

## Letter

### ***Frail Phenotype Might Be Associated With Higher Appendicular but Not Truncal Fat Among End-Stage Renal Disease Patients***

To the Editor:

Frailty, a medical syndrome characterized by an increased vulnerability to external stressors independent of comorbidity and disability, places patients at higher risk of adverse health-related outcomes. Frail phenotype is operationalized by the presence of at least three features of five dimensions (exhaustion/fatigue, low physical activity, slow gait speed, weight loss, and weakness),<sup>1</sup> and its clinical importance is increasingly recognized, rendering the identification of frail individuals of clinical importance.

Frailty is highly prevalent in patients with end-stage renal disease (ESRD) regardless of age, up to 67% among those newly starting dialysis.<sup>2</sup> ESRD and dialysis per se lead to a rapid accumulation of functional deficits and a decline in physiologic reserve, simulating the process of aging. ESRD patients with frailty have a higher risk of adverse outcomes including hospitalization, falls, and overall mortality.<sup>3</sup> The presence of frailty is associated with more severe symptomatology among ESRD patients, and frailty dialysis phenotype might be an important criterion for identifying potential candidates eligible for renal supportive care.

In geriatric populations, the pathophysiologic mechanisms related to frailty include malnutrition, long-term inflammation, and an alteration in body composition, characterized by central obesity and increased adiposity.<sup>4</sup> Among ESRD patients, the presence of frailty is similarly associated with higher body fat mass and fat percentage,<sup>5,6</sup> but few studies have addressed the association between lean body mass and frailty in these patients. In addition, the pattern of fat distribution is an important outcome determinant among the general population and those with metabolic syndrome; the proportion of visceral, or truncal adiposity has been distinctly related to pathologies including insulin resistance, cancer predisposition, and infectious complications.<sup>7</sup> However, none of the

existing studies evaluates the relationship between frailty and fat as well as lean mass distribution among ESRD patients. We hypothesize that such a relationship might exist, particularly between frailty and truncal adiposity or lean mass in these patients.

### ***Methods***

The present study was approved by the ethical review board of National Taiwan University Hospital (No. 201505154RINB), and was a pilot attempt at analyzing the relationship between lean, fat mass distribution, and frailty in ESRD patients, an issue that has not been addressed before and can contribute significantly to the understanding of frailty when providing supportive care to affected patients. The inclusion criteria were ESRD patients receiving maintenance hemodialysis in our institute, and the exclusion criteria comprised those who refused to provide informed consent or those who had disturbed consciousness at the time of frailty assessment. A total of 44 patients were consecutively screened for eligibility, and five refused to participate in this study. Finally, we enrolled 39 ESRD patients receiving long-term hemodialysis during 2015 and collected their clinical (sociodemographic profile including age and gender, dialysis duration, and comorbidities) and laboratory data, including hemogram serum biochemistry and nutritional parameters, at baseline. After recruitment, all participants received body composition analysis immediately after their regular dialysis session, using dual energy x-ray absorptiometry (Hologic, Waltham, MA) with dedicated software.<sup>8</sup> All participants were interviewed by nurse researchers using the simple FRAIL scale (SFS), a self-report instrument evaluating five dimensions of frailty (fatigue, resistance, ambulation, illnesses, and weight loss); scores of 1 to 2 indicate prefrailty and 3 to 5 indicate frailty.<sup>1</sup> We then compared total body mass, lean body mass, and fat percentage of different anatomic sites between ESRD patients with and without frailty/prefrailty. In univariate analyses, we assessed the correlation between continuous variables (age, dialysis duration, hemogram, and biochemical data) and body composition parameters. Subsequently, stepwise multivariate linear regression analyses with backward

variable selection incorporating variables with significant associations detected in univariate analysis were used to evaluate the relationship between body composition parameters in different anatomical sites and frail/prefrail status as well as SFS scores.

## Results

Overall, 15.4% and 51.3% participants (aged  $68.3 \pm 10.6$  years, 49% men, mean 3.5 years of dialysis) were frail and prefrail, respectively. No significant differences regarding age ( $P = 0.11$ ), gender ( $P = 0.08$ ), dialysis duration ( $P = 0.6$ ), comorbidities including diabetes mellitus ( $P = 0.12$ ), hypertension ( $P = 0.51$ ), heart failure ( $P = 0.36$ ), malignancy ( $P = 0.74$ ), body mass index (BMI;  $P = 0.5$ ), and laboratory panels were observed between ESRD patients

with and without frailty/prefrailty (Table 1), except higher serum creatinine among nonfrail/prefrail ones ( $P = 0.03$ ). Frail/prefrail ESRD patients had significantly lower total body mass and total lean mass of the whole body and of all anatomical sites, than nonfrail ones (Table 1). However, we found that frail/prefrail ESRD patients had significantly higher fat percentage of all appendices, but not that of their trunk ( $P = 0.26$ ) or cephalic area ( $P = 0.99$ ) (Table 1).

Univariate analyses revealed that age, serum creatinine, total cholesterol, low density lipoprotein, and SFS scores (all complying with normal distribution, with a Kolmogorov-Smirnov test  $P > 0.05$ ) exhibited significant associations with total lean mass, fat percentages, and those of different anatomical sites, whereas BMI, dialysis duration, serum albumin, blood urea nitrogen, potassium, high-density lipoprotein, and triglyceride

Table 1  
Comparison of Laboratory Panels and Body Composition Analysis Results Between Groups

Clinical Variables	Frail/Prefrail Presence	Frail/Prefrail Absence	P-Value
Hemogram and serum biochemistry			
Hemoglobin, g/dL	$9.6 \pm 1.3$	$10.1 \pm 1.3$	0.23
Albumin, mg/dL	$3.7 \pm 0.3$	$3.9 \pm 0.3$	0.19
Blood urea nitrogen, mg/dL	$80.2 \pm 17.6$	$82 \pm 23$	0.79
Creatinine, mg/dL	$10.4 \pm 2.2$	$12.2 \pm 2.5$	0.03
Potassium, meq/L	$4.7 \pm 0.7$	$4.9 \pm 0.8$	0.43
Total cholesterol, mg/dL	$162.3 \pm 39.5$	$165.5 \pm 38.7$	0.82
Triglyceride, mg/dL	$156 \pm 119$	$183.4 \pm 103$	0.48
High density lipoprotein, mg/dL	$41.5 \pm 12.1$	$35.3 \pm 8.2$	0.1
Low density lipoprotein, mg/dL	$98.2 \pm 28.3$	$102.5 \pm 30.4$	0.66
Body composition analysis—whole body			
Total mass, kg	$55.9 \pm 7.3$	$64 \pm 11.4$	0.01
Lean mass, kg	$34.7 \pm 4.7$	$43.1 \pm 8.4$	<0.001
Fat mass, kg	$18.9 \pm 7.5$	$18.8 \pm 6.6$	0.95
Fat percentage, %	$34.2 \pm 8.8$	$29.2 \pm 8.3$	0.1
Cephalic area			
Total mass, g	$4635 \pm 419$	$4926 \pm 526$	0.049
Lean mass, g	$3059 \pm 272$	$3288 \pm 342$	0.03
Fat mass, g	$1063 \pm 101$	$1128 \pm 117$	0.08
Fat percentage, %	$22.9 \pm 0.7$	$22.9 \pm 0.39$	0.99
Trunk area			
Total mass, kg	$29.4 \pm 4.3$	$33.5 \pm 6.7$	0.03
Lean mass, kg	$17.4 \pm 3.9$	$22.1 \pm 4.5$	0.002
Fat mass, kg	$10.7 \pm 4.1$	$10.8 \pm 4.5$	0.95
Fat percentage, %	$35.8 \pm 10$	$31.9 \pm 10.1$	0.26
Right upper limb			
Total mass, g	$3204 \pm 537$	$3720 \pm 612$	0.01
Lean mass, g	$1831 \pm 438$	$2493 \pm 588$	<0.001
Fat mass, g	$1256 \pm 478$	$1055 \pm 396$	0.2
Fat percentage, %	$38.7 \pm 12.1$	$28.7 \pm 11.1$	0.02
Left upper limb			
Total mass, g	$3265 \pm 618$	$3803 \pm 750$	0.02
Lean mass, g	$1869 \pm 436$	$2515 \pm 658$	0.001
Fat mass, g	$1282 \pm 530$	$1125 \pm 380$	0.35
Fat percentage, %	$38.6 \pm 11.7$	$30.2 \pm 10.6$	0.04
Right lower limb			
Total mass, g	$7749 \pm 1187$	$9021 \pm 1756$	0.01
Lean mass, g	$4920 \pm 717$	$6114 \pm 1695$	0.004
Fat mass, g	$2532 \pm 902$	$2277 \pm 669$	0.37
Fat percentage, %	$32.1 \pm 8.2$	$25.5 \pm 7$	0.02
Left lower limb			
Total mass, g	$7688 \pm 1143$	$9078 \pm 1694$	0.004
Lean mass, g	$4650 \pm 1116$	$6349 \pm 1326$	<0.001
Fat mass, g	$2579 \pm 918$	$2339 \pm 745$	0.42
Fat percentage, %	$33 \pm 8.9$	$25.9 \pm 7.1$	0.02

levels did not. Stepwise multivariate linear regression with lean body mass and fat percentages as the dependent variables, incorporating significant variables identified in univariate analyses, showed that SFS scores were independently associated with higher appendicular fat percentage (for left, right lower and left, right upper extremities,  $\beta = 0.34, 0.3, 0.37$ , and  $0.43$ ,  $t = 2.32, 2.05, 2.66$ , and  $3.09$ ,  $P = 0.03, 0.048, 0.01$ , and  $<0.01$ , respectively), but not with those of truncal ( $\beta = 0.12$ ,  $t = 0.76$ ,  $P = 0.45$ ) and cephalic ( $\beta = 0.13$ ,  $t = 0.72$ ,  $P = 0.48$ ) areas. In addition, being frail/prefrail was also independently associated with higher appendicular fat percentages (for left, right lower and right upper extremities,  $\beta = 0.33, 0.32$ , and  $0.33$ ,  $t = 2.31, 2.28$ , and  $2.35$ ,  $P = 0.03, 0.03$ , and  $0.03$ , respectively), but not with fat percentages of trunk ( $P = 0.39$ ) and cephalic ( $P = 0.99$ ) areas. On the contrary, being frail/prefrail was uniformly associated with significantly lower lean mass of all anatomical sites examined. Finally, to satisfy the presumptions of multivariate linear regression analyses and to ensure model validity, we checked the distribution pattern of the residuals of these models and evaluated the possibility of multicollinearity. The residuals for all models were normally distributed (Kolmogorov-Smirnov test  $P = 0.2$ ), and variance inflation factor for all models were lower than five, suggesting the absence of multicollinearity.

### Comment

Past studies revealed that in ESRD patients, body composition components, especially whole body adiposity, might outweigh the importance of BMI regarding their relationship with adverse outcomes.<sup>8</sup> Postorino et al. discovered that central obesity, a surrogate for truncal fat accumulation, prominently increases the risk for cardiovascular and all-cause mortality in ESRD patients independent of BMI.<sup>9</sup> These findings suggest that the distribution pattern of fat mass can be an under-recognized contributor to adverse prognosis besides the quantitative amount of fat mass. However, whether the fat distribution modifies the association between fat mass and frailty in ESRD patients remains unanswered. In this study, we found that appendicular fat percentage exhibited significant association with frailty, whereas truncal fat percentage did not. In conjunction with the literature, our finding raises the possibility that the site of fat accumulation exerts differential prognostic influences among ESRD patients; truncal fat accumulation is more closely associated with atherosclerosis, long-term inflammation, and insulin resistance,<sup>10</sup> whereas appendicular fat accumulation might predispose individuals to developing frailty. This appendicular fat-frailty relationship might be explained by the concept of sarcopenia, because the loss of appendicular

skeletal muscle mass is frequently accompanied by a relative increase in fat, a state termed sarcopenic obesity. We did identify significantly lower lean body mass of appendices among frail/prefrail ESRD patients than those among nonfrail ones (Table 1). In addition, frail phenotype has been linked to neuroendocrine dysregulation including androgen and growth hormone insufficiency, common scenarios in ESRD patients as well.<sup>4</sup> Inadequate testosterone levels can also result in increased adipogenesis.

Our study had its limitations. The size of participant number is low, and the ethnic origin of participants is homogeneous, precluding generalizability to other ESRD patients. The sample size of the linear regression analyses can significantly limit their applicability and render the results error-prone, but we used several statistical tests to ensure the validity of our findings. However, the focus of this study, the association between frailty and body composition parameters of different anatomical sites, might be of potential importance for understanding the pathophysiology of frailty. In line with our findings, the existence of an association between frailty and appendicular fat but not truncal fat might underline the prognostic importance of differential fat distribution among ESRD patients.

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