ORIGINAL RESEARCH

Frailty and the Quality of Life in Hemodialysis Patients: The Importance of Waist Circumference

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Objective: Frailty among the end-stage renal disease (ESRD) population is highly prevalent and has been associated with mortality. Little is known about the relation of different aspects of body composition, a modifiable risk factor, with the risk of frailty in ESRD population.

Design and methods: One hundred and fifty-one patients including 85 men and 66 women, aged ≥18 years with ESRD who had been receiving conventional maintenance hemodialysis (HD) for at least 3 months were included. Body fat and muscle mass from both bioimpedance spectroscopy and skin-fold thickness and waist circumference as a surrogate of abdominal obesity were measured. Frailty was defined based on Fried's criteria. Health-related quality of life was collected using the RAND version of the Kidney Disease Quality of Life (KDQOL-36) Survey.

Results: We performed single and multiple predictor logistic regression analyses to determine factors associated with frailty. After adjustment for age, sex, and comorbidities, fat mass (both by bioimpedance spectroscopy and anthropometry) and waist circumference, but not muscle mass remained the main predictors of frailty. The odds ratio of frailty in the third tertile compared with the first was 4.97 (1.70-14.55) and 3.84 (1.39-10.61) for fat mass and waist circumference, respectively (P for trends for both $<.05$). The scores of physical health and kidney disease effect component of quality of life were lower in frail compared with nonfrail patients (40.7 ± 9.2 vs. 33.7 ± 10.2, $P < .01$ and 66.8 ± 22.4 vs. 51.6 ± 25.7, $P < .05$ for physical health and effects of disease, respectively).

Conclusions: Frailty, which is associated with poor outcomes in chronic HD patients, is common and predicted by fat mass and waist circumference but not by body mass index and muscle mass. Interventions to modify abdominal obesity, reflected by waist circumference, could potentially lower the incidence of frailty and hence improve the quality of life in the HD population.

Introduction

THE PROBLEMS FACED by patients with chronic kidney disease (CKD) are multifactorial and the patients' morbidity and mortality are linked to more than just simple kidney function, but also to the overall performance of their various biological systems.[1,2] Frailty is a common and important comorbidity and there is increasing interest in the factors which determine frailty in different populations, particularly in the CKD population. Frailty among the end-stage renal disease (ESRD) population is highly prevalent and has been associated with hospitalization and mortality independent of other comorbidities and disabilities.[3-5] Frailty is defined as "declined function across multiple physiological systems," which is distinct from normal aging.[3,6-9] Clinically, it can be described by Fried's classification in which 3 or more of the following criteria are present: unintentional weight loss, exhaustion, low strength, slow walking speed, and low physical activity.[9] Although the causes of frailty and protein-energy wasting are well reviewed especially in the elderly,[10] little is known about the relation of body composition, as a modifiable risk factor, with the risk of frailty in ESRD population.

The concept of health-related quality of life (HRQOL) is not new. In 1946, the World Health Organization defined health as "a state of complete physical, mental, and social well-being and not merely the absence of disease or infirmity."[11] The HRQOL concept addresses the effects of the individual's health on physical, cognitive, and social functioning in day-to-day life. Hemodialysis (HD) patients have a diminished HRQOL, both from the myriad of symptoms of ESRD and from the physical and mental burden of the dialysis treatment itself and the associated limitations of diet and travel.[12] HRQOL has also been demonstrated to be independently associated with cardiovascular events and death in patients with CKD.[13]

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Therefore, for these patients, the careful assessment of HRQOL may help guide provision of medical management to optimize their health experience. The separate influences of frailty and quality of life on CKD patients who are on dialysis treatment is relatively well documented, but few studies have examined both frailty and HRQOL and little is known about the influence of frailty on HRQOL in HD patients.

Hence, the objective of this study is to identify the body composition components that predict frailty in the chronic HD population and to investigate the contribution of frailty to the HRQOL of HD patients. Our hypothesis is that the patients' relative amounts of fat and muscle would predict frailty and in turn impact on quality of life. This information might be useful in determining appropriate interventions to reduce frailty and ultimately hospitalization and mortality in the dialysis population.

Methods

Study Design

This is a cross-sectional study of prevalent in-center HD patients at St. Michael's Hospital, a tertiary care, inner city teaching hospital in Toronto, Canada. Adults aged ≥8 years with ESRD who had been receiving conventional maintenance HD for at least 3 months were eligible for this study. Exclusion criteria for the study were pregnancy, blindness, cognitive impairment, or limb amputation. All patients were receiving conventional HD (4 hours per session, 3-4 times weekly) at the time of assessment. The dialysis machine was the Fresenius 5008 (Fresenius Medical Care, Bad Homburg, Germany) and the dialyzers were Fx 1000, Fx Cordiax 120 (Fresenius Medical Care), and the Toray BG-U series (Toray industries, Inc., Tokyo, Japan). We collected relevant demographic and clinical data, which included age, race, gender, cause of ESRD, dialysis vintage, history of coronary artery disease (defined as previous myocardial infarction or revascularization procedure), and diabetes status from the patient's clinical record. This study was approved by the Hospital Research Ethics Board. Since the bioimpedance spectroscopy (BIS) data and frailty assessment for this study was also used to guide routine patient care, a waiver of patient-level consent was authorized.

Anthropometric Measurements

Participants were weighed wearing minimal clothing and no footwear. Body weight was measured to the nearest 0.1 kg on a TORNIX digital platform scale (TRONIX 5702 Bariatric Stand-On Scale, www.scale-tronix.com). Height was measured to the nearest 0.1 cm using a wall mounted stadiometer (TRONIX 5702) with participants standing erect and arms hanging freely at their sides. Waist circumference (WC) was measured in centimeter at the midpoint between the inferior margin of the last rib and the crest of the ilium[14] with the observer at eye level to the tape and at the end of a normal expiration. Mid-arm circumference was measured at the mid-point between the tip of the shoulder and the tip of the elbow (olecranon process and the acromion). The values were recorded to the nearest 0.1 cm. Skinfold thicknesses were measured pre-dialysis at 4 sites (biceps, triceps, subscapular, and supra iliac) using a Harpenden skinfold caliper (Baty International RH15 9LR, England). If an arteriovenous fistula or graft was present, biceps and triceps thicknesses were measured on the contralateral arm. Skinfold thickness from each location was used to calculate body density (Appendix Table 1) which subsequently permitted the calculation of fat mass as described by Durnin and Womersley.[15] As surrogates of muscle mass, mid-arm muscle circumference (MAMC) was calculated as follows: MAMC = mid-arm circumference − 3.142 × triceps-skinfold thickness.[16] All measurements were performed by 1 observer (N.N.).

BIS Measurement of Body Composition

We used the Body Composition Monitor (BCM; Fresenius Medical Care) to measure body compartments using BIS. Electrodes were attached to 1 hand and 1 foot (the limb contralateral to the arteriovenous access) after a 2 to 3 minute resting period in the supine position before the dialysis session. The recorded parameters were total body water (L), intra- and extra-cellular water (ICW and ECW), overhydration (L), fat mass and lean mass (kilogram). To determine muscle mass for our study purpose, we used Kaysen's formula to calculate skeletal muscle mass[17]:

Muscle mass = 9.52 + 0.331 × BIS measured ICW + 2.77 (male) + 0.180 × dry weight (kg) − 0.133 × age.

Quality of Life Assessment

HRQOL was measured using the RAND version of the Kidney Disease Quality of Life (KDQOL-36) Survey, a 36-item short form survey with 5 subscales,[18] which included mental component summary, physical component summary, burden of kidney disease (burden), effects of kidney disease (effects), and symptoms and problems of kidney disease (symptoms; scales from the KDQOL-SF, v1.3). A paper KDQOL-36 form was self-completed by participants after verbal instructions from study personnel unless reading or comprehension problems precluded self-administration, in which cases, a research associate, or family member assisted participants in the questionnaire completion.

Laboratory Measurements

Laboratory data from within the month previous to doing the BIS including serum hemoglobin, albumin, intact parathyroid hormone, total cholesterol, creatinine, calcium, and phosphorus were collected.

Dialysis session data for the session at which the BIS was measured (dialysis session duration, dialysate composition, ultrafiltration volume, relative blood volume changes), systolic and diastolic pressure (recorded pre-dialysis, after

initiation of therapy and end of dialysis), and Kt/V (measured by the dialysis machine using sodium dialysance as generated by the Fresenius 5008 dialysis machines using the Watson equation value for V) were recorded.

Frailty

We ascertained frailty based on a validated scoring system that incorporates 5 domains: weight loss, weakness, exhaustion, low physical activity, and slow walking speed.[9] Each domain was given a dichotomous score of 0 or 1 based on the following 5 criteria.

1. Weight loss was defined as unintentional weight loss of >10 lb (4.5 kg) in the last 1 year. Patients were asked the following question: "In the past 12 months, have you lost more than 10 lbs unintentionally (i.e., not due to dieting or exercise)?" In case they were not sure of the amount of their weight loss, it was confirmed by assessing their medical charts.
2. Weakness was based on measurement of handgrip strength by a handheld dynamometer immediately before a dialysis session. Patients performed 2 tests of maximum grip strength with the dominant hand, and the higher value was used. The strength measurement was assessed with reference to gender and body mass index (BMI; Appendix Table 2).
3. Exhaustion was measured by responses to questions about endurance and energy from the Center for Epidemiologic Studies depression scale.[19]
4. Low physical activity was ascertained from the short version of the Minnesota Leisure Time Physical Activity Questionnaire, which asks about the frequency and duration of various activities over a 2-week period.[20]
5. Slow walking speed was scored based on the time to walk 15 ft. Patients were asked to walk 15 ft at their usual pace immediately before a dialysis session. Times were measured to the nearest tenth of 1 second. Walking aids were permitted. The walking speed was assessed with reference to gender and height (Appendix Table 2).

A score of 3 or more points was considered frail.

Statistical Methods

Patients demographic and dialysis characteristics were summarized by standard descriptive statistics (e.g., mean and standard deviation). We performed single and multiple predictor logistic regression analyses to determine factors associated with frailty. First, we included each variable separately; Then the first model included case mix variables (age, sex, race, dialysis vintage, hypertension [HTN], diabetes mellitus [DM], coronary artery disease serum albumin, and cholesterol) plus the independent variable which was BMI, serum creatinine, and ECW to ICW separately in the model; The second model included case mix variables and body composition variables estimated by BIS; The third model included case mix variables and body composition variables estimated by anthropometry (fat mass and MAMC), and the fourth model included case mix variables plus other aspects of body composition estimated by anthropometry (WC instead of fat mass). All continuous variables were expressed as continuous covariables in the adjusted models. We also assessed the association of body composition with the individual components of frailty through logistic regression modeling and tested the various demographic and metabolic characteristics' ability to predict frailty by comparing the associated statistics corresponding to areas under the receiver operating characteristics curves of the models.

The aggregate frailty score was calculated as the sum of the component scores (range 0-5); nonfrail was defined as a score of 0 to 2, frail was defined as a score of 3, and severely frail was defined as a score of 4 or 5. We evaluated the amount of fat and muscle mass by BIS and anthropometry in patients with different score categories of frailty. Finally, we compared the components of KDQOL between frail and nonfrail patients. We used SAS version 9.4 (SAS Institute, Cary, NC) for all analyses, and 2-tailed nominal P values $< .05$ were considered to indicate statistical significance.

Results

After excluding patients based on the exclusion criteria, of a total of 163 patients, 151 patients provided all the information necessary to determine frailty status, and 114 patients also had KDQOL data available. In the cohort of 151 patients, the mean age and dialysis vintage of our participants was 64 ± 14 and 6.2 (interquartile range 0.3-30) years respectively. In all, 37.6% were Caucasian, 18.8% were black, 55% had diabetes, and 84% had HTN (Table 1). Forty-nine percent of this prevalent HD cohort met the classic definition of frailty. In comparison with nonfrail patients, frail patients had a higher BMI and fat mass and lower serum albumin, total and high-density lipoprotein cholesterol levels. The prevalence of DM was higher in frail patients, whereas the prevalence of cardiovascular disease (CVD) and HTN was the same in both groups.

We evaluated the odds ratio (OR) of frailty across the different tertiles of demographic and anthropometric characteristics (Table 2). After adjustment for sex and comorbidities (HTN, DM, and CVD), fat mass (both by BIS and anthropometry), WC and ECW/ICW remained the main predictors of frailty. The OR of frailty in the third tertile compared with the first was 3.85 (1.18-10.50), 4.97 (1.70-14.55), and 3.84 (1.39-10.61) for ECW/ICW, fat mass, and WC, respectively. Higher muscle mass measured by both Kaysen formula and anthropometry (represented by MAMC) was not associated with lower odds of frailty.

With respect to the criteria for frailty, we found that HD patients were least likely to meet the weight loss criterion (25%) and most likely to meet the weak grip strength criterion (85%) (Table 3). We also evaluated the correlation of

Table 1. Characteristics of the 151 HD Patients

Characteristic	All Patients	Nonfrail Patients (N = 77)	Frail Patients (N = 74)	*P* Value
Age (y)	64 ± 14	59 ± 15	69 ± 11	<.001
Women, %	44	39	49	.26
Race, %				.9
Caucasian	37	35	40	
Black	19	21	16	
Asian*	26	26	25	
South Asian†	17	17	18	
Other	1	1	1	
Comorbidity (%)				
Diabetes	55	45	65	.02
Coronary artery disease	30	26	35	.23
Hypertension	84	88	81	.23
Dialysis vintage; median (IQR) (y)	6.2 (0.3-30.0)	5.4 (0.3-20.0)	7.1 (0.3-30.0)	.08
Postdialysis weight (kg)	69.2 ± 16.5	66.6 ± 1.7	72.0 ± 17.6	.05
Body mass index (kg/m^2)	27.0 ± 5.4	25.6 ± 4.5	28.3 ± 5.8	.001
Waist circumference (cm)	97.8 ± 14.8	93.6 ± 14.3	103.0 ± 13.8	<.001
Kt/V by Watson formula	1.51 ± 0.34	1.58 ± 0.36	1.44 ± 0.30	.03
Total body fat (%)‡	37.7 ± 9.9	35.0 ± 9.9	40.7 ± 9.0	<.001
Fat mass (kg)‡	27.4 ± 11.3	24.4 ± 10.5	30.7 ± 11.3	<.001
Muscle mass (kg)‡	19.9 ± 5.8	20.1 ± 5.7	19.7 ± 5.7	.71
Blood hemoglobin (g/dL)	10.4 ± 1.4	10.4 ± 1.5	10.5 ± 1.3	.62
Serum albumin (g/dL)	3.8 ± 0.4	3.9 ± 0.4	3.7 ± 0.4	.02
Serum creatinine (mg/dL)	8.25 ± 3.55	8.77 ± 3.64	7.70 ± 3.39	.06
Total cholesterol (mg/dL)	139 ± 34	148 ± 38	134 ± 35	.02
LDL cholesterol (mg/dL)	73 ± 31	76 ± 29	67 ± 31	.06
HDL cholesterol (mg/dL)	43 ± 16	46 ± 19	40 ± 12	.02
Serum calcium (mg/dL)	8.88 ± 2.28	8.96 ± 0.92	8.76 ± 1.12	.16
Serum phosphorus (mg/dL)	4.73 ± 1.85	4.67 ± 1.70	4.82 ± 2.20	.62
Serum PTH (pg/mL)	41.9 ± 47.7	41.9 ± 45.9	41.8 ± 49.8	.9
Serum urea (mg/dL)	60.7 ± 18.8	60.7 ± 20.2	60.7 ± 17.6	.9

IQR, interquartile range; HD, hemodialysis; HDL, high-density lipoprotein; LDL, low-density lipoprotein; PTH, parathyroid harmone.
*Asian; Chinese, Japanese, Korean, Filipino, Laotian, Vietnamese.
†South Asian; Indian, Indo-Caribbean, Pakistani, Sri Lankan.
‡Fat mass and muscle mass were measured by bioimpedance spectroscopy.

fat and muscle mass with the OR of individual components of frailty. Measures of fat mass using BIS and skinfold thickness were associated with multiple components of frailty when included simultaneously in a multiple predictor model while these associations were not significant for muscle mass. Higher fat mass measured by BIS was associated with higher odds of muscle weakness, low physical activity, and slow walking speed (OR [confidence interval (CI)]: 1.07 [1.01-1.13], 1.06 [1.02-1.10], 1.04 [1.01-1.08], respectively). The same correlations were present for the fat mass measured by skinfold thickness.

The concordance (c) statistic (area under the receiver operating characteristics curve) for predicting frailty for the base model including age, sex, race, dialysis vintage, CVD, diabetes and HTN was 0.76 (95% CI, 0.68-0.83). In second model adding weight and height to the first model did not significantly increase the C-statistic (0.78 [95% CI, 0.69-0.86], $P = .31$, data not shown). Adding WC in the third model significantly improved the model discrimination in comparison with second model (C-statistic = 0.82; 95% CI, 0.74-0.89; $P = .04$; Fig. 1).

Fat mass as the total amount and as a proportion of the body weight and also WC as a surrogate of abdominal fat mass were compared between different frailty categories. Severely frail patients (score 4-5) had a larger fat mass, fat mass percent, and higher WC compared with frail (score 3) or nonfrail (score 0-2) patients (Fig. 2); fat mass percent was 34.6 ± 10.0, 40.5 ± 8.4, and 43.1 ± 8.1, and the WC was 93.3 ± 14.3, 100.1 ± 13.7, and 110.5 ± 9.7 cm in nonfrail, frail, and severely frail patients respectively ($P < .01$ for both). The amount of muscle mass by BIS and the Kaysen formula did not correlate with the frailty score (data not shown).

The crude scores in the KDQOL questionnaire of physical health, mental health, effects of disease, and symptoms were lower in frail than nonfrail patients (Table 4). After adjustment for age, sex, race, BMI, and comorbidities, the score of physical health (how the patient feels about their physical health) and kidney disease effect (how much impact kidney disease has on the patient's day) still remained significantly lower in frail patients.

Table 2. Unadjusted and Adjusted Odds Ratio of Frailty Across Tertiles of Body Composition in 151 HD Patients

Characteristic	Each Variable Separate	Model 1	Model 2	Model 3	Model 4
Serum Creatinine					
Second T (7-9.3 mg/dL)	**2.61 (1.17-5.80)**	0.53 (0.12-2.22)	–	–	–
Third T	1.61 (0.73–3.59)	0.25 (0.03–2.24)	–	–	–
BMI					
Second T (24-28.7 kg/m^2)	0.02 (0.90-4.55)	2.84 (0.99-8.13)	–	–	–
Third T	**2.50 (1.13-5.54)**	1.89 (0.69-5.13)	–	–	–
Fat mass by BIS					
Second T (21.3-31.2 kg)	**2.63 (1.14-6.06)**	–	**3.27 (1.17-9.09)**	–	–
Third T	**4.59 (1.97-10.68)***	–	**4.97 (1.70-14.55)***	–	–
Muscle mass by BIS					
Second T (16.9-22.1 kg)	0.81 (0.37-1.79)	–	2.21 (0.73-6.67)	–	–
Third T	0.69 (0.31-1.53)	–	2.49 (0.69-9.04)	–	–
Fat mass by skinfold					
Second T (16.7-24.8 kg)	1.44 (0.65-3.17)	–	–	1.12 (0.41–3.08)	–
Third T	**2.12 (1.01-4.60)***	–	–	**2.91 (1.08-10.80)***	–
MAMC					
Second T (24.2-27.3 cm)	1.23 (0.57-2.65)	–	–	1.20 (0.44-3.29)	1.28 (0.44-3.70)
Third T	1.47 (0.67-3.25)	–	–	0.78 (0.19-3.13)	1.15 (0.28-4.66)
Waist circumference					
Second T (91-103 cm)	1.71 (0.77-3.80)	–	–	–	2.08 (0.75-5.74)
Third T	2.07 (0.93-4.31)*	–	–	–	**3.84 (1.39-10.61)***
ECW to ICW					
Second T (0.95-1.06)	1.70 (0.72-4.20)	1.28 (0.45-3.65)	–	–	–
Third T	**9.42 (3.81-19.26)***	**3.85 (1.18-10.50)***	–	–	–

BIS, bioimpedance spectroscopy; BMI, body mass index; ECW, extracellular water; ICW, intracellular water; MAMC, mid-arm muscle circumference.

T, tertile; T1, <lower limit of T2; T3, >upper limit of T2.

All tertiles are compared with the first tertile as the reference.

Significant results ($P < .05$) are shown in bold.

Model 1 includes case mix variables (age, sex, race, dialysis vintage, hypertension, diabetes mellitus, coronary artery disease, serum albumin, and cholesterol) + BMI or serum creatinine or ECW/ICW.

Model 2 includes case mix variables + body composition variables estimated by BIS.

Model 3 includes case mix variables + body composition variables estimated by anthropometry.

Model 4 includes case mix variables + other aspects of body composition estimated by anthropometry (waist circumference instead of fat in model 3).

*P for trend <.05.

Discussion

We found that 49% of this prevalent HD cohort met the classic definition of frailty. Higher adiposity (especially abdominal) was associated with higher risk of frailty in HD patients but not higher BMI. Higher muscle mass measured by BIS using Kaysen formula and as reflected by the serum creatinine (as a surrogate) was not associated with lower risk of frailty. With respect to HRQOL, physical health and effect of disease scores were significantly lower in frail patients compared with nonfrail patients.

The prevalence of frailty among ESRD patients in our study was much (5 to 7-fold) higher than in community-

Table 3. Body Fat and Muscle as Continuous Variables and Multivariable Adjusted Odds Ratio of Components of Frailty in 151 HD Patients

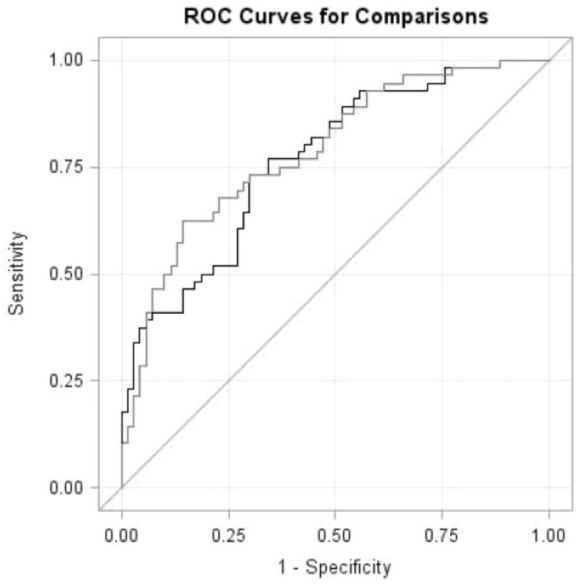
		BIS Measurements		Skinfold Measurements	
Components of Frailty	Prevalence (%)	Fat Mass	Muscle Mass	Fat Mass	Muscle Mass*
Weakness	85	1.07 (1.01-1.13)†	0.98 (0.85-1.13)	1.09 (1.02-1.15)†	1.04 (0.88-1.22)
Low physical activity	52	1.06 (1.02-1.10)†	1.05 (0.96-1.15)	1.07 (1.02-1.13)†	1.07 (0.93-1.22)
Exhaustion	45	1.02 (0.98-1.06)	1.01 (0.91-1.16)	1.02 (0.96-1.07)	1.03 (0.92-1.16)
Slow walking speed	39	1.04 (1.01-1.08)†	1.14 (1.00-1.29)	1.06 (1.01-1.12)†	1.08 (0.93-1.26)
Weight loss	25	1.02 (0.98-1.06)	1.08 (0.97-1.20)	1.06 (1.01-1.11)†	1.08 (0.93-1.24)

BIS, bioimpedance spectroscopy; HD, hemodialysis.

All values are adjusted for age, sex, race, dialysis vintage, hypertension, diabetes mellitus, and coronary artery disease.

*Mid-arm muscle circumference used as a surrogate of muscle mass.

†$P < .05$.



	AUC	95% CI	P Value
Model including weight and height	0.7771	0.6899 to 0.8643	0.04
Previous + waist circumference in the model	0.8179	0.7382 to 0.8949	

Figure 1. Comparison of the receiver operating characteristics (ROC) curve for predicting frailty without and with waist circumference. AUC, area under the curve. Other variable in both models included age, race, sex, dialysis vintage, cardiovascular disease, diabetes, hypertension.

dwelling older adults.[9] The proportion of frail patients in our study was close to the 42%, reported in the study by Mac-Adams et al[3] but much higher than the 30% reported by the study of Johansen et al,[21] both of these studies were in the ESRD population. However, the latter study had a lower mean age (57.1 ± 14 vs. 64 ± 14 years, respectively) and lower dialysis vintage (3.0 [0.1-30.1] vs. 6.2 [0.3-30.0] years respectively) compared with our population, which may be the basis for this difference.

The BCM measures lean tissue mass, but does not directly measure muscle mass. It measures ICW and

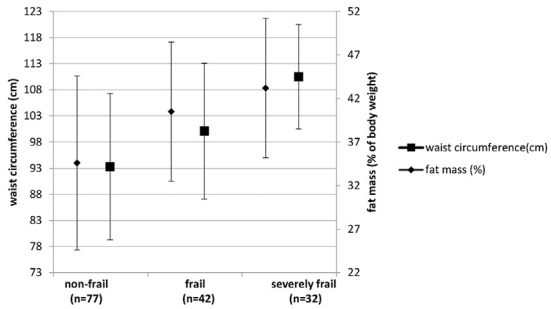


Figure 2. Waist circumference and fat mass (percent of body weight) in nonfrail, frail, and severely frail patients. Nonfrail was defined as a score of 0 to 2, frail was defined as a score of 3 and severely frail was defined as a score of 4 or 5.

ECW. We determined the muscle mass using the Kaysen formula which is a formula based on ICW measured by BCM.[17] Kaysen et al showed that estimate of muscle mass by their equation correlates well with isotopic methods in approximating values obtained by magnetic resonance imaging and can be used to estimate limb muscle mass. He also demonstrated that the ICW, on which their equation is based, is not affected by the removal of ECW during dialysis.[17] Wabel et al also confirmed their results and showed that the change in the patients' fluid status induced by the ultrafiltration was accurately reflected in ECW, TBW, and overhydration. It follows therefore that the ICW, on which Kaysen's equation is based, should remain unchanged by the treatment, despite fluid removal. Therefore, our determination of muscle mass which was done before dialysis is not be affected by hydration status.[22]

To our knowledge, this is the first study that has carried out a comprehensive anthropometric measurement of fat and muscle mass and their correlation with frailty and its components, in a chronic HD population. The results of this study suggest that higher adiposity (WC and total fat mass) as well as higher ECW to ICW (as an integrated marker reflecting both fluid overload and malnutrition)[23] is associated with higher risk of frailty in HD patients, whereas higher muscle mass did not decrease the risk of frailty. Our results are in agreement with some other studies

Table 4. Comparison of Components of KDQOL Between Frail and Nonfrail Patients

KDQOL Components	Nonfrail Patients (n = 50)	Frail Patients (n = 64)	*P* Value	Adjusted *P* Value*
Physical health	40.7 ± 9.2	33.7 ± 10.2	<.01	<.01
Mental health	48.9 ± 10.5	43.6 ± 11.4	<.01	.07
Effects of disease	66.8 ± 22.4	51.6 ± 25.7	<.01	<.05
Burden of disease	36.8 ± 25.6	32.2 ± 25.3	.30	.69
Symptoms	79.1 ± 16.7	67.8 ± 20.4	<.01	.08

KDQOL, Kidney Disease Quality of Life Survey which was available for 114 of the patients.
*Model adjusted for age, sex, race, body mass index, dialysis vintage, hypertension, and diabetes mellitus.

including the study of Johansen et al among 638 adult patients receiving maintenance HD at 14 centers in the United States.[21,24] The association of adiposity with higher frailty in dialysis patients could be because of the fact that low physical activity is a risk factor for weight gain and obesity. Also adipose tissue can itself produce proinflammatory cytokines which may contribute to muscle wasting, weakness and low walking speed, components of frailty which were correlated with higher fat mass.[25] This is however in conflict with the reverse epidemiology phenomenon reported in other studies among dialysis patients which showed traditional risk factors for CVD including BMI, fat mass, and serum cholesterol are found to be correlated with better survival in the ESRD population.[26–31] A recent study however showed that the protective effect of fat was only observed in inflamed patients and was not present in noninflamed patients.[32] Thus, the obesity paradox may be modified by the presence of inflammation and so when individuals are subjected to the stressors associated with ESRD, the protective effect of fat stores may outweigh the adverse effects of high fat mass on survival, including worse physical functioning and frailty.[21] This protection may not exist in noninflamed dialysis patients. Although we did not measure specific markers of inflammation, our frail patients did have a lower serum albumin which may reflect an inflamed state.

To our knowledge, no previous study has evaluated the associations between WC, a surrogate of visceral fat, and frailty. Most previous studies including the ones on reverse epidemiology are based on BMI[28,33] and evidence is emerging that BMI is an imperfect metric for obesity, in part because it fails to differentiate between fat and muscle mass.[34] We also found WC a better predictor for frailty than the commonly used BMI. Our findings which showed higher WC was correlated with severe frailty underscore the importance of visceral adiposity, measured by WC, as an important and easily obtained metric with significant predictive value in long-term outcomes for HD patients. In support of this concept, a study in healthy women aged 17 to 74 years also showed in comparison with BMI, WC had much higher sensitivity and specificity to identify subjects with risk factors (HTN, dyslipidemia, and diabetes). They concluded that WC is the best screening measure for cardiovascular risk factors, compared with BMI and waist-to-hip ratio.[35] WC is strongly associated with sarcopenic obesity and insulin resistance,[36] both of which are related to functional decline, frailty, and disability and thought to be partially mediated by an increase in proinflammatory markers, including interleukin 1, interleukin 6, and tumor necrosis factor alpha.[37] In addition, other studies found that WC predicts death independent of inflammation measured by inflammatory markers suggesting mechanism(s) other than inflammation might contribute to the high risk of visceral fat mass in the ESRD population.[24] Some adipocyte-derived hormones including adiponectin, a cardiovascular protective factor,[38,39] which is reduced in obesity, and Leptin, which is increased in patients with ESRD and predicts adverse cardiovascular outcomes in overweight and obese patients with ESRD[40] are other potential contributing factors to the risk of visceral fat mass. In another unrelated study (under review), we found that WC was a better predictor than BMI in the calculation of TBW.

One might expect to observe a relationship between muscle mass measured by both BIS and MAMC (a surrogate of muscle mass) with frailty, but that was not the case. Our findings are consistent with recent findings in the ACTIVE/ADIPOSE study demonstrating no association of BIS measures of muscle mass with mortality.[41] Although muscle mass is the strongest determinant of muscle function and strength (a feature of frailty), recent clinical data suggest that these 3 are not unconditionally correlated.[42,43] The quality and function of muscle mass have been shown to change independent of the amount of the muscle mass in different conditions such as aging.[44,45] The mechanisms might be related to the intramuscular fat infiltration which was found to be greater, based on magnetic resonance imaging in CKD patients than for age- and sex-matched controls.[46] The lack of the association between muscle mass and frailty in our study might direct one toward more focus on the amount of muscular adipose tissue infiltration and muscle fibrosis because of the uremic milieu rather than muscle mass itself. Furthermore, our results might highlight the importance of the recent consensus statement by the FNIH Sarcopenia project indicating more emphasis should be placed on the central functional role of muscle which is to provide force for body movements and actions (muscle strength) rather than muscle mass itself.[47]

A clinically relevant finding was the association of frailty and KDQOL. After adjustment for age and comorbidities, the KDQOL of frail patients still had lower physical and effect of disease scores than nonfrail patients, which supports the claim that frailty is an independent significant predictor of quality of life. This finding is important because KDQOL per se has been shown to be a predictor of survival in the CKD patient population.[48,49] In a study of 1,000 patients at 3 dialysis facilities in the United States, lower scores on the physical component of KDQOL were associated with greater death risk and hospitalization in the next 2 years.[50] In addition to the physical component, our study showed that the frail patients had a lower score in the "effects of kidney disease on daily life" subscale which includes items about how bothered the respondent feels by fluid limits, diet restrictions, and other circumstances caused by their kidney disease. Hence, as frailty is associated with lower physical health component of the KDQOL, WC a predictor of frailty could also be a potential modifiable predictor of the KDQOL.

The strengths of this study include the measurement of a validated, objective construct of frailty, the comprehensive assessment of body composition using validated technology (BIS) plus detailed anthropometry and a validated measure of the quality of life and correlating them with the existence of frailty, in this high-risk population. The identification of WC (a more specific representation of the metabolic status of the patient) rather than BMI, as a predictor of frailty, may focus more attention on the use of WC as an important patient characteristic to correlate with comorbidities, in general.

There are some weaknesses of the present study. The cross-sectional study design limits the ability to determine causal relationships. The sample size was small and we also did not measure the inflammatory markers to see if the relation of WC and frailty is mediated by inflammation, although serum albumin may be viewed as a marker of inflammation, and it was significantly lower in the frail patients.

In summary, we confirmed that frailty, which is associated with poor outcomes in chronic HD patients, is common and predicted by fat mass and WC, but not by muscle mass. We have identified WC as an important anthropometric characteristic, perhaps more specific than BMI, to monitor in patients on chronic HD, as a predictor of adverse outcomes. We also highlight the fact that interventions to modify abdominal obesity, reflected by WC, could potentially lower the incidence of frailty and hence improve the quality of life in the HD population.

Practical Implications

We consider that these findings are valuable because they support the fact that a comprehensive program of lifestyle modification to modify abdominal obesity could potentially lower the incidence of frailty and hence improve survival in the HD population.

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Supplementary Data

Supplementary data related to this article can be found at http://dx.doi.org/10.1053/j.jrn.2017.07.007.

References

1. Kurella M, Lo JC, Chertow GM. Metabolic syndrome and the risk for chronic kidney disease among nondiabetic adults. *J Am Soc Nephrol*. 2005;16:2134-2140.

2. Stengel B, Tarver-Carr ME, Powe NR, Eberhardt MS, Brancati FL. Lifestyle factors, obesity and the risk of chronic kidney disease. *Epidemiology*. 2003;14:479-487.

3. McAdams-DeMarco MA, Law A, Salter ML, et al. Frailty as a novel predictor of mortality and hospitalization in individuals of all ages undergoing hemodialysis. *J Am Geriatr Soc*. 2013;61:896-901.

4. Bao Y, Dalrymple L, Chertow GM, Kaysen GA, Johansen KL. Frailty, dialysis initiation, and mortality in end-stage renal disease. *Arch Intern Med*. 2012;172:1071-1077.

5. Alfaadhel TA, Soroka SD, Kiberd BA, Landry D, Moorhouse P, Tennankore KK. Frailty and mortality in dialysis: evaluation of a clinical frailty scale. *Clin J Am Soc Nephrol*. 2015;10:832-840.

6. Woo J, Leung J, Morley JE. Comparison of frailty indicators based on clinical phenotype and the multiple deficit approach in predicting mortality and physical limitation. *J Am Geriatr Soc*. 2012;60:1478-1486.

7. Bouillon K, Sabia S, Jokela M, et al. Validating a widely used measure of frailty: are all sub-components necessary? Evidence from the Whitehall II cohort study. *Age (Dordr)*. 2013;35:1457-1465.

8. Jeoung BJ, Lee YC. A study of relationship between frailty and physical performance in elderly women. *J Exerc Rehabil*. 2015;11:215-219.

9. Fried LP, Tangen CM, Walston J, et al. Frailty in older adults: evidence for a phenotype. *J Gerontol A Biol Sci Med Sci*. 2001;56:M146-M156.

10. Kim JC, Kalantar-Zadeh K, Kopple JD. Frailty and protein-energy wasting in elderly patients with end stage kidney disease. *J Am Soc Nephrol*. 2013;24:337-351.

11. World Health Organization. Preamble to the Constitution of the World Health Organization as adopted by the International Health Conference, New York, 19–22 June, 1946. In: *Constitution of the World Health Organization*. Geneva, Switzerland: World Health Organization; 1948:100.

12. Mujais SK, Story K, Brouillette J, et al. Health-related quality of life in CKD patients: correlates and evolution over time. *Clin J Am Soc Nephrol : CJASN*. 2009;4:1293-1301.

13. Porter AC, Lash JP, Xie D, et al. Predictors and outcomes of health-related quality of life in adults with CKD. *Clin J Am Soc Nephrol : CJASN*. 2016;11:1154-1162.

14. Waist Circumference and Waist–Hip Ratio: Report of a WHO Expert Consultation Geneva, 2008:8–11.

15. Durnin JV, Womersley J. Body fat assessed from total body density and its estimation from skinfold thickness: measurements on 481 men and women aged from 16 to 72 years. *Br J Nutr*. 1974;32:77-97.

16. Heymsfield SB, McManus C, Smith J, Stevens V, Nixon DW. Anthropometric measurement of muscle mass: revised equations for calculating bone-free arm muscle area. *Am J Clin Nutr*. 1982;36:680-690.

17. Kaysen GA, Zhu F, Sarkar S, et al. Estimation of total-body and limb muscle mass in hemodialysis patients by using multifrequency bioimpedance spectroscopy. *Am J Clin Nutr*. 2005;82:988-995.

18. Hays RD, Kallich JD, Mapes DL, Coons SJ, Carter WB. Development of the kidney disease quality of life (KDQOL) instrument. *Qual Life Res*. 1994;3:329-338.

19. Orme JG, Reis J, Herz EJ. Factorial and discriminant validity of the Center for Epidemiological Studies Depression (CES-D) scale. *J Clin Psychol.* 1986;42:28-33.

20. Taylor HL, Jacobs DR Jr, Schucker B, Knudsen J, Leon AS, Debacker G. A questionnaire for the assessment of leisure time physical activities. *J Chronic Dis.* 1978;31:741-755.

21. 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.

22. Wabel P, Rode C, Moissl U, Chamney P, Wizemann V. Accuracy of bioimpedance spectroscopy (BIS) to detect fluid status changes is hemodialysis patients. Poster presentation ERAEDTA 2007.

23. Kim EJ, Choi MJ, Lee JH, et al. Extracellular fluid/intracellular fluid volume ratio as a novel risk indicator for all-cause mortality and cardiovascular disease in hemodialysis patients. *PLoS One.* 2017;12:e0170272.

24. Postorino M, Marino C, Tripepi G, Zoccali C, Group CW. Abdominal obesity and all-cause and cardiovascular mortality in end-stage renal disease. *J Am Coll Cardiol.* 2009;53:1265-1272.

25. Kamycheva E, Berg V, Jorde R. Insulin-like growth factor I, growth hormone, and insulin sensitivity: the effects of a one-year cholecalciferol supplementation in middle-aged overweight and obese subjects. *Endocrine.* 2013;43:412-418.

26. Kalantar-Zadeh K, Abbott KC, Salahudeen AK, Kilpatrick RD, Horwich TB. Survival advantages of obesity in dialysis patients. *Am J Clin Nutr.* 2005;81:543-554.

27. Park J, Jin DC, Molnar MZ, et al. Mortality predictability of body size and muscle mass surrogates in Asian vs white and African American hemodialysis patients. *Mayo Clin Proc.* 2013;88:479-486.

28. Ricks J, Molnar MZ, Kovesdy CP, et al. Racial and ethnic differences in the association of body mass index and survival in maintenance hemodialysis patients. *Am J kidney Dis.* 2011;58:574-582.

29. Kalantar-Zadeh K, Streja E, Molnar MZ, et al. Mortality prediction by surrogates of body composition: an examination of the obesity paradox in hemodialysis patients using composite ranking score analysis. *Am J Epidemiol.* 2012;175:793-803.

30. Johansen KL, Young B, Kaysen GA, Chertow GM. Association of body size with outcomes among patients beginning dialysis. *Am J Clin Nutr.* 2004;80:324-332.

31. Noori N, Kovesdy CP, Dukkipati R, et al. Survival predictability of lean and fat mass in men and women undergoing maintenance hemodialysis. *Am J Clin Nutr.* 2010;92:1060-1070.

32. Stenvinkel P, Gillespie IA, Tunks J, et al. Inflammation modifies the paradoxical association between body mass index and mortality in hemodialysis patients. *J Am Soc Nephrol.* 2016;27:1479-1486.

33. Kalantar-Zadeh K, Kopple JD, Kilpatrick RD, et al. Association of morbid obesity and weight change over time with cardiovascular survival in hemodialysis population. *Am J kidney Dis.* 2005;46:489-500.

34. Romero-Corral A, Somers VK, Sierra-Johnson J, et al. Accuracy of body mass index in diagnosing obesity in the adult general population. *Int J Obes (Lond).* 2008;32:959-966.

35. Esmaillzadeh A, Mirmiran P, Azizi F. Comparative evaluation of anthropometric measures to predict cardiovascular risk factors in Tehranian adult women. *Public Health Nutr.* 2006;9:61-69.

36. Stenholm S, Harris TB, Rantanen T, Visser M, Kritchevsky SB, Ferrucci L. Sarcopenic obesity: definition, cause and consequences. *Curr Opin Clin Nutr Metab Care.* 2008;11:693-700.

37. Batsis JA, Zbehlik AJ, Barre LK, Mackenzie TA, Bartels SJ. The impact of waist circumference on function and physical activity in older adults: longitudinal observational data from the osteoarthritis initiative. *Nutr J.* 2014;13:81.

38. Zoccali C, Mallamaci F, Tripepi G, et al. Adiponectin, metabolic risk factors, and cardiovascular events among patients with end-stage renal disease. *J Am Soc Nephrol.* 2002;13:134-141.

39. Zoccali C, Mallamaci F. Adiponectin and renal disease progression: another epidemiologic conundrum? *Kidney Int.* 2007;71:1195-1197.

40. Mallamaci F, Tripepi G, Zoccali C. Leptin in end stage renal disease (ESRD): a link between fat mass, bone and the cardiovascular system. *J Nephrol.* 2005;18:464-468.

41. Kittiskulnam P, Chertow GM, Carrero JJ, Delgado C, Kaysen GA, Johansen KL. Sarcopenia and its individual criteria are associated, in part, with mortality among patients on hemodialysis. *Kidney Int.* 2017;92:238-247.

42. Isoyama N, Qureshi AR, Avesani CM, et al. Comparative associations of muscle mass and muscle strength with mortality in dialysis patients. *Clin J Am Soc Nephrol.* 2014;9:1720-1728.

43. Lee DY, Wetzsteon RJ, Zemel BS, et al. Muscle torque relative to cross-sectional area and the functional muscle-bone unit in children and adolescents with chronic disease. *J Bone Miner Res.* 2015;30:575-583.

44. Shimokata H, Ando F, Yuki A, Otsuka R. Age-related changes in skeletal muscle mass among community-dwelling Japanese: a 12-year longitudinal study. *Geriatr Gerontol Int.* 2014;14(Suppl 1):85-92.

45. Stenvinkel P, Carrero JJ, von Walden F, Ikizler TA, Nader GA. Muscle wasting in end-stage renal disease promulgates premature death: established, emerging and potential novel treatment strategies. *Nephrol Dial Transplant.* 2016;31:1070-1077.

46. Sakkas GK, Kent-Braun JA, Doyle JW, Shubert T, Gordon P, Johansen KL. Effect of diabetes mellitus on muscle size and strength in patients receiving dialysis therapy. *Am J kidney Dis.* 2006;47:862-869.

47. Studenski SA, Peters KW, Alley DE, et al. The FNIH sarcopenia project: rationale, study description, conference recommendations, and final estimates. *J Gerontol A Biol Sci Med Sci.* 2014;69:547-558.

48. Kalantar-Zadeh K, Unruh M. Health related quality of life in patients with chronic kidney disease. *Int Urol Nephrol.* 2005;37:367-378.

49. Mapes DL, Lopes AA, Satayathum S, et al. Health-related quality of life as a predictor of mortality and hospitalization: the Dialysis Outcomes and Practice Patterns Study (DOPPS). *Kidney Int.* 2003;64:339-349.

50. DeOreo PB. Hemodialysis patient-assessed functional health status predicts continued survival, hospitalization, and dialysis-attendance compliance. *Am J kidney Dis.* 1997;30:204-212.