Body composition is associated with clinical outcomes in patients with non–dialysis-dependent chronic kidney disease

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An inverse relationship between body mass index (BMI) and mortality (the obesity paradox) has been found in patients with non-dialysis-dependent chronic kidney disease (CKD). However, it is unclear whether increased muscle mass or body fat confers the survival advantage. To resolve this we investigated the impact of body makeup on a composite outcome of death or cardiovascular events in a prospective cohort of 326 patients with stage 3–5 CKD not yet on dialysis. Lean mass and body fat were determined using the Body Composition Monitor, a multifrequency bioimpedance spectroscopy device, and were expressed as the lean tissue or fat tissue index, respectively. Patients were stratified as High (above median) or Low (below median) BMI, High or Low lean tissue index, or as High or Low fat tissue index. During a median follow-up of 4.6 years, there were 40 deaths and 68 cardiovascular events. In Cox proportional hazards models, a High lean tissue index, but not High BMI or High fat tissue index, predicted a lower risk of both the composite or its component outcomes (reference: below median). When patients were further stratified into four distinct body composition groups based on both the lean and fat tissue index, only the High lean/fat tissue index group had a significantly lower risk of the composite outcome (hazard ratio 0.36, 95% confidence interval 0.14–0.87; reference: Low lean/fat tissue index group). Thus, the lean tissue index can provide better risk prediction than the BMI alone in non-dialysis-dependent patients with CKD. The High lean/fat tissue index appears to be associated with best outcomes. An optimal body composition for improving the prognosis of CKD needs to be determined.

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In contrast to the general population, a higher body mass index (BMI) is associated with better survival among patients with chronic kidney disease (CKD); this is referred to as the "obesity paradox".[1–6] BMI is strongly correlated with percentage of body fat, but it does not distinguish fat from lean mass. It is thus unknown which component of body composition—fat mass or lean mass—confers survival advantage. In addition, patients with CKD are more likely to develop fluid retention,[7,8] and BMI fails to differentiate this factor. As a result, more sophisticated measures of body composition are needed to determine whether higher body fat mass, lean mass, or both are associated with longer survival among patients with CKD.[9]

The Body Composition Monitor (BCM; Fresenius Medical Care, Bad Homburg, Germany) is a novel bioimpedance spectroscopy device that has been commonly used for assessing fluid status in CKD patients undergoing dialysis.[10,11] The accuracy of body composition measurements has been validated against available gold standard reference methods.[12,13] The BCM, based on a unique 3-compartment model, allows the separation of body fat and lean mass from pathologic fluid retention (overhydration).[14] Accumulating evidence suggests that body composition, as determined by the BCM, is an important predictor of survival in chronic hemodialysis (HD) patients.[15,16] However, limited data exist concerning body fat or lean mass and clinical outcomes in patients with nondialysis-dependent CKD. Moreover, although the obesity paradox has been well documented for short-term mortality, whether this protection persists for the long term is unclear. Therefore, we examined the association between body fat and lean mass as measured by the BCM and the composite outcome of all-cause mortality or cardiovascular (CV) events during a median follow-up of 4.6 years in a prospective cohort of stage 3 to 5 CKD patients who were not yet on dialysis.

RESULTS

Patient characteristics

A total of 326 patients (224 men and 102 women; mean age 65.8 ± 13.3 years) were enrolled and included in the analysis.

All patients had moderate to severe CKD (median estimated glomerular filtration rate [eGFR] 27.2 ml/min per 1.73 m^2), with 44.8% in CKD stage 3 ($n = 146$), 32.8% in CKD stage 4 ($n = 107$), and 22.4% in CKD stage 5 (n = 73). In this population, 85.3% had hypertension ($n = 278$), 45.4% had diabetes ($n = 148$), 23.6% had cardiovascular disease (CVD) ($n = 77$), and 12.3% had peripheral artery disease ($n = 40$). The baseline demographic and clinical characteristics for the patient groups divided based on the median of lean tissue index (LTI) are presented in Table 1. Patients with LTI below median were more likely to be older and female, with higher prevalence of CVD, and had a significantly lower BMI, eGFR, and serum albumin levels but a significantly higher fat tissue index (FTI), brachial-ankle pulse wave velocity (baPWV), and inflammatory markers including interleukin-6 (IL-6) and tumor necrosis factor-α (TNF-α). The primary outcome and its components occurred in a significantly lower percentage in patients with LTI above median than in those with LTI below median. The results of the analysis according to the median of BMI and FTI are presented in Supplementary Tables S1 and S2 online.

Table 1 | Baseline characteristics of chronic kidney disease patients stratified by median of lean tissue index

Characteristics	LTI (kg/m²) <15.1 (n = 163)	LTI (kg/m²) >15.1 (n = 163)	P value
Body composition			
BMI (kg/m²)	25.0 ± 3.8	26.7 ± 4.2	0.000
FTI (kg/m²)	11.4 ± 3.9	8.1 ± 4.0	0.000
LTI (kg/m²)	12.6 ± 1.8	17.9 ± 1.9	0.000
Demographics			
Age (yr)	70.1 ± 12.4	61.5 ± 12.9	0.000
Male sex, n (%)	75 (46%)	149 (91.4%)	0.000
Smoking history, n (%)	29 (17.8%)	38 (23.3%)	0.217
DM, *n* (%)	82 (50.3%)	66 (40.5%)	0.075
CVD, *n* (%)	48 (29.4%)	29 (17.8%)	0.013
CAD, *n* (%)	24 (14.7%)	14 (8.6%)	0.084
CHF, *n* (%)	15 (9.2%)	12 (7.4%)	0.547
Stroke, *n* (%)	19 (11.7%)	6 (3.7%)	0.007
PAD, *n* (%)	33 (20.2%)	7 (4.3%)	0.000
Clinical parameters			
Systolic BP (mm Hg)	137.8 ± 18.4	137.5 ± 15.9	0.867
baPWV (m/s)	16.7 ± 3.3	15.2 ± 2.6	0.000
eGFR (ml/min per 1.73 m²)	22.9 (13.1–34.6)	31.5 (20.2–45.0)	0.000
UPCR (g/g)	0.96 (0.37–2.55)	0.75 (0.28–2.25)	0.162
Albumin (g/dl)	3.5 ± 0.4	3.7 ± 0.4	0.000
Fasting glucose (mg/dl)	121 ± 41	121 ± 43	0.877
Total cholesterol (mg/dl)	173 ± 42	176 ± 39	0.554
Triglycerides (mg/dl)	140 (92–192)	139 (93–209)	0.509
hs-CRP (mg/l)	4.5 (1.4–11.1)	3.6 (1.3–8.3)	0.188
IL-6 (pg/ml)	4.28 (2.47–8.54)	3.06 (1.76–4.83)	0.000
TNF-α (pg/ml)	7.74 (5.13–10.24)	6.17 (4.34–8.27)	0.000
Outcomes			
Primary composite outcome	62 (38.0%)	24 (14.7%)	0.000
All-cause mortality	31 (19.0%)	9 (5.5%)	0.000
Cardiovascular events	49 (30.1%)	19 (11.7%)	0.000

baPWV, brachial-ankle pulse wave velocity; BMI, body mass index; BP, blood pressure; CAD, coronary artery disease; CHF, congestive heart failure; CVD, cardiovascular disease; DM, diabetes mellitus; eGFR, estimated glomerular filtration rate; FTI, fat tissue index; hs-CRP, high-sensitivity C-reactive protein; IL-6, interleukin-6; LTI, lean tissue index; PAD, peripheral artery disease; TNF-α, tumor necrosis factor-α; UPCR, urine protein creatinine ratio.

Mutual relationships among components of body composition are presented in Figure 1. BMI was positively and strongly correlated with FTI ($r = 0.726$) (Figure 1a) and modestly correlated with LTI ($r = 0.284$) (Figure 1b), and an inverse association was found between LTI and FTI ($r = -0.432$) (Figure 1c). Correlations between body composition and other variables are shown in Table 2. BMI was positively correlated with systolic blood pressure, triglycerides, and eGFR, but negatively correlated with age. FTI was positively correlated with systolic blood pressure, triglycerides, and IL-6. LTI was positively correlated with eGFR, but negatively associated with age, urine protein creatinine ratio, and IL-6.

Outcomes

During a median follow-up of 4.6 years, 86 patients reached the primary composite outcome. There were 68 CV events, including hospitalization for myocardial ischemia ($n = 13$), fatal and nonfatal myocardial infarction ($n = 14$), congestive heart failure ($n = 29$), stroke ($n = 5$), and sudden cardiac death ($n = 7$). A total of 40 patients died. The majority of these deaths were due to non-CV causes ($n = 23$), whereas 17 patients died of CVD. The most common causes of non-CV death were infections ($n = 7$), malignancies ($n = 4$), and gastrointestinal bleeding ($n = 4$).

We explored whether higher body composition indices are associated with better outcomes among patients with CKD. To address this question, patients were stratified as high (above median) or low (below median) BMI, high or low FTI, and high or low LTI. In fully adjusted models, high LTI, but not high BMI or high FTI, predicted a lower risk of the composite outcome (hazard ratio [HR] 0.52, 95% confidence interval [CI] 0.30–0.91, $P = 0.021$), with the corresponding below-median categories as the reference (Table 3). The predictability of high LTI was unchanged after controlling for BMI (HR 0.51, 95% CI 0.29–0.89, $P = 0.018$), FTI (HR 0.54, 95% CI 0.30–0.96, $P = 0.034$), or overhydration (HR 0.53, 95% CI 0.30–0.93, $P = 0.027$). We further performed analyses in which LTI was treated as a continuous variable. Higher LTI remained associated with a lower hazard for the composite outcome (Supplementary Table S3). In a restricted cubic spline illustrating the multivariable adjusted relationship between LTI and the composite outcome (Figure 2), a reverse U-shape was observed, with a value of 9 kg/m^2 representing the highest risk and values greater than 15 kg/m^2 associated with the protective effect. Superiority of LTI over BMI in the prediction of the composite outcome was verified via likelihood ratio tests and C-statistics. We observed statistically significant improvements in the C-statistic when LTI was added to the adjusted Cox proportional hazards model 2 for the composite outcome (C-statistic 0.818, $P = 0.020$ for likelihood ratio test). However, adding BMI to the model 2 did not significantly improve model prediction