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),[1] 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.[2] 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.[3] 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.[4] Among ESRD patients, the presence of frailty is similarly associated with higher body fat mass and fat percentage,[5,6] 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.[7] 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.[8] 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.[1] 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

0885-3924/$ - see front matter

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

01
rick Yihong Wu
2-3
2 notes:
4-5
2 notes:
6-7
2 notes:
8-10
3 notes:
11-12
2 notes:
13-14
2 notes:
15-16
2 notes:

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 T scores were independently associated with higher appendicular fat percentage (for left, right lower and left, right upper extremities, β = 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 (β = 0.12, t = 0.76, P = 0.45) and cephalic (β = 0.13, t = 0.72, P = 0.48) areas. In addition, being frail/prefrail was also independently associated with higher appendicular fat percentage (for left, right lower and right upper extremities, β = 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 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.

17-18 2 notes:

19-20 2 notes:

21

rick Yihong Wu

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.[8] 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.[9] 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,[10] 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.[4] 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 sties, 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.

Chia-Ter Chao, MD
Department of Medicine
National Taiwan University Hospital Jin-Shan Branch
New Taipei City, Taiwan
Graduate Institute of Toxicology
National Taiwan University College of Medicine
Taipei, Taiwan
Division of Nephrology
Department of Internal Medicine
National Taiwan University Hospital
Taipei, Taiwan

Ding-Cheng Chan, MD, PhD
Department of Geriatrics and Gerontology
National Taiwan University Hospital
Taipei, Taiwan

Jenq-Wen Huang, MD, PhD
Division of Nephrology
Department of Internal Medicine
National Taiwan University Hospital
Taipei, Taiwan
E-mail: 007378@ntuh.gov.tw
On behalf of the COGENT study group
(COhort of GEriatric Nephrology in NTUH)
National Taiwan University Hospital
Taipei, Taiwan

http://dx.doi.org/10.1016/j.jpainsymman.2017.01.004

Disclosures and Acknowledgments

The present study was financially sponsored by a National Taiwan University Hospital grant (No. 105-N3206) and the Ministry of Science and Technology,

Taiwan (MOST-105−2314-B-002−176-). The authors have no conflicts of interest.

The authors express their gratitude to the colleagues of the NTUH Jin-shan Branch and those of the second core laboratory of the National Taiwan University Hospital (NTUH) for their kind support.

References

1. Chao CT, Hsu YH, Chang PY, et al. Simple self-report FRAIL scale might be more closely associated with dialysis complications than other frailty screening instruments in rural chronic dialysis patients. Nephrology 2015;20:321−328.

2. Johansen KL, Chertow GM, Jin C, et al. Significance of frailty among dialysis patients. J Am Soc Nephrol 2007;18:2960−2967.

3. Bao Y, Dalrymple L, Chertow GM, et al. Frailty, dialysis initiation, and mortality in end-stage renal disease. Arch Intern Med 2012;172:1071−1077.

4. Bauer JM, Sieber CC. Sarcopenia and frailty: a clinician's controversial point of view. Exp Gerontol 2008;43:674−678.

5. Johansen KL, Dalrymple LS, Delgado C, et al. Association between body composition and frailty among prevalent hemodialysis patients: a US Renal Data System special study. J Am Soc Nephrol 2014;25:381−389.

6. Johansen KL, Dalrymple LS, Delgado C, et al. Comparison of self-report-based and physical performance-based frailty definitions among patients receiving maintenance hemodialysis. Am J Kidney Dis 2014;64:600−607.

7. Shuster A, Patlas M, Pinthus JH, et al. The clinical importance of visceral adiposity: a critical review of methods for visceral adipose tissue analysis. Br J Radiol 2012;85:1−10.

8. Kakiya R, Shoji T, Tsujimoto Y, et al. Body fat and lean mass as predictors of survival in hemodialysis patients. Kidney Int 2006;70:549−556.

9. Postorino M, Marino C, Tripepi G, et al. Abdominal obesity and all-cause and cardiovascular mortality in end-stage renal disease. J Am Coll Cardiol 2009;53:1265−1272.

10. Cordeiro AC, Qureshi AR, Stenvinkel P, et al. Abdominal fat deposition is associated with increased inflammation, protein-energy wasting and worse outcomes in patients undergoing haemodialysis. Nephrol Dial Transplant 2010;25:562−568.

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

Chao, Chia-Ter; Chan, Ding-Cheng; Huang, Jenq-Wen

01 Patrick Yihong Wu Page 2
1/3/2019 10:41

02 Patrick Yihong Wu Page 2
1/3/2019 10:39

03 Patrick Yihong Wu Page 2
1/3/2019 10:39

04 Patrick Yihong Wu Page 2
1/3/2019 10:40

05 Patrick Yihong Wu Page 2
1/3/2019 10:39

06 Patrick Yihong Wu Page 2
1/3/2019 10:40

07 Patrick Yihong Wu Page 2
1/3/2019 10:40

08 Patrick Yihong Wu Page 2
1/3/2019 10:40

09 Patrick Yihong Wu Page 2
1/3/2019 10:40

10 Patrick Yihong Wu Page 2

1/3/2019 10:40

11 Patrick Yihong Wu Page 2

1/3/2019 10:40

12 Patrick Yihong Wu Page 2

1/3/2019 10:40

13 Patrick Yihong Wu Page 2

1/3/2019 10:40

14 Patrick Yihong Wu Page 2

1/3/2019 10:40

15 Patrick Yihong Wu Page 2

1/3/2019 10:41

16 Patrick Yihong Wu Page 2

1/3/2019 10:41

17 Patrick Yihong Wu Page 3

1/3/2019 10:42

18 Patrick Yihong Wu Page 3

1/3/2019 10:42

19 Patrick Yihong Wu Page 3

1/3/2019 10:42

20 Patrick Yihong Wu Page 3

1/3/2019 10:42