboratory measurements were drawn from the antecubital vein 2 hours after the first PD exchange with 1.5% dextrose dialysate while the patient was in an overnight fasting state. The preceding overnight dwell was regulated to 1.5% dextrose dialysate to standardize the glucose load.

LABORATORY MEASUREMENTS

Plasma was separated from blood within 30 minutes and stored at –70°C until analysis. Fasting blood glucose was determined by the glucose oxidase method. Plasma total cholesterol, high-density lipoprotein (HDL) cholesterol, and triglycerides (TG) were measured with an autoanalyzer (Hitachi 7150: Hitachi, Tokyo, Japan) using an enzymatic colorimetric method. Low-density lipoprotein (LDL) cholesterol was calculated using the Friedewald formula, and high-sensitivity C-reactive protein (hsCRP) was determined with a BN II analyzer (Dade Behring, Newarkand, DE, USA) using a latex-enhanced immunonephelometric method. Plasma adiponectin (B-Bridge International, Sunnyvale, CA, USA) and leptin (R&D Systems, Minneapolis, MN, USA) were measured using enzyme-linked immunosorbent assays.

ASSESSMENT OF DIALYSIS ADEQUACY AND LEAN BODY MASS USING CREATININE KINETICS

Urea kinetic studies were conducted based on a 24-hour collection of dialysate and urine at the time of study enrollment. Dialysis adequacy was determined by using standard methods (16) to measure total weekly urea clearance (Kt/V urea). The normalized protein catabolic rate was calculated using the Randerson equation and normalized to actual dry weight (17). Lean body mass (LBM) was estimated by creatinine kinetics, and the percentage LBM was calculated as LBM normalized to dry weight (18). Residual renal function was determined as the average of urea and creatinine clearances from a 24-hour urine collection (16).

FOLLOW-UP AND ENDPOINTS

Patients were prospectively followed from April 2005 to June 2010 or until death or transfer to an alternative dialysis method. The dates of transfer to HD, renal transplantation, and death were defined as the endpoints. Mortality within 3 months of dialysis modality change was considered PD-related. Patients who were transferred to HD or who received a kidney graft were censored in the survival analysis.

STATISTICAL ANALYSIS

Statistical analyses were performed using SPSS for Windows (version 13.0: SPSS, Chicago, IL, USA). All data are expressed as mean ± standard deviation. Because of log-normal distributions of hsCRP, triglycerides, and leptin, natural log values were used in the analysis. Geometric means for all log-normally distributed continuous variables were calculated and are reported with 95% confidence intervals (CIs). The duration of PD and the CCI score are reported as median values and ranges. The

L/A ratios are expressed as the absolute value of plasma leptin (nanograms per milliliter) divided by the absolute value of plasma adiponectin (micrograms per milliliter). The statistical differences between the survivor and non-survivor groups were determined using the Student t-test or the Mann–Whitney U-test for continuous variables and the chi-square test for categorical variables. To assess cross-sectional interrelationships between variables and adipokines, Spearman partial correlation coefficients were used after adjustment for age and sex. Multivariate Cox proportional hazards regression analyses using variables that reached a significance level of $p < 0.05$ in a univariate analysis were performed to identify independent risk factors for mortality. Factors of specific interest were also included in the multivariate analyses. Values of p less than 0.05 were considered statistically significant.

RESULTS

BASELINE CHARACTERISTICS OF THE STUDY POPULATION

Table 1 lists baseline patient characteristics. Mean age was 50.8 ± 12.1 years, 55 patients (42.0%) were men, the median PD duration was 81.3 months (range: 7.1 – 202.9 months), and the median CCI score was 2 (range: 2 – 10). All patients were on continuous ambulatory PD.

TABLE 1
Baseline Characteristics of the Study Patients

Variable	Value
Mean age (years)	50.8±12.1
Sex (*n* men/women)	55/76
Mean BMI (kg/m^2)	24.6±3.1
Duration of PD (months)	
Median	81.3
Range	7.1–202.9
CCI score	
Median	2
Range	2–10
Weekly Kt/V urea	1.9±0.3
RRF (mL/min/1.73 m^2)	0.3±1.1
Daily nPCR (g/kg)	1.0±0.2
Primary kidney disease [*n* (%)]	
Hypertension	49 (37.4)
Glomerulonephritis	46 (35.1)
Others	17 (13.0)
Unknown	19 (14.5)

BMI = body mass index; PD = peritoneal dialysis; CCI = Charlson comorbidity index; RRF = residual renal function; nPCR = normalized protein catabolic rate.

CLINICAL OUTCOMES

During the follow-up period, 22 patients died (Table 2). The most common cause of death was cardiovascular disease (45.5%), followed by malignancy (22.7%) and infection (22.7%).

COMPARISON BETWEEN SURVIVORS AND NON-SURVIVORS

Table 3 shows the clinical characteristics of survivors and non-survivors. The non-survivors were significantly older (58.9 ± 9.3 years vs 49.2 ± 12.0 years, $p = 0.001$) and had higher CCI scores (3 vs 2; range: 2 – 10 vs 2 – 6; $p = 0.02$), lower percentage LBM (66.8% ± 13.0% vs 74.8% ± 9.9%, $p = 0.001$), and higher hsCRP (2.38 mg/dL vs 1.17 mg/dL; 95% CI: 1.23 to 4.61 mg/dL vs 0.90 to 1.59 mg/dL; $p = 0.03$). The L/A ratio (1.06 vs 0.49; 95% CI: 0.53 to 2.13 vs 0.37 to 0.66; $p = 0.03$) was significantly higher in the non-survivor group, but serum leptin levels (15.45 ng/mL vs 8.75 ng/mL; 95% CI: 8.88 to 26.88 ng/mL vs 6.73 to 11.39 ng/mL; $p = 0.06$) and adiponectin levels (16.7 ± 7.5 µg/mL vs 19.6 ± 7.4 µg/mL, $p = 0.08$) were not significantly different between the groups.

THE ASSOCIATION OF ADIPOKINES AND L/A RATIO WITH METABOLIC FACTORS AND INFLAMMATORY MARKERS

After adjustment for age and sex, correlations between adipokines and cardiometabolic risk factors were estimated using Spearman correlation coefficients (Table 4). Plasma leptin was positively correlated with BMI ($r = 0.42$, $p < 0.001$), LBM ($r = 0.28$, $p = 0.001$), hsCRP ($r = 0.30$, $p = 0.001$), and triglycerides ($r = 0.36$, $p < 0.001$), and adiponectin was positively correlated with HDL cholesterol ($r = 0.28$, $p = 0.002$). Negative relations were found between leptin and percentage LBM ($r = –0.35$, $p < 0.001$) and HDL cholesterol ($r = –0.29$, $p = 0.002$), and adiponectin was negatively correlated with BMI ($r = –0.38$, $p < 0.001$), hsCRP ($r = –0.26$, $p = 0.005$), and triglycerides ($r = –0.40$, $p < 0.001$). On the other

TABLE 2
Deaths in the Study Cohort

Cause of death	[*n* (%)]
Cardiovascular disease	10 (45.5)
Malignancy	5 (22.7)
Infection	5 (22.7)
Others	2 (9.1)
TOTAL	22

TABLE 3
Demographic and Laboratory Parameters for Survivors and Non-survivors at Study Entry

Variable	Patient group Survivors	Non-survivors	*p* Value
Patients (*n*)	109	22	
Mean age (years)	49.2±12.0	58.9±9.3	0.001
Sex (*n* men/women)	43/66	12/10	0.24
Mean BMI (kg/m^2)	24.4±2.6	25.0±2.9	0.38
Duration of PD (months)			
Median	79.6	85.9	0.48
Range	7.1–198.4	20.3–202.9	
CCI score			
Median	2	3	0.02
Range	2–6	2–10	
Weekly Kt/V urea	2.0±0.3	1.8±0.3	0.09
RRF (mL/min/1.73 m^2)	0.3±1.2	0.3±0.9	0.86
Daily nPCR (g/kg)	1.0±0.2	1.0±0.2	0.67
LBM (kg)	43.5±9.5	42.7± 8.8	0.73
Percentage LBM (%)	74.8±9.9	66.8±13.0	0.001
hsCRP (mg/dL)			0.03
Geometric mean	1.17	2.38	
95% CI	0.90 to 1.59	1.23 to 4.61	
Fasting glucose (mg/dL)	94.1±17.3	103.5±44.7	0.10
Serum albumin (g/dL)	3.6±0.4	3.4±0.3	0.08
Cholesterol (mg/dL)			
Total	187.3±41.3	185.2±36.8	0.82
HDL	46.1±13.8	41.1±8.8	0.11
LDL	111.2±38.8	113.3±33.2	0.82
Triglycerides (mg/dL)			
Geometric mean	128.6	137.6	0.60
95% CI	59.4 to 118.3	113.3 to 173.2	
Leptin (ng/mL)			
Geometric mean	8.75	15.45	0.06
95% CI	6.73 to 11.39	8.88 to 26.88	
Adiponectin (µg/mL)	19.6±7.4	16.7±7.5	0.08
Leptin/adiponectin ratio			
Geometric mean	0.49	1.06	0.03
95% CI	0.37 to 0.66	0.53 to 2.13	

BMI = body mass index; PD = peritoneal dialysis; CCI = Charlson Comorbidity Index; RRF = residual renal function; nPCR = normalized protein catabolic rate; LBM = lean body mass; hsCRP = high sensitivity C-reactive protein; CI = confidence interval; HDL = high-density lipoprotein; LDL = low-density lipoprotein.

hand, the L/A ratio was positively correlated with BMI ($r = 0.47$, $p < 0.001$), LBM ($r = 0.32$, $p < 0.001$), hsCRP ($r = 0.32$, $p < 0.001$), and triglycerides ($r = 0.43$, $p < 0.001$). Negative associations were observed between the L/A ratio and percentage LBM ($r = -0.30$, $p = 0.001$) and HDL cholesterol ($r = -0.31$, $p = 0.001$).

TABLE 4
Correlations of Adipokines and Leptin/Adiponectin (L/A) Ratio with Metabolic Factors and Inflammatory Markers, Adjusted for Age and Sex

	Log leptin	Adiponectin	Log L/A ratio
Log leptin	—	−0.51[a]	0.95[a]
Adiponectin	−0.51[a]	—	−0.74[a]
Body mass index	0.42[a]	−0.38[a]	0.47[a]
Daily nPCR	−0.03	0.01	−0.04
LBM	0.28[b]	−0.26[b]	0.32[b]
Percentage LBM	−0.35[b]	0.10	−0.30[a]
Log hsCRP	0.30[b]	−0.26[b]	0.32[a]
Serum albumin	−0.02	−0.14	0.04
Cholesterol			
Total	0.83	−0.12	0.67
HDL	−0.29[b]	0.28[b]	−0.31[b]
LDL	−0.05	0.13	−0.10
Log triglycerides	0.36[a]	−0.40[a]	0.43[a]

nPCR = normalized protein catabolic rate; LBM = lean body mass; hsCRP = high sensitivity C-reactive protein; HDL = high-density lipoprotein; LDL = low-density lipoprotein.
[a] $p < 0.001$.
[b] $p < 0.05$.

L/A RATIO AS A PREDICTOR OF PATIENT SURVIVAL

Table 5 shows the results of the univariate Cox proportional hazard analysis for mortality. Higher plasma leptin [relative risk (RR): 1.01; 95% CI: 1.01 to 1.03; $p = 0.03$], lower plasma adiponectin (RR: 0.94; 95% CI: 0.89 to 0.99; $p = 0.03$), and higher L/A ratio (RR: 1.13; 95% CI: 1.04 to 1.22; $p = 0.003$) were significant risk factors for mortality. Age (RR: 1.08; 95% CI: 1.04 to 1.13; $p = 0.001$), lower serum albumin (RR: 0.31; 95% CI: 0.13 to 0.84; $p = 0.01$), higher hsCRP (RR: 1.07; 95% CI: 1.03 to 1.10; $p = 0.001$), and higher CCI score (RR: 1.42; 95% CI: 1.15 to 1.78; $p = 0.001$) were also found to be associated with mortality.

Multivariate Cox proportional hazards analyses of the adipokines and L/A ratio revealed that higher leptin (RR: 1.02; 95% CI: 1.01 to 1.04; $p = 0.01$), lower adiponectin (RR: 0.93; 95% CI: 0.87 to 0.99; $p = 0.01$), and higher L/A ratios (RR: 1.17; 95% CI: 1.07 to 1.27; $p = 0.001$) remained significant predictors of mortality even after adjustments for age and serum albumin. However, when adjustment was made for age and BMI, the association between the L/A ratio and mortality remained significant (RR: 1.15; 95% CI: 1.05 to 1.27; $p = 0.003$), but serum leptin and adiponectin were no longer significantly

associated with mortality. When hsCRP was inserted in the model, L/A ratio was no longer associated with mortality (Table 6).

DISCUSSION

In the present study, higher L/A ratios were significantly associated with increased mortality in nondiabetic PD patients. The impact of the L/A ratio on patient survival remained significant even after adjustments for BMI and other confounding variables, including age, serum albumin, and BMI.

Although high plasma leptin and low plasma adiponectin have been demonstrated to be risk factors for cardiovascular diseases in the nonuremic population (5,7), similar evidence is less clear in chronic kidney disease patients. Low plasma adiponectin was found to be independently associated with cardiovascular outcomes in ESRD patients (19,20), but high (rather than low) plasma adiponectin was linked with increased mortality in early chronic kidney disease patients (21). In addition, a relevant relationship between plasma leptin and vascular diseases was not definitive in a cohort of mixed HD and PD patients (13). Moreover, a recent report showed that low plasma leptin predicted mortality in ESRD patients on HD (12), which did not accord with results of previous studies in the general population or with the results of the present study.

We surmise that the opposing results for the association between plasma leptin and death are partly a result of differences in the study populations. Unlike the case in HD, PD is characterized by a gain of fat mass because of the excessive glucose load from the dialysate (22). This altered glucose and fat metabolism leads to an extraordinarily high plasma leptin level in PD patients (4). Compared with the results of the aforementioned study (12), BMI (mean: 22.9 kg/m^2 vs 24.5 kg/m^2) and plasma leptin (median: 2.6 ng/mL vs 10.1 ng/mL) were higher in the present study. As mentioned by Scholze *et al.* (12), low plasma leptin in HD patients might represent a state of malnutrition, but the distinctively high plasma leptin in PD patients might be a consequence of altered glucose and fat metabolism.

Leptin and adiponectin have pleiotropic functions that might influence outcomes. However, the impacts of these two adipokines on clinical outcome seem to be commonly attributed to their effect on inflammation. In addition to its accepted effect in limiting food intake (23), leptin affects the production of proinflammatory

TABLE 5
Hazard Ratios (HRs) and 95% Confidence Intervals (CIs) for Mortality by Univariate Cox Proportional Hazards Analysis

Variable	HR	95% CI	*p* Value
Age (years)	1.08	1.04 to 1.13	0.001
Sex (male)	0.58	0.25 to 1.34	0.20
CCI score	1.42	1.15 to 1.78	0.001
Serum albumin (g/dL)	0.31	0.13 to 0.84	0.01
hsCRP (mg/dL)	1.07	1.03 to 1.10	0.001
BMI (kg/m^2)	1.08	0.91 to 1.28	0.36
Leptin (ng/mL)	1.01	1.01 to 1.03	0.03
Adiponectin (μg/mL)	0.94	0.89 to 0.99	0.03
L/A ratio	1.13	1.04 to 1.22	0.003

CCI = Charlson comorbidity index; hsCRP = high sensitivity C-reactive protein; BMI = body mass index; L/A = leptin/adiponectin.

TABLE 6
Hazard Ratios (HRs) and 95% Confidence Intervals (CIs) for Mortality According to Serum Level of Adipokines and Leptin/Adiponectin (L/A) Ratio, by Multivariate Cox Proportional Hazards Analysis

	Leptin			Adiponectin			L/A ratio		
	HR	95% CI	*p* Value	HR	95% CI	*p* Value	HR	95% CI	*p* Value
Model 1[a]	1.02	1.01 to 1.03	0.03	0.94	0.89 to 0.99	0.03	1.17	1.07 to 1.27	0.001
Model 2[b]	1.02	1.01 to 1.04	0.01	0.93	0.87 to 0.99	0.01	1.17	1.07 to 1.27	0.001
Model 3[c]	1.02	0.99 to 1.03	0.06	0.95	0.89 to 1.02	0.14	1.15	1.05 to 1.27	0.003
Model 4[d]	1.01	0.99 to 1.03	0.17	0.95	0.90 to 1.01	0.09	1.10	0.97 to 1.25	0.15

[a] Adjusted for age.
[b] Adjusted for age and serum albumin.
[c] Adjusted for age and body mass index.
[d] Adjusted for age and high sensitivity C-reactive protein.

cytokines (24). On the other hand, beyond its primary insulin-sensitizing effect (25), adiponectin has a direct anti-inflammatory effect, partially because of reduced production of tumor necrosis factor α (24). The actions of these adipokines on inflammation are also supported by the findings of the present study, in which plasma leptin and adiponectin and the L/A ratio are all significantly correlated with hsCRP. In addition, even though the L/A ratio predicted mortality, the fact that its significance disappeared after adjustment for hsCRP suggests that the association between L/A ratio and mortality may be mediated through inflammation.

Leptin and adiponectin are closely related to adipocyte mass. Leptin increases and adiponectin decreases with the increase of fat mass (5,7,26). Recently, it has also been postulated that adipose tissue contributes to the chronic inflammatory state commonly observed in PD patients (27,28). To evaluate whether changes in adipokine levels play a direct role in patient outcomes or merely act as an epiphenomenon of adiposity influencing systemic inflammation, adjustments were made for BMI in the Cox proportional hazards analysis. Although the significances of leptin and adiponectin disappeared after adjustments including BMI, the L/A ratio remained a considerable risk. Those findings suggest that the balance of these adipokines may influence clinical outcomes in PD patients independently of the well-known cardiovascular problems caused by adiposity itself.

Interestingly, in the present study, we observed a positive correlation between plasma leptin and LBM, and an inverse association between plasma leptin and percentage LBM. Because LBM was estimated by creatinine kinetics, we presumed that LBM represented not only the actual fat-free component of the body, but also nutrition status. Peritoneal dialysis patients with higher LBM were therefore supposed to be in better state of nutrition and thus to have both higher fat and muscle mass. By contrast, the percentage LBM was considered better than LBM at representing the fat-free portion. That assumption was partially supported by the results of the present study, in that LBM was strongly positively correlated with BMI ($r = 0.23$, $p = 0.005$), but we observed a trend of negative correlation between percentage LBM and BMI ($r = -0.14$, $p = 0.09$). Consequently, given that previous studies have demonstrated that leptin is closely related to fat mass, we speculate that the positive association between leptin and LBM in the present study is rather a result of the relationship with fat content, and that the inverse correlation of leptin with percentage LBM reflects the negative relationship between leptin and fat-free mass. To verify that hypothesis, further studies that include a precise measurement of fat mass will be needed.

On the other hand, a recent study by Stenvinkel *et al.* (29) found a negative correlation between plasma leptin and the change in LBM over time. Even though they found that patients with higher baseline levels of leptin eventually lost LBM after 1 year, no significant association was observed between baseline leptin and baseline LBM, which differs from the results in the present study. The fact that the former study population consisted of both diabetic and nondiabetic patients and that our study included only nondiabetic patients and also used a different method to assess LBM may in part contribute to the discrepancy.

Previous studies have demonstrated a wide variation in the L/A ratio depending on the study population. No solid ranges of normal L/A values have yet been reported in the Asian population. A recent study showed that the mean L/A ratio was 0.85 for non-obese men in the general population; in obese patients, the mean L/A ratio was 2.81 (10). In ESRD patients, higher levels of plasma leptin with comparable levels of plasma adiponectin were observed in PD patients compared with HD patients (13), resulting in higher L/A ratios in PD patients, which is in part attributed to the weight gain caused by the excessive glucose load from PD fluid (22) and to the impact of PD solutions on adipokine levels [they increase leptin while adiponectin in adipocytes decreases (4,30)].

The present study has several limitations. First, even though the cohort was relatively large for a single-center study, the number of events was rather small, limiting the power of the statistical analysis to identify independent risk factors for mortality. Therefore, to maintain the statistical power, only two factors at a time could be evaluated in the multivariate analysis. Second, single measurements of adipokines at baseline were used for the analysis. Still, measurements of plasma leptin and adiponectin have been reported to show a high degree of reproducibility even when taken 1 – 4 years apart, suggesting that a single measurement may be sufficient for risk assessment (31). Lastly, the measurement of body composition, especially muscle and fat, was incomplete and not precise. A more accurate method to assess body composition should be used in future studies to better understand the relationship between adipokines and body composition.

CONCLUSIONS

Higher L/A ratios were associated with increased mortality even after adjusting for various confounding variables such as age, serum albumin, and BMI in

nondiabetic PD patients, suggesting that the balance between those two adipokines may play a significant role in clinical outcomes in this population with metabolic disturbance. Further studies are required to confirm whether therapeutic strategies that lower the L/A ratio, such as the use of glucose-sparing PD regimens and treatment with peroxisome proliferator-activated receptor agonists, might improve survival in nondiabetic PD patients.

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DISCLOSURES

No author has a financial conflict of interest to declare.

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