Truncal fat mass as a contributor to inflammation in end-stage renal disease1–3

Jonas Axelsson, Abdul Rashid Qureshi, Mohammed E Suliman, Hirokazu Honda, Roberto Pecoits-Filho, Olof Heimbürger, Bengt Lindholm, Tommy Cederholm, and Peter Stenvinkel

ABSTRACT
Background: An activated inflammatory response is a common feature of end-stage renal disease (ESRD) and predicts outcome. Adipose tissue is an endocrine organ that may contribute to an inflammatory burden by secreting adipocytokines such as interleukin 6 (IL-6).

Objective: The objective was to relate plasma concentrations of IL-6 in ESRD patients to body composition, regional fat mass distribution, and blood lipid profiles.

Design: One hundred ninety-seven ESRD patients (123 men; $\bar{X} \pm SE$ age: $52 \pm 1$ y) were evaluated shortly before dialysis started. Lean body mass and truncal and nontruncal fat mass were estimated by dual-energy X-ray absorptiometry. Nutritional status was evaluated on the basis of subjective global assessment and handgrip strength. Inflammatory biomarker and blood lipid concentrations were also evaluated.

Results: Median IL-6 (8.5 compared with 4.5 pg/mL; $P < 0.001$) concentrations were significantly greater in malnourished than in well-nourished patients. Moreover, negative correlations were observed between IL-6 and serum creatinine ($p = -0.19, P < 0.01$), handgrip strength ($p = -0.24, P < 0.001$), and serum albumin ($p = -0.34, P < 0.001$). A significantly higher truncal fat mass (12.8 ± 0.7 compared with 10.5 ± 0.4 kg; $P < 0.005$) was observed in ESRD patients with inflammation (C-reactive protein ≥ 10 mg/L). Inverse correlations were observed between plasma IL-6 and HDL cholesterol ($p = -0.16, P < 0.05$) and apolipoprotein A ($p = -0.23, P < 0.001$).

Conclusions: Plausible relations exist between inflammatory biomarkers, such as IL-6 and high-sensitivity C-reactive protein, and regional fat distribution in ESRD patients. Moreover, the strong inverse relations between HDL cholesterol and apolipoprotein A and biomarkers of inflammation suggest that the chronic inflammatory response observed in ESRD patients is an important contributor to the atherogenic lipoprotein profile in uremia.


KEY WORDS Inflammation, cytokines, fat mass, body composition, malnutrition, cholesterol, end-stage renal disease

INTRODUCTION
Human adipose tissue was recently shown to be a hormonally active system that secretes various adipocytokines, such as leptin, interleukin 6 (IL-6), tumor necrosis factor $\alpha$ (TNF-$\alpha$), resistin, plasminogen activator inhibitor, adiponectin, and serum amyloid A (1–4). Additionally, the hormonal activity of adipose tissue is thought to differ according to body location. Intraperitoneal (truncal) fat is the most hormonally active adipose tissue and plays an important role in the development of insulin resistance, type 2 diabetes, and premature atherosclerosis (5, 6). It is well known that an elevated serum IL-6 concentration is predictive of future cardiovascular problems (7, 8), and body adipose tissue may account for as much as 20% of systemic IL-6 concentrations (1). Indeed, a functional and molecular overlap between fat cells and macrophages was recently reported (9).

The quantity and distribution of body adipose tissue are also related to the blood lipid profile (10), and studies have shown independent negative associations between inflammatory biomarkers and serum HDL and LDL particles (11, 12), which have also been shown to modulate the immune response through the binding and inactivation of endotoxins (13).

These observations are of special interest in the management of patients with end-stage renal disease (ESRD), in whom serologic evidence of an activated inflammatory response [on the basis of C-reactive protein (CRP) concentrations] exists in ≈30–50% of European and North American predialysis, hemodialysis, and peritoneal dialysis patients and is a powerful predictor of outcome and cardiovascular disease (14). Because the hepatic synthesis of CRP is largely under the regulation of IL-6, it is not surprising that the activity of this cytokine also is markedly up-regulated in ESRD patients (15) or that elevated plasma IL-6 concentrations are associated with a higher mortality rate in ESRD patients (15–17). The causes of elevated plasma concentrations of IL-6 in ESRD are multifactorial and only partly elucidated, but they may include the uremic syndrome (18), age (19), chronic heart failure (20), persistent infections (21, 22), and the bioincompatibility of the dialyzer membrane and endotoxin absorption from contaminated dialysate or from the gut (14).

Considering these findings and those of recent studies in the general population that link obesity with the presence of low-grade systemic inflammation (23, 24), we hypothesize that...
body fat mass (FM) and distribution may influence the systemic inflammation of ESRD. The objective of the present study was thus to relate plasma concentrations of IL-6 in ESRD patients to their body composition, regional FM distribution, and blood lipid profile.

SUBJECTS AND METHODS

Patients

One hundred ninety-seven ESRD patients (123 men; 62%) with a mean age of 52 ± 1 y were evaluated shortly before the beginning of dialysis (glomerular filtration rate: 7 ± 1 mL/min). They were selected from an ongoing prospective study, and part of this patient material was previously described (18, 25). The study exclusion criteria were as follows: age > 70 y, malignancy, overt infectious complications, and unwillingness to participate in the study. The Ethics Committee of the Karolinska Institute approved the study protocol at Huddinge University Hospital, Stockholm, and informed consent was obtained from the patients. On the basis of subjective global assessment (SGA), 65 patients (33%) were characterized as malnourished (SGA > 1), whereas 132 patients were characterized as well-nourished. Fifty-six patients (28%) had type 1 or 2 diabetes mellitus. Most patients were taking antihypertensive medications as well as other drugs commonly used in ESRD, such as phosphate and potassium binders, diuretics, and supplements of vitamins B, C, and D.

Methods

After the subjects fasted overnight, venous blood samples were taken for analysis. The samples were kept frozen at -70 °C if not analyzed immediately. The glomerular filtration rate, estimated as the mean of urea and creatinine clearance, was calculated from 24-h urinary samples collected from 179 of the patients. Plasma IL-6 was analyzed by enzyme-linked immunosorbent assay (Boehringer Mannheim, Mannheim, Germany). The sensitivity was 75 pg/mL, intraassay CV was 3%, interassay CV was 6%, and correlation (R²) between repeated measurements was 0.93. High sensitivity (hs) CRP was measured by using nephelometry (n = 157), whereas the white blood cell (WBC) count (n = 151), fibrinogen (n = 157), and serum albumin (bromcresol purple) were measured by using routine methods at the Department of Clinical Chemistry, Huddinge University Hospital. The concentrations of serum cholesterol and triacylglycerols were analyzed by using standard enzymatic procedures (Boehringer Mannheim). HDL cholesterol was determined after precipitation of apo B-containing lipoproteins by phosphotungstic acid. Concentrations of apolipoprotein A-I (apo A) and apo B were determined by using an immunonephelometric procedure (Behring AG, Marburg, Germany). Handgrip strength (HGS) was evaluated in both the dominant and non-dominant arms by using the Harpenden Handgrip Dynamometer (Yamar, Jackson, MI). The HGS measurement was repeated 3 times, and the highest value was noted. Subjective global assessment (SGA) was used to obtain an overall clinical estimate of malnutrition as previously described (26). Lean body mass (LBM) and total FM were estimated by dual-energy X-ray absorptiometry (DXA) with the use of the DPX-L device (Lunar Corp, Madison, WI). Regional estimations of trunkal arm and leg FM were performed in all patients with the use of the same method. With this technique, fat and LBM distribution are directly estimated without making assumptions about the 2-compartment model. DXA has proved superior to other simple noninvasive methods for determining body composition in renal failure, especially if repeated measurements are made (27). However, it must be kept in mind that, although the state of hydration does not affect the estimate of FM with DXA, it does affect the estimate of LBM.

Statistical analysis

Results are expressed as means ± SEs, unless otherwise indicated. P values < 0.05 indicated significance. Comparisons between 2 groups were made by using Student’s t test or Mann-Whitney’s U test as appropriate. Comparisons of nominal variables between groups were made by chi-square test. Because most values were not normally distributed, correlations between variables were calculated with the use of Spearman’s ρ test. A three-factor multivariate analysis of variance with Wilk’s lambda was used to measure the degree of correlation between variables. The model included a test for the effect of order. The general linear model procedure with least-squares means was used to identify significant interactions between factors. When significant interactions were found between factors (A × B), they were identified with simple main effects tests. Stepwise multivariate regression analysis was used to assess the predictors for log IL-6. All analyses were performed by using statistical software SAS (version 8.2; SAS Campus Drive, Cary, NC).

RESULTS

Clinical characteristics, nutritional status, and body composition

Basal clinical characteristics and nutritional and body-composition data of the 197 ESRD patients close to the start of dialysis are given in Table 1. The patients were divided into 8 groups by sex, nutritional status, and inflammatory status. As expected, significant differences in body composition were noted between the 2 sexes. Compared with the men, the women had a higher body FM content (23.1 ± 1.0 compared with 19.4 ± 0.8 kg; P < 0.01) and a lower LBM (39.5 ± 0.8 compared with 54.8 ± 0.6 kg; P < 0.001). However, whereas a marked difference in nontruncal FM was observed between women and men (10.1 ± 0.4 and 7.3 ± 0.3 kg, respectively; P < 0.001), we found no significant difference in truncal FM between the women and men (11.6 ± 0.5 compared with 10.9 ± 0.4 kg, respectively). Whereas marked differences in serum creatinine concentrations (8.7 ± 0.2 and 6.7 ± 0.2 mg/dL, respectively; P < 0.0001) and in HGS (36 ± 1 and 24 ± 1 kg, respectively; P < 0.0001) were shown between the men and women, no significant differences in inflammatory biomarkers were noted between the sexes.

As expected, the 65 patients with signs of mild (SGA 2) or moderate (SGA 3) malnutrition (grouped as SGA > 1) were older (57.5 ± 1.4 compared with 50.1 ± 1.0 y; P < 0.001), more often diabetics (42% compared with 22%; P < 0.01), and had a lower body mass index [BMI (in kg/m²): 22.9 ± 0.4 compared with 25.1 ± 0.3; P < 0.001], HGS (26 ± 2 compared with 34 ± 1 kg; P < 0.001), and LBM (45.6 ± 1.2 compared with 50.7 ± 0.8 kg; P < 0.001) compared with the 132 patients classified as well nourished (SGA 1). The differences in total (21.6 ± 0.8 compared with 19.1 ± 1.2 kg; P < 0.05) and truncal (11.7 ± 0.4
TABLE 1
Clinical status, nutritional status, inflammatory biomarkers, and blood lipid concentrations in 197 patients with end-stage renal disease shortly before dialysis treatment began, divided according to sex, nutritional status, and inflammation.²

<table>
<thead>
<tr>
<th></th>
<th>Men (n = 123)</th>
<th>Women (n = 74)</th>
<th>MANOVA²</th>
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<tbody>
<tr>
<td></td>
<td>Noninflamed</td>
<td>Inflamed</td>
<td>Noninflamed</td>
</tr>
<tr>
<td>Age (y)</td>
<td>48 ± 1</td>
<td>53 ± 2</td>
<td>54 ± 3</td>
</tr>
<tr>
<td>GFR (mL/min)³</td>
<td>7 ± 1</td>
<td>7 ± 1</td>
<td>7 ± 1</td>
</tr>
<tr>
<td>Diabetes mellitus (%)</td>
<td>22</td>
<td>23</td>
<td>47</td>
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Nutritional status

<table>
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<tr>
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<th>Serum albumin (g/L)</th>
<th>Serum creatinine (mg/dL)⁴</th>
<th>Handgrip strength (kg)³</th>
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<tr>
<td>Men</td>
<td>34.8 ± 0.7</td>
<td>9.5 ± 0.3</td>
<td>40 ± 1</td>
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<tr>
<td>Women</td>
<td>30.0 ± 1.2</td>
<td>9.8 ± 0.5</td>
<td>37 ± 2</td>
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Body composition

<table>
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<tr>
<th></th>
<th>BMI (kg/m²)</th>
<th>Body fat mass (kg)</th>
<th>Truncal fat mass (kg)</th>
<th>Nontruncal fat mass (kg)</th>
<th>Lean body mass (kg)</th>
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<tbody>
<tr>
<td>Men</td>
<td>24.7 ± 0.5</td>
<td>26.2 ± 0.8</td>
<td>21.7 ± 0.9</td>
<td>23.3 ± 0.9</td>
<td>56.1 ± 0.5</td>
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<tr>
<td>Women</td>
<td>18.8 ± 0.5</td>
<td>23.7 ± 0.8</td>
<td>16.0 ± 0.9</td>
<td>13.7 ± 0.9</td>
<td>56.1 ± 0.5</td>
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Inflammatory biomarkers

<table>
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<tr>
<th></th>
<th>hs-CRP (mg/L)⁵</th>
<th>Interleukin 6 (pg/mL) ⁶</th>
<th>Fibrinogen (g/L)⁶</th>
<th>White blood cells (10⁹/L)²</th>
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<tr>
<td>Men</td>
<td>3.2 ± 2.2</td>
<td>5.4 ± 0.7</td>
<td>4.5 ± 0.2</td>
<td>7.7 ± 0.4</td>
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<tr>
<td>Women</td>
<td>22.6 ± 3.2</td>
<td>9.1 ± 1.3</td>
<td>5.8 ± 0.3</td>
<td>10.5 ± 0.6</td>
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</tbody>
</table>

Blood lipids

<table>
<thead>
<tr>
<th></th>
<th>Serum cholesterol (mmol/L)</th>
<th>Triglycerides (mmol/L)</th>
<th>HDL-cholesterol (mmol/L)</th>
<th>apo A (g/L)</th>
<th>apo B (g/L)</th>
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<tbody>
<tr>
<td>Men</td>
<td>5.4 ± 0.1</td>
<td>2.2 ± 0.1</td>
<td>1.2 ± 0.1</td>
<td>1.33 ± 0.04</td>
<td>1.08 ± 0.04</td>
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<tr>
<td>Women</td>
<td>5.2 ± 0.1</td>
<td>2.1 ± 0.1</td>
<td>0.9 ± 0.1</td>
<td>1.33 ± 0.04</td>
<td>1.08 ± 0.04</td>
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Comparison: The malnourished patients had significantly higher (8.5 compared with 4.5 pg/mL; P < 0.001) median IL-6 concentrations than did the well-nourished patients.

The presence of inflammation (CRP ≥ 10 mg/L) was associated with body composition (Table 1). Whereas the 63 patients with inflammation had higher total body (23.2 ± 1.1 compared with 19.6 ± 0.7 kg; P < 0.01) and truncal (12.8 ± 0.7 compared with 10.5 ± 0.4 kg; P < 0.005) BMI than did the 134 patients with no inflammation, no significant difference in LBM was observed between the 2 groups. Moreover, whereas patients with inflammation had significantly lower total cholesterol (5.4 ± 0.2 compared with 5.7 ± 0.1 mmol/L; P < 0.05), HDL-cholesterol (1.05 ± 0.06 compared with 1.37 ± 0.04 mmol/L; P < 0.001), and apo A (1.18 ± 0.04 compared with 1.40 ± 0.03 g/L; P < 0.001) concentrations, no significant differences in triglycerides or apo B concentrations were observed.

Relation between inflammatory biomarkers and nutritional status and body composition

Median IL-6 concentrations did not differ significantly between the diabetic (6.1 pg/mL) and nondiabetic (5.6 pg/mL) subjects or between men (5.4 pg/mL) and women (6.2 pg/mL). As expected, IL-6 was significantly positively correlated with age (ρ = 0.49, P < 0.001), hs-CRP (ρ = 0.60, P < 0.001), WBC (ρ = 0.24; P < 0.01), and fibrinogen (ρ = 0.34; P < 0.001). All correlations between the 4 inflammatory biomarkers (IL-6, hs-CRP, WBC, and fibrinogen) and the nutritional and body-composition data are given in Table 2. Of note, negative correlations were observed between IL-6 and the nutritional markers serum creatinine (ρ = −0.19, P < 0.01), HGS (ρ = −0.34, P < 0.001), and serum albumin (ρ = −0.34, P < 0.001). The correlation between IL-6 and HGS is depicted in Figure 1. No significant correlations were observed between hs-CRP or IL-6 and LBM.
Significant positive correlations were observed between plasma IL-6 and both total (ρ = 0.18, P < 0.05) and truncal (ρ = 0.21, P < 0.01) FM in the whole group of patients (Figure 2). As shown in Figure 2, no significant correlation was shown between IL-6 and nontruncal FM. Significant positive correlations were observed between hs-CRP and both total-body (ρ = 0.20, P < 0.05) and truncal (ρ = 0.23, P < 0.01) FM. Whereas a near-significant correlation (ρ = 0.15, P = 0.06) was observed between WBC and total FM, a significant positive correlation was observed between fibrinogen and total FM (ρ = 0.18, P < 0.05).

Both WBC (ρ = 0.17, P < 0.05) and fibrinogen (ρ = 0.22, P < 0.01) concentrations correlated with truncal FM.

To evaluate the independent relation between body composition and circulating IL-6 concentrations, we performed a forward multivariate regression model (adjusted total $R^2 = 0.33$) that included age, sex, serum albumin, LBM, truncal FM, nontruncal FM, SGA, and diabetes (all of which likely influence systemic inflammation). In this model, only age (P = 0.001), serum albumin (P < 0.001), SGA (P < 0.05), and truncal FM (P < 0.01) were significantly associated with log IL-6 (Table 3).

### Relations between inflammatory biomarkers and blood lipids

A correlation matrix between the 4 investigated inflammatory biomarkers and blood lipid concentrations are given in Table 2. Whereas strong negative correlations were observed between HDL cholesterol and apo A and hs-CRP (Figure 3), the correlations between the other inflammatory biomarkers (IL-6, WBC, and fibrinogen) and HDL cholesterol or apo A were weak or nonsignificant. Weak, but significant, inverse correlations were observed between serum cholesterol and both hs-CRP and WBC but not IL-6 or fibrinogen, as shown in Table 2.

### DISCUSSION

The present study demonstrates plausible relations between IL-6 and regional FM distribution in ESRD patients. Although markedly elevated plasma concentrations of proinflammatory cytokines, such as IL-6, have been documented in most ESRD patients (28), we do not fully understand the exact causes of the hypercytokinemia observed in the uremic patient group. However, it seems likely that both nondialysis-related factors (such as comorbidity, decreased renal clearance, and infections) and...
onstrated in vivo (1), and it has been estimated that production by human subcutaneous adipose tissue has been a significant source of IL-6 production in ESRD patients. IL-6 increased concentrations of IL-6, which suggests that FM is a body FM (particularly increased truncal FM) was associated with the production of IL-6 (1). In the present study, increased FM has been speculated to play a central role in the loss of muscle mass (sarcopenia), which is often observed in ESRD patients (28). In the present study, clinical nutritional status (SGA) and surrogate markers of muscle protein stores (HGS and serum creatinine) were correlated with plasma IL-6, which indicates an important role for this cytokine in the development of protein malnutrition and muscle catabolism in ESRD. A relation between protein malnutrition and elevated concentrations of IL-6 was previously described in elderly nonrenal patients by Visser et al (41). They found that higher serum concentrations of IL-6 and TNF-α correlated with decreased muscle mass and muscle strength independently of race and sex. Moreover, increased concentrations of IL-6 are associated with various markers of malnutrition in cross-sectional analyses (15, 42). In older patients without renal disease, cachexia is usually associated with higher-than-normal concentrations of TNF-α, IL-1, and IL-6 (43, 44). An important role for IL-6 in this scenario could be proposed as it stimulates the breakdown of muscle protein (44) and promotes cancer cachexia (45). Treatment with IL-6 receptor antibody has been shown to inhibit muscle atrophy in IL-6 transgenic mice (46). Moreover, because IL-6 inhibits the secretion of insulin-like growth factor

shows that adipose tissue in obesity is characterized by macrophage infiltration (9, 33) and that weight loss is associated with a reduction in circulating concentrations of inflammatory biomarkers, such as IL-6 (23, 34).

It is notable that the relation between FM and inflammatory biomarkers seemed to differ between truncal and nontruncal FM. Truncal FM is closely related to visceral FM, which is the fat-tissue depot considered to be the most metabolically active and that has been identified as a key factor in the development of insulin resistance, type 2 diabetes, and premature atherosclerosis (5, 6). Importantly, visceral and subcutaneous adipose tissue depots are biologically distinct (35), and omental adipose tissue releases 2–3 times the amount of IL-6 than does subcutaneous fat tissue (36). Clearly, in future studies evaluating BMI and obesity as risk factors for outcome, inflammation, and cardiovascular events in ESRD patients, a distinction between FM of visceral and subcutaneous origin should be made.

Several studies have shown that inflammatory biomarkers, such as CRP (37), WBC (38), fibrinogen (39), and IL-6 (15–17), are strong independent predictors of all-cause and cardiovascular mortality in ESRD patients. This suggests that inflammation plays a pivotal role in the development of both malnutrition and atherosclerosis (malnutrition, inflammation, and atherosclerosis hypothesis; 40) in this patient group. IL-6, especially, has been speculated to play a central role in the loss of muscle mass (sarcopenia), which is often observed in ESRD patients (28). In the present study, clinical nutritional status (SGA) and surrogate markers of muscle protein stores (HGS and serum creatinine) were correlated with plasma IL-6, which indicates an important role for this cytokine in the development of protein malnutrition and muscle catabolism in ESRD. A relation between protein malnutrition and elevated concentrations of IL-6 was previously described in elderly nonrenal patients by Visser et al (41). They found that higher serum concentrations of IL-6 and TNF-α correlated with decreased muscle mass and muscle strength independently of race and sex. Moreover, increased concentrations of IL-6 are associated with various markers of malnutrition in cross-sectional analyses (15, 42). In older patients without renal disease, cachexia is usually associated with higher-than-normal concentrations of TNF-α, IL-1, and IL-6 (43, 44). An important role for IL-6 in this scenario could be proposed as it stimulates the breakdown of muscle protein (44) and promotes cancer cachexia (45). Treatment with IL-6 receptor antibody has been shown to inhibit muscle atrophy in IL-6 transgenic mice (46). Moreover, because IL-6 inhibits the secretion of insulin-like growth factor

<table>
<thead>
<tr>
<th>Table 3</th>
<th>Significant predictors of log serum interleukin 6 (IL-6) in a forward stepwise multivariate regression analysis of likely predictors in 197 patients with end-stage renal disease</th>
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<tbody>
<tr>
<td>Intercept</td>
<td>—</td>
</tr>
<tr>
<td>Serum albumin (g/L)</td>
<td>—</td>
</tr>
<tr>
<td>Truncal fat (kg)</td>
<td>0.17</td>
</tr>
<tr>
<td>SGA &gt;1</td>
<td>0.15</td>
</tr>
<tr>
<td>Age (y)</td>
<td>0.36</td>
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</table>

r^2: 0.26.
I (IGF-I), the negative effect of IL-6 on muscle function and strength may be mediated via IGF-I (47).

Whereas hypercholesterolemia is a well-established risk factor for cardiovascular mortality and morbidity in the general population, hypocholesterolemia is associated with a significantly higher risk of death in ESRD patients, a phenomenon termed “reverse epidemiology” (48). A recent study by Liu et al (49) showed that the inverse association of total cholesterol concentrations with mortality is due to the cholesterol-lowering effects of systemic inflammation and malnutrition in dialysis patients. Indeed, chronic IL-6 injections have been shown to cause acquired hypocholesterolemia and weight loss in nonhuman primates (50). Additionally, it is possible that HDL or its associated apo A may have specific antiinflammatory effects due to an ability to bind and inactivate endotoxins (51, 52), decreasing the amount available to bind to cell surface Toll-like receptor 4, either directly or via cell membrane CD14 (53), and thus modulating the immunologic response. Inverse correlations between inflammatory biomarkers and total serum cholesterol were previously shown in both nonrenal (11) and renal (49) patients. The present study showed significant inverse correlations between inflammatory biomarkers and total cholesterol, HDL cholesterol, and apo A concentrations (Figure 3), which supports the link between cholesterol metabolism and chronic inflammation.

It may seem paradoxical that we found associations between plasma IL-6 concentrations and both increased FM (indicating adequate energy stores) and surrogate markers of sarcopenia (indicating protein malnutrition). However, the processes of protein and energy malnutrition may not always evolve simultaneously. Thus, the presence of obesity and increased truncal FM may not necessarily imply adequate protein intake and nutritional status. Indeed, we (H Honda, AR Qureshi, O Heimbürger et al, unpublished observations, 2004) found markedly elevated plasma IL-6 concentrations in malnourished (on the basis of the SGA) ESRD patients with both high (>25) and low (<20) BMIs. Actually, it could be speculated that the enhanced generation of proinflammatory cytokines (such as IL-1 and IL-6), resulting from increased truncal FM, may be an important factor that contributes to the sarcopenia often encountered in chronic nonmalignant disorders and aging. Thus, in cross-sectional studies such as this, the true associations between IL-6 and body composition may not be evident because ESRD patients with a wide range of comorbid conditions and differences in the duration of disease and age are studied. Clearly, long-term prospective studies are needed to evaluate the evolution of inflammatory biomarkers and their relation to changes in regional body composition as renal function declines.

Some limitations of the present study should be considered. First, because the study was based on a cross-sectional and post hoc evaluation of a heterogeneous group of patients, the associations between inflammatory biomarkers and body composition may be obscured by many factors not controlled for in the present study, such as age, comorbidity, and duration of kidney disease. In addition, only one single measurement of hs-CRP and IL-6 was used in the present study, even though inflammatory biomarkers may vary with time. Furthermore, this study did not measure sex hormone concentrations (particularly testosterone), which are known to suppress the activation of proinflammatory cytokines (54). Moreover, there remains the possibility that had we studied prevalent patients with a dialysis time of more than a few months, truncal FM might have had an even more significant influence. Also, although the present study included 197 patients, size and a heterogeneous population may still limit it, making it difficult to draw clear conclusions. Finally, it should be emphasized that plasma inflammatory biomarkers may not adequately reflect local fat tissue inflammation (55).

In conclusion, the present cross-sectional study showed a relation between systemic inflammation (on the basis of measured IL-6) and regional fat distribution in ESRD patients and also showed the existence of inverse relations between cholesterol, HDL cholesterol, and apo A and markers of inflammation in these patients. We speculate that a chronic inflammatory response, partly related to truncal FM, may be a part of the metabolic syndrome and may contribute to the atherogenic lipoprotein profile and to the loss of muscle mass in ESRD.
JA, BL, OH, and PS were responsible for the study design. JA and PS wrote most of the final manuscript. OH and PS were involved in the patient recruitment and data collection. JA, PS, and ARQ performed the statistical calculations. MES, HH, TC, and RP-F conducted the serum measurements and helped interpret the data. BL is affiliated with Baxter Healthcare Inc.

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