Obese sarcopenia in patients with end-stage renal disease is associated with inflammation and increased mortality\(^1\)–\(^3\)

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ABSTRACT

**Background:** Adipose tissue in overweight patients with end-stage renal disease (ESRD) is a source of proinflammatory mediators, which could contribute to protein-energy wasting (PEW), cardiovascular disease, and increased mortality. Overweight in ESRD patients, however, is reported to be associated with better survival.

**Objective:** We investigated the associations between overweight [body mass index (BMI; in kg/m\(^2\)) \(> 25\)], inflammation, PEW, and mortality in ESRD patients starting dialysis.

**Design:** In 328 ESRD patients (age: 53 ± 12 y; 201 men), inflammatory biomarkers, nutritional status, and dual-energy X-ray absorptiometry data were analyzed close to the start of treatment. We compared clinical and laboratory data in patients in 3 BMI groups, with and without PEW.

**Results:** The prevalence of PEW was high in patients in all 3 BMI groups. PEW was associated with both high fat body mass index (FBMI) and low lean body mass index (LBMI). Both PEW and high BMI were associated with inflammation. The highest concentrations of inflammatory mediators and the highest FBMI were seen in overweight patients with PEW. BMI as such did not predict clinical outcome; however, for each BMI group, the presence of PEW was associated with increased mortality. With BMI 20–25 as the reference group, BMI \(< 20\) did not predict mortality, overweight (BMI \(> 25\)) was associated with a survival advantage, and low FBMI was found to be an independent predictor of mortality.

**Conclusions:** PEW is common in overweight ESRD patients and is associated with high FBMI, low LBMI, and inflammation. PEW was a predictor of mortality in both obese and nonobese sarcopenia patients. BMI as such, however, was a poor predictor of mortality, but after adjustment for various confounders, including PEW, a high BMI and a high FBMI were associated with survival advantage.


KEY WORDS Protein-energy wasting, inflammation, body composition, body mass index, mortality, end-stage renal disease (4, 5), and inflammation is one of several important contributors to PEW in ESRD patients (3, 6, 7).

In the nonrenal population, overweight is associated with dyslipidemia and type 2 diabetes mellitus and is a strong risk factor for higher CVD-related mortality (8). The mechanisms behind the development of CVD in overweight patients are not fully understood but are likely associated with metabolic and hormonal changes as well as higher circulating concentrations of proinflammatory adipokines, including IL-6, which are released from adipose tissue (9, 10). Overweight is also associated with an inflammatory state in ESRD patients (11).

Whereas overweight is an independent risk factor for mortality in the general population (12), the survival of overweight ESRD patients is reported to be better than that of nonoverweight ESRD patients, presumably because a high body mass index (BMI) is usually linked to improved nutrition, which is associated with better survival (13–17). However, because overweight is linked to inflammation, this could be a contributing factor to PEW and the increased mortality in overweight ESRD patients.

The aims of the present study were to investigate the relations between systemic inflammation, PEW [assessed by subjective global assessment (SGA)], and body composition [assessed by dual-energy X-ray absorptiometry (DXA)] in nonoverweight [BMI (in kg/m\(^2\)) \(\leq 25\)] and overweight (BMI \(> 25\)) ESRD patients and to analyze how these factors were associated with the clinical outcome in these patients.

SUBJECTS AND METHODS

**Subjects**

The study comprised 328 ESRD patients (201 men) with a mean age of 53 ± 12 y (range: 22–70 y) who were investigated...
in conjunction with the planned start of renal replacement therapy (RRT). Most of the subjects (227 patients; 69%) were investigated before the start of RTT (median predialysis time: 21 d), whereas 101 patients (31%) were investigated after the start of RTT (median postdialysis time: 9 d). Patients above the age of 70 y, patients who had clinical signs of overt infection, acute vasculitis, or liver disease, and patients who were unwilling to participate were not included in the study. The causes of ESRD were chronic glomerulonephritis in 94 patients (29%), diabetic nephropathy in 97 patients (30%), polycystic kidney disease in 31 patients (9%), interstitial nephritis in 6 patients (2%), nephrosclerosis in 6 patients (2%), and other or unknown etiologies in 94 patients (28%). One hundred twelve patients (34%) had CVD, as defined by medical history or clinical symptoms of atherosclerosis, cerebrovascular (stroke), and CVD or peripheral vascular disease, or both. As initial RRT, 174 patients started peritoneal dialysis, and 151 patients started hemodialysis. Only 3 patients did not initiate RRT during the observation period. Most of the peritoneal dialysis patients were on a schedule of 4 to 5 exchanges per day of 2 L glucose-based standard dialysis solutions. Hemodialysis was performed 3 times a week (4–5 h per session) by using bicarbonate dialysate and standard cellulose acetate or polysulfone dialysis membranes. Most (81%) of the patients were taking antihypertensive medications and other drugs commonly used in ESRD, such as phosphate and potassium binders, diuretics, and supplements of vitamins B, C, and D. The study protocol was approved by the Ethics Committee of the Karolinska Institute, Karolinska University Hospital Huddinge, Stockholm, Sweden, and informed consent was obtained from each patient.

Methods

At baseline, after the patients had fasted overnight, blood samples were drawn for analyses of serum creatinine, urea, albumin, CRP, IL-6, tumor necrosis factor-α (TNF-α), insulin-like growth factor I, and leptin. The median glomerular filtration rate, as estimated by the mean of creatinine and urea clearance from a 24-h collection of urine, was 7.0 mL/min (range: 1.5-16.5 mL/min; n = 209). IL-6 was measured by enzyme-linked immunosorbent assay (R&D System Inc, Minneapolis, MN). High-sensitivity CRP was measured by means of nephelometry (Department of Clinical Chemistry, Karolinska University Hospital Huddinge, Stockholm, Sweden). TNF-α and insulin-like growth factor I were analyzed with an Immulite system (Diagnostic Products Corp, Los Angeles, CA) according to the instructions of the manufacturer. Leptin was measured by using a commercially available enzyme-linked immunosorbent assay (IBL Immuno-Biological Laboratories, Hamburg, Germany). Concentrations of serum creatinine, urea, albumin (bromcresol purple), and urinary excretion of creatinine and urea were measured by routine methods at the Department of Clinical Chemistry, Karolinska University Hospital Huddinge.

Nutritional status

SGA was used to evaluate the overall protein-energy nutritional status of the patients. SGA includes 6 subjective assessments: 3 that are based on the patient’s history of weight loss, incidence of anorexia, and incidence of vomiting and 3 that are based on the physician’s grading of muscle wasting, presence of edema, and loss of subcutaneous fat. On the basis of these assessments, each patient was given a score that reflected the nutritional status as follows: 1, no PEW (PEW −); 2, mild PEW; 3, moderate PEW; and 4, severe PEW. Patients with an ordinal SGA score between 2 and 4 were grouped together as wasted (PEW +3). BMI was calculated. Lean body mass (LBM) and fat body mass (FBM) were evaluated (n = 242) by DXA with the use of LUNAR software (version 3.4; Lunar Corp, Madison, WI). With this technique, bone mineral, fat, and LBM distribution are directly estimated without making assumptions about the 2-compartment model. The CV for the DXA measurement was 2.0 ± 0.7%. FBM index (FBMI) and LBM index (LBMI) were calculated according to the method of Kyle et al (18) and expressed as kg/m². Protein intake was estimated from the protein equivalent of nitrogen appearance, which was calculated on the basis of urea kinetic modeling, which measures urea excretion in a 24-h urine collection (n = 209) as 6.25 × [(0.028 × urea excretion rate (in mmol/24 h)] + [0.031 × body weight (in kg)]). Energy intake was not assessed. Urine was collected from all of the patients before the start of dialysis therapy. The protein equivalent of nitrogen appearance was normalized to actual body weight and to standard body weight with calculations based on the patient’s height, sex, age, and frame size with the use of National Health and Nutrition Examination Survey tables (19).

Survival analysis

Survival was measured from the day of examination and was analyzed after a median follow-up period of 20.9 mo (range: 0.7–72 mo), with no loss of follow-up of any patient. Patients were censored at transplantation or on completion of the study. In the patients who died (n = 88), the primary cause of death was recorded, as obtained from the death certificate or from the patient’s records. One hundred thirty-one patients received kidney transplants subsequent to entering the study and were censored from the time of transplantation.

Statistical analyses

All values are expressed as means ± SDs, means ± SEMs, or medians (ranges) as appropriate. A P value < 0.05 was considered statistically significant. Comparisons between 2 groups were performed by using Wilcoxon’s rank-sum test. Comparisons between >2 groups were made by nonparametric analysis of variance. To measure the degree of association between variables in Table 1, a 2-factor multivariate analysis of variance with Wilks lambda was used. The general linear model procedure was used to identify significant interactions between factors. A Tukey-Kramer post hoc test was used when an interaction was detected. Correlations were performed by Spearman’s rank test (r). Receiver operating characteristics (ROC) analysis was performed to estimate the cutoffs of continuous variables (20, 21). To evaluate the factors associated with malnutrition, logistic regression analysis was performed with forward stepwise analysis. The variables included in the stepwise analysis were selected from the variables significantly associated with PEW and BMI. Cox proportional hazards models were performed to analyze survival. The multivariate Cox models included the variables that in the univariate analysis had a significant association with mortality; however, the number of selected variables was restricted to equal the square root of the number of events (death) divided by 2. All analyses were performed by using SAS statistical software (version 9.1; SAS Institute Inc, Cary, NC).
TABLE 1
Clinical characteristics and variables that reflect the inflammation and nutritional status in 328 end-stage renal disease patients starting dialysis in relation to BMI and protein-energy wasting (PEW).

<table>
<thead>
<tr>
<th>BMI &lt;20</th>
<th>BMI 20–25</th>
<th>BMI &gt;25</th>
</tr>
</thead>
<tbody>
<tr>
<td>PEW−</td>
<td>PEW+</td>
<td>PEW−</td>
</tr>
<tr>
<td>Age (y)</td>
<td>39 ± 9 4 6</td>
<td>55 ± 12</td>
</tr>
<tr>
<td>(n = 18)</td>
<td>(n = 26)</td>
<td>(n = 87)</td>
</tr>
<tr>
<td>Sex (% men)</td>
<td>44 42</td>
<td>63 68</td>
</tr>
<tr>
<td>Diabetes mellitus (%)</td>
<td>11 23</td>
<td>21 43</td>
</tr>
<tr>
<td>Cardiovascular disease (%)</td>
<td>6 35</td>
<td>15 63</td>
</tr>
<tr>
<td>Serum albumin (g/L)</td>
<td>37 11 6</td>
<td>32 11 6</td>
</tr>
<tr>
<td>Serum creatinine (µmol/L)</td>
<td>73 0 12</td>
<td>71 0 12</td>
</tr>
<tr>
<td>IGF-I (ng/mL)</td>
<td>186 7 11</td>
<td>173 7 11</td>
</tr>
<tr>
<td>Leptin (ng/mL)</td>
<td>11 1 11</td>
<td>11 1 11</td>
</tr>
<tr>
<td>Serum CRP (mg/L)</td>
<td>7.5 2 25</td>
<td>2.7 2 25</td>
</tr>
<tr>
<td>IL-6 (pg/mL)</td>
<td>6.7 2 25</td>
<td>6.7 2 25</td>
</tr>
<tr>
<td>FBMI (kg/m²)</td>
<td>0.7 0 3</td>
<td>0.7 0 3</td>
</tr>
<tr>
<td>LBMI/FBMI</td>
<td>0.27 0 4</td>
<td>0.26 0 4</td>
</tr>
</tbody>
</table>

1 PEW+, presence of PEW (subjective global assessment score >1); PEW−, no signs of PEW; MANOVA, multivariate analysis of variance; IGF-I, insulin-like growth factor I; CRP, C-reactive protein; IL-6, interleukin-6; TNF-α, tumor necrosis factor-α; nPNA, normalized protein equivalent of nitrogen appearance; ABW, actual body weight; SBW, standard body weight; GFR, glomerular filtration rate; BMI, body mass index; LBMI, lean body mass index.

2 2-Factor MANOVA. Significant (P < 0.05) effects are given for BMI (marked as A); PEW (marked as B), and BMI × PEW interaction (marked as A X B).

3 ± SD (all such values).

4 Significantly different from normal nutritional status (BMI: 20–25; PEW−), P < 0.01, Tukey-Kramer post hoc test.

5 Calculated according to Kyle et al (18).

RESULTS

The patients were divided into 6 groups on the basis of BMI and the presence of PEW (SGA > 1) in each BMI group (Table 1). BMI was classified according to World Health Organization criteria (22): BMI > 25 (overweight) and BMI < 20 and BMI 20–25 (both considered as nonoverweight). As shown in Table 1, the prevalence of diabetes mellitus and CVD was significantly different between the patient groups and was more common in patients with BMI 20–25 and BMI > 25 than in patients with BMI < 20. The prevalence of diabetes mellitus and CVD and serum concentrations of CRP and IL-6 were significantly higher in patients with PEW than in patients with normal nutritional status. FBMI was higher in patients with BMI > 25 and in patients with BMI 20–25 than in patients with BMI < 20 (Table 1). FBMI was significantly higher in overweight patients with PEW than in overweight patients with normal nutritional status (Table 1). Moreover, LBMI was significantly associated with PEW but had no interaction with BMI (Table 1). Also, LBMI was lower in male overweight patients with wasting than in nonwasted male overweight patients. In both women and men, the ratio of FBMI to LBMI was significantly higher in overweight patients than in nonoverweight patients and was higher in wasted patients than in well-nourished patients. Interestingly, the highest FBMI was found in the overweight patients with wasting.

CRP and IL-6 concentrations were higher in wasted patients than in nonwasted patients for all 3 BMI groups (Table 1). Our results showed that the overweight patients with wasting had a higher prevalence of inflammation and a higher FBMI than did the other patient groups, whereas LBMI did not differ significantly between the 6 patient groups. Because this pattern was similar in men and women, we showed only the combined data for men and women. In a subanalysis that included only the overweight patients (BMI > 25), FBMI and concentrations of inflammatory markers (CRP, IL-6, and TNF-α) were significantly higher in wasted patients than in nonwasted patients, whereas LBMI and insulin-like growth factor I were significantly lower in overweight patients with wasting than in overweight patients without wasting. In the same patients, serum albumin and leptin concentrations did not differ significantly between wasted patients and overweight patients without wasting.

Factors contributing to PEW

To estimate the association between body composition and PEW, ROC curves were calculated and a logistic regression multivariate analysis was performed (Table 2 and Table 3). According to the ROC curves (Table 2), BMI, LBMI, and FBMI predicted PEW in both men and women, although this association was stronger in men than in women. Moreover, logistic regression multivariate analysis (Table 3) showed that low LBMI and low FBMI were associated with PEW.

Clinical outcome in overweight and nonoverweight ESRD patients

Eighty-eight of the patients died during the observation period, and fifty-seven (65%) of these patients were malnourished.
On the basis of the 3 BMI groups, Kaplan-Meier analysis did not show an association between BMI and mortality, although patients with BMI > 25 tended to have the best survival (Figure 1, top). However, when the BMI groups were further divided into 6 groups on the basis of the presence of PEW, Kaplan-Meier analysis showed that, in each BMI group, the patients with wasting had a worse survival than did the patients with normal nutritional status (Figure 1, bottom).

With the use of a multivariate Cox proportional hazards model (Table 4), which was adjusted for age (> 55 compared with ≤ 55 y), sex, diabetes mellitus state, CVD state, and CRP (> 10 compared with ≤ 10 mg/L), we found that PEW (hazard ratio: 1.9) and low fat mass (hazard ratio: 2.2) were independent risk factors for high mortality, whereas overweight (BMI > 25) patients had significantly better survival than did the patients with normal BMI. There was no significant difference in the mortality rate between patients with low BMI (BMI < 20) and patients with normal BMI. Moreover, LBMI was not associated with mortality in the multivariate Cox regression analysis (Table 4).

**DISCUSSION**

Clinical characteristics of PEW in ESRD patients are usually presumed to include a decrease in BMI, FBMI, and LBMI (23). In the present study, the prevalence of PEW in patients with BMI < 20 was high (60%); however, PEW was common also in the BMI 20–25 (39%) and BMI > 25 (16%) patient groups. Interestingly, PEW in patients with BMI > 25 was associated with a high FBMI, and the ratio of FBMI to LBMI in wasted patients with BMI > 25 was higher than that in the other groups. Thus, a higher FBMI may, in fact, be one of the characteristics of PEW in overweight ESRD patients, a condition that can be called *obese sarcopenia*. It should be noted that these patients tended to be elderly patients (although patients above the age of 70 y were not included in the study) with a high prevalence of comorbidities, in particular, CVD and diabetes mellitus (Table 1).

PEW in ESRD patients is induced by several factors (3, 6, 7, 23) and may be divided into at least 2 different types: one linked to uremia per se and one linked to the presence of inflammation...
and comorbidity (24). In the present study, inflammation (elevated concentrations of CRP, IL-6, and TNF-α) was more prevalent in wasted than in nonwasted patients and was more prominent in patients with BMI > 25 than in patients with BMI < 20. Because proinflammatory cytokines contribute to anorexia, to the inhibition of protein synthesis, and to catabolism (23, 25), the higher IL-6 concentrations in patients with BMI > 25 may contribute to PEW in this group of ESRD patients. Interestingly, in wasted overweight patients in the present study, the higher concentrations of inflammation biomarkers were associated with the presence of higher fat mass.

In the present study, LBMI in wasted patients with BMI > 25 was similar to LBMI in patients with BMI < 20 and BMI 20–25 (Table 1), although the logistic regression analysis showed that a low LBMI predicted PEW. The mechanisms behind changes in LBMI in ESRD patients are complex. In ESRD patients, deficient plasma amino acid and protein pools may contribute to a negative protein balance as well as influence the concentrations of hormones and cytokines (26, 27). Aging is also associated with a low LBMI as a consequence of muscle reduction (28). In the present study, a low LBMI was associated with inflammation and also with high age, and the results of the present study suggest that high IL-6 concentrations, concomitant with high fat mass, are a typical finding in wasted overweight patients (obese sarcopenia), who tended to be elderly patients with a high prevalence of CVD and diabetes mellitus.

PEW is known to be a strong predictor of clinical outcome, and the mortality of ESRD patients with a low BMI (BMI < 20) who have a higher prevalence of PEW has repeatedly been reported to be significantly worse than that of patients with a high BMI. A high BMI in ESRD patients is therefore thought to have a “protective” effect (13, 15–17). Although overweight is an independent risk factor for mortality in the general population, a high BMI in ESRD patients seems to contribute to better survival, presumably because it is associated with better maintained nutritional status. Beddhu et al (13) showed in a large retrospective study that the appearance of CVD in hemodialysis patients was associated with higher mortality in “malnourished” patients, defined as a low BMI (<18.5) and low urinary excretion of creatinine; however, inflammation was not analyzed. In the present study, the Kaplan-Meier survival analysis showed that BMI as such was not associated with mortality (Figure 1, top). However, when the BMI groups in the present analysis were further stratified by PEW (Figure 1, bottom), the wasted patients had a worse survival rate in each of the 3 BMI groups. Moreover, the Cox proportional hazards model showed that, whereas BMI (BMI < 20) did not predict mortality, PEW and low fat mass were independent predictors of mortality. Interestingly, overweight (BMI > 25) as compared with BMI 20–25 was associated with a survival advantage (Table 4).

Notably, the overweight patients with PEW, ie, patients with obese sarcopenia, had a higher degree of inflammation, a greater fat mass, and a lower LBMI than did the patients without signs of PEW. In a previous study, it was suggested that patients with a high BMI and low muscle mass, estimated by a low urinary excretion of creatinine, may have a higher FBM, which could contribute to a higher CVD prevalence and higher mortality (29). This may suggest that wasted overweight ESRD patients have a high FBM and a low LBMI because of the effects of inflammatory mediators released from excess fat mass, which may contribute to poor survival. However, one conclusion from the present study is that the association of obese sarcopenia with higher mortality in ESRD patients is due to the sarcopenia component and not to the increased FBM, even though higher fat mass in these patients is linked to inflammation. In a recent study in 808 hemodialysis patients, increased fat mass was found to be associated with better clinical outcomes (30). Furthermore, Kalantar-Zadeh et al (31) reported that a low baseline fat percentage was associated with higher mortality in 535 maintenance hemodialysis patients. One might speculate that the adipose tissue in ESRD patients is also a source of antiinflammatory cytokines or other protective substances that may counterbalance the presumed negative effects of the higher degree of inflammation in the obese ESRD patients.

Some limitations of the present study should be noted. First, the findings are limited to a relatively small number of patients and thus may not have provided enough statistical power to show these associations fully. Second, because both body weight and DXA can be affected by the hydration state, fluid status may have influenced the estimates of BMI and LBMI. However, in a previous analysis of serial measurements of multiple-frequency
bioimpedance in peritoneal dialysis patients, the changes in hydration status were not associated with the observed changes over time (27). Third, because patients aged ≥70 y were not enrolled in the study, the results may not reflect the situation in the whole cohort of ESRD patients starting dialysis therapy. Finally, nutritional status was assessed by SGA, which is a reproducible and reliable method to distinguish malnutrition (in the present study referred to as protein-energy wasting) from normal nutritional status (32, 33); however, it is not an ideal method for grading the severity of malnutrition (23).

In conclusion, PEW is not uncommon in overweight ESRD patients and is associated with high FBM and low LBM. This condition, ie, obese sarcopenia, is associated with inflammation and with higher mortality; however, the poor prognosis in these patients appears to be entirely due to the sarcopenia component and not to the increased FBM, despite the relation of FBM with higher concentrations of proinflammatory cytokines.

The authors’ responsibilities were as follows—H Honda: designed the study, analyzed the data, and wrote the manuscript; AR Qureshi: analyzed the data and wrote the manuscript; J Axelsson: designed the experiment and collected the data; ME Suliman: analyzed the data and wrote the manuscript; P Barany: designed the experiment and collected the data; Pr Stenvinkel: designed the experiment, collected and analyzed the data, and wrote the manuscript; B Lindholm: designed the experiment, analyzed the data, and wrote the manuscript. B Lindholm is employed by Baxter Healthcare. None of the other authors had any conflicts of interest to disclose.

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