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Mid-Arm Muscle Circumference and Quality of Life and Survival in Maintenance Hemodialysis Patients

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Background and objectives: Maintenance hemodialysis (MHD) patients with larger body or fat mass have greater survival than normal to low mass. We hypothesized that mid-arm muscle circumference (MAMC), a conveniently measured surrogate of lean body mass (LBM), has stronger association with clinical outcomes than triceps skinfold (TSF), a surrogate of fat mass.

Design, settings, participants, & measurements: The associations of TSF, MAMC, and serum creatinine, another LBM surrogate, with baseline short form 36 quality-of-life scores and 5-year survival were examined in 792 MHD patients. In a randomly selected subsample of 118 subjects, LBM was measured by dual-energy x-ray absorptiometry.

Results: Dual-energy x-ray absorptiometry–assessed LBM correlated most strongly with MAMC and serum creatinine. Higher MAMC was associated with better short form 36 mental health scale and lower death hazard ratios (HRs) after adjustment for case-mix, malnutrition-inflammation-cachexia syndrome, and inflammatory markers. Adjusted death HRs were 1.00, 0.86, 0.69, and 0.63 for the first to fourth MAMC quartiles, respectively. Higher serum creatinine and TSF were also associated with lower death HRs, but these associations were mitigated after multivariate adjustments. Using median values of TSF and MAMC to dichotomize, combined high MAMC with either high or low TSF (compared with low MAMC/TSF) exhibited the greatest survival, *i.e.*, death HRs of 0.52 and 0.59, respectively.

Conclusions: Higher MAMC is a surrogate of larger LBM and an independent predictor of better mental health and greater survival in MHD patients. Sarcopenia-correcting interventions to improve clinical outcomes in this patient population warrant controlled trials.

I ndividuals with advanced chronic kidney disease (CKD), who undergo chronic dialysis treatment, have a high mortality rate (1,2). Although some studies have evaluated the association of nutrition with mortality (3,4), others have focused on body mass index (BMI) and suggested that dialysis patients with higher BMI enjoy a survival advantage in even such high BMI ranges that are ordinarily considered harmful for the general population (5–11). BMI, however, is an imperfect measure of adiposity (6,8,10) and does not differentiate lean from fat mass (12). Lean body mass (LBM) can serve as an index of muscle mass and somatic protein, whereas fat mass more directly reflects energy storage. Higher fat mass has been associated with inflammation and adverse outcomes in the general population (13), whereas higher muscle mass seems to be as-

sociated with better clinical outcomes (14). If CKD patients are similar, interventions to improve sarcopenia in CKD patients may improve survival.

In the general population, BMI is more strongly correlated with body fat mass and less with LBM when measured by such methods as dual-energy x-ray absorptiometry (DEXA) (15,16). However, in maintenance hemodialysis (MHD) patients, BMI may be equally correlated with both fat and lean mass (17). Other measures of body size or composition may better represent LBM or muscle mass in MHD patients. A large epidemiologic study used urinary creatinine before the start of dialysis treatment as a muscle mass surrogate and suggested that the survival advantage of obese MHD patients is mostly because of higher LBM (11). To our knowledge, only a few studies have compared outcome predictability of surrogates of body mass components in MHD patients.

In this study, we first examined the correlations of several anthropometric and biochemical measures with the DEXA-measured LBM as the reference standard in a small group of MHD patients to determine which serves as a better surrogate for LBM. In a larger cohort, we subsequently studied the outcome predictability of two surrogates of LBM, mid-arm muscle

circumference (MAMC) and serum creatinine, and compared them with triceps skinfold (TSF) as a surrogate of fat mass after controlling for demographics, nutritional status, and inflammation. We also examined the association of MAMC with health-related quality of life (QoL) at the start of the cohort. We hypothesized that MAMC is a reliable correlate of LBM and a predictor of better QoL and greater survival in MHD patients.

Materials and Methods
Patient Population

We studied MHD patients who participated in the National Institutes of Health–sponsored Nutritional and Inflammatory Evaluation in Dialysis (NIED) Study (18–22). The original patient cohort was derived from a pool of approximately 1300 MHD outpatients in eight DaVita dialysis facilities in the South Bay Los Angeles area (see NIED Study website at www.NIEDStudy.org for more details). Inclusion criteria were outpatients who had been undergoing MHD for at least 8 weeks, who were 18 years of age or older, and who signed the Institutional Review Board–approved consent form. From October 1, 2001, through December 31, 2006, 893 MHD patients signed the informed consent form, and 792 of them underwent the periodic evaluations of the NIED Study. A modified version of the Charlson comorbidity index, *i.e.*, without the age and kidney disease components, was used to assess the severity of comorbidities (23,24). The 792 MHD patients were followed for up to 63 months. A total of 118 of these patients (of approximately 200 randomly invited subjects) also agreed attend a substudy to undergo additional body compositions tests including DEXA at the Harbor-UCLA General Clinical Research Center. In each patient, body composition assessments were performed on the day after a routine hemodialysis treatment. All participants refrained from eating and drinking for at least 4 hours before the tests.

Anthropometric Measures

Body weight assessment and anthropometric measurements were performed while patients underwent hemodialysis treatment or within 5 to 20 minutes thereafter. Biceps and triceps skinfold thicknesses were measured with a conventional skinfold caliper using standard techniques (18,25). The mid-arm circumference was measured with a plastic tape. The average value of the triplicate measurements of the non–dialysis vascular access arm was obtained. MAMC was calculated as follows (26):

$$\text{MAMC (cm)} = \text{mid-arm circumference (cm)} - 3.142 \times \text{TSF (cm)}$$

Dual Energy X-Ray Absorptiometry

As the reference test of body composition in the substudy of 118 subjects, DEXA was performed with a Hologic Series Delphi-A Fan Beam x-ray Bone Densitometer with software version 12.4 (Hologic, Bedford, MA), with participants wearing a hospital gown with no metal snaps and all artifacts removed (27–29). Participants were lying supine on the table, centered in the scan field with arms at their sides, palms down, and thighs separated. Scans were analyzed using the whole body fan beam method to determine LBM, fat mass, bone mineral content, and total body fluid as described elsewhere (28,29).

Near Infrared Interactance

To estimate the percentage of body fat and fat-free body mass at the start of the main cohort, near infrared (NIR) interactance technology was used at the time of anthropometric measurements. A commercial NIR interactance sensor with a coefficient of variation of 0.5% for total body fat measurements (portable 6100; Futrex, Gaithersburg, MD; www.

futrex.com) was used. NIR measurements of body fat have been shown to be highly correlated with other body fat measures in MHD patients (20,29).

Laboratory Tests

Predialysis blood samples and postdialysis serum urea nitrogen were obtained on a mid-week day, which coincided chronologically with the drawing of quarterly blood tests in the DaVita clinics. The single-pool Kt/V was used to represent the weekly dialysis dose. Except as indicated below, all laboratory measurements were performed by DaVita Laboratories (Deland, FL) using automated methods. In this study, 3-month averaged values of routine laboratory measures were used.

Additionally, serum high sensitivity C-reactive protein (CRP) was measured by a turbidimetric immunoassay (21,22). IL-6 and TNF-α were measured with immunoassay (30,31). CRP and the cytokines were measured in the General Clinical Research Center Laboratories. Plasma total homocysteine concentrations were determined by HPLC in the Harbor-UCLA Clinical Laboratories. Serum transthyretin (prealbumin) was measured using immunoprecipitin analysis (32).

Statistical Analyses

Pearson's correlation coefficient (r) was used for analyses of linear associations. Multivariate regression analyses were performed to obtain adjusted P values controlled for case-mix and other covariates. A restricted cubic splines graph was used as an exploratory data analysis strategy to show systematic relations between MAMC and mortality and to examine the linearity assumptions (33). Thereafter, to calculate the relative risks of death, hazard ratios (HRs) were obtained using Cox proportional hazard models after controlling for relevant covariates. Kaplan-Meier analyses were used to assess the differences in surviving proportions between quartiles of MAMC.

We performed incremental levels of multivariate adjustment: (*1*) case-mix variables included age, gender, race/ethnicity, diabetes, dialysis vintage, insurance (Medicare *versus* others), marital status, modified Charlson comorbidity score, dialysis dose (Kt/V), and residual renal function; (*2*) malnutrition inflammation complex syndrome (MICS) variables included serum phosphorus, albumin, creatinine, bicarbonate, calcium, ferritin, blood hemoglobin, white blood cell count, and lymphocyte percent; prescribed erythropoietin; normalized protein nitrogen appearance; and BMI; and (*3*) additional adjustment for three inflammatory markers (CRP, IL-6, and TNFα). Fiducial limits are given as means $\pm$ SD or median and interquartile range, when appropriate; hazard ratios include 95% confidence interval levels. Descriptive and multivariate statistics were carried out with Stata statistical software version 10.0 (Stata Corporation, College Station, TX).

Results
LBM Measurement in the Validation Substudy

In the substudy, 118 participating MHD patients were 56.0 $\pm$ 12.4 (SE) years old and included 60% men, 41% African Americans, 36% Hispanics, and 51% diabetics. Postdialysis average dry weight was 74.1 $\pm$ 18.1 kg (minimum: 36.9 kg; maximum: 131.0 kg), and averaged Kt/V (single pool) was 1.70 $\pm$ 0.27. Calculated LBM and total body fat mass by DEXA were 49.9 $\pm$ 10.7 (minimum: 30.2 kg, maximum: 90.8 kg) and 21.8 $\pm$ 11.1 kg (minimum: 4.8 kg, maximum: 53.0 kg), respectively. Table 1 shows the correlation coefficients of DEXA-measured LBM with MAMC, TSF, and serum levels of creatinine, albumin, and prealbumin. After multivariate adjustments, MAMC ($r = 0.54$, $P < 0.001$) and serum creatinine ($r = 0.36$, $P < 0.01$) had the

Table 1. Pearson's correlation coefficients between LBM, measured by DEXA, and its possible surrogates in 118 randomly selected MHD patients

Variable	Model 1[a]	Model 2[b]	Model 3[c]	Model 4[d]
Mid-arm muscle circumference	**0.72**[e]	**0.58**[e]	**0.65**[e]	**0.54**[e]
Serum creatinine	**0.40**[e]	**0.19**[f]	**0.25**[g]	**0.36**[g]
Serum albumin	**0.24**[g]	−0.08	−0.08	−0.10
Serum prealbumin	0.02	0.05	−0.14	−0.12
Triceps skinfold	0.02	−0.03	−0.11	−0.12

Bold = statistically significant correlation coefficients >0.10.
[a]Model 1 includes each surrogate separately as dependent variable and LBM as independent variable in the model without adjustment.
[b]Model 2 includes each surrogate separately plus case-mix variables include age, gender, race/ethnicity, diabetes, dialysis vintage, insurance (medicare), marital status, modified Charlson comorbidity score, dialysis dose (Kt/V), and kidney residual urine in the model.
[c]Model 3 includes all five surrogates in the model.
[d]Model 4 includes all five surrogates plus case mix variables in the model.
[e]$P < 0.001$.
[f]$P = 0.05$ to 0.01.
[g]$P = 0.01$ to 0.001.

strongest correlations with DEXA-measured LBM. We also validated TSF against DEXA-measured total body fat mass. The correlation coefficients before and after adjustment for case-mix were 0.74 ($P < 0.001$) and 0.76 ($P < 0.001$), respectively.

Characteristics of the Main Cohort Subjects

Baseline demographic, clinical, and laboratory values in 792 participating MHD patients of the main cohort are shown in Table 2. Patient mean age was 53 ± 15 (SE) years; 47% were women ($n = 372$), 51% were Hispanic ($n = 404$), and 31% were African American ($n = 245$). The median (and interquartile range) of dialysis vintage was 19 (7 to 42) months. We categorized participants into population-based quartiles of MAMC as a surrogate of LBM, which resulted in 196 to 199 subjects in each quartile. Table 2 also shows the relevant demographic, clinical, and laboratory measures within each MAMC quartile at baseline. In the higher MAMC quartiles, the proportions of women and Hispanics were lower and African Americans were higher. There were no significant differences in the prevalence of diabetes mellitus and other comorbidities according to the modified Charlson comorbidity score. The groups of patients with higher MAMC had higher BMI, biceps and triceps skinfold thicknesses, and NIR-measured total body fat.

Health-Related QoL

Table 3 shows the baseline short form 36 scores among the 792 MHD patients who answered this QoL questionnaire (34). The scores are grouped according to the selected MAMC quartiles presented in Table 2. Some trends toward better scores, in particular better reported mental health scale, in the highest MAMC groups were observed ($P < 0.01$).

Linear Associations

Examining the fully adjusted correlation coefficients of relevant clinical, nutritional, and inflammatory measures with MAMC at baseline in the 792 MHD patients, the MAMC was correlated with BMI ($r = +0.58$), triceps skinfold thicknesses ($r = -0.27$), NIR-measured lean body mass ($r = +0.33$), and serum creatinine concentration ($r = +0.148$; all $P < 0.01$). Figure 1 shows the unadjusted associations between MAMC and some relevant variables. The scatter plots exhibit widespread correlation especially for serum creatinine.

Survival Predictability of Body Composition Surrogates

Over the 5 years of the cohort of 792 MHD patients, 222 (28%) patients died. Median and interquartile range for follow-up time were 730 and 927 days, respectively. Figure 2 shows the cubic splines graph illustrating the multivariate-adjusted association between baseline MAMC and mortality rate. Decreased risk of death was observed in MHD patients with higher MAMC (Cox model, $P < 0.01$). Figure 3 shows the Kaplan-Meier proportion of surviving patients across the four MAMC quartiles, indicating that the two lowest MAMC quartiles were incrementally associated with the highest mortality ($P < 0.01$). The death hazard ratios are shown in Table 4. The higher quartiles of MAMC tended to correlate with lower death hazard ratio in all adjusted models examined (P for trend < 0.05). A similar, albeit somewhat weaker, trend was also noticed for the survival predictability of serum creatinine, which is another surrogate of LBM (Table 4). As shown in Table 4, the highest quartile of TSF, a surrogate of fat mass, was associated with decreased death hazard ratio (95% confidence interval) in the case-mix–adjusted model (0.69; 0.45 to 1.07). This relationship was attenuated after additional multivariate adjustment for MICS and inflammatory markers.

The highest *versus* lowest MAMC quartile tended to correlate with the greatest survival across almost all demographic, clinical, and laboratory subgroups (data not shown). The BMI was the only variable with a relatively strong effect modification (P for interaction of BMI and MAMC was <0.001); the death hazard ratio (95% confidence interval) of the highest *versus*

Table 2. Baseline demographic, clinical, and laboratory values in 792 MHD patients at the start of the 5-year cohort study according to the quartiles of their mid-arm muscle circumference

Variables	All Patients (n = 792)	Mid-Arm Muscle Circumference Quartiles				P for Trend[a]
		Quartile 1 (n = 199)	Quartile 2 (n = 198)	Quartile 3 (n = 199)	Quartile 4 (n = 196)	
Demographic						
Age, years	53 ± 15	52 ± 15	55 ± 15	54 ± 15	52 ± 14	0.47
Women, %	47	66	46	33	42	<0.01
Race: % African-American	31	22	27	28	46	<0.01
Ethnicity: % Hispanic	51	61	56	55	34	<0.01
Primary insurance: Medicare%	52	47	52	52	56	0.14
Diabetes mellitus, %	53	53	57	46	57	0.45
Marital status: % married	47	47	49	49	43	0.50
Charlson comorbidity score	1.87 ± 1.61	1.74 ± 1.65	1.91 ± 1.55	1.78 ± 1.60	2.02 ± 1.66	0.20
Mortality, %	28	33	28	25	28	0.06
Body composition						
Body mass index	26.5 ± 6.1	22.4 ± 3.6	25.2 ± 4.5	26.3 ± 4.6	31.9 ± 7.0	<0.01
Triceps skinfold, mm	17.5 ± 9.8	16.2 ± 8.0	17.5 ± 9.3	16.1 ± 10.2	20.1 ± 11.1	0.02
Biceps skinfold, mm	9.8 ± 7.7	7.9 ± 8.7	9.5 ± 6.8	9.0 ± 7.4	13.0 ± 7.1	<0.01
MAMC, cm	25.8 ± 4.41	20.7 ± 2.1	24.2 ± 0.7	26.9 ± 0.9	31.6 ± 3.0	<0.01
NIR measured body fat, %	26.5 ± 10.7	24.0 ± 9.0	26.0 ± 10.1	25.1 ± 10.8	31.1 ± 11.5	<0.01
Hemodialysis treatment						
Dialysis vintage, months[b]	19 (7 to 42)	17 (6 to 44)	18 (6 to 38)	20 (9 to 44)	22 (9 to 48)	0.23
Dialysis dose, Kt/V single pool	1.61 ± 0.31	1.74 ± 0.33	1.66 ± 0.32	1.57 ± 0.25	1.49 ± 0.27	<0.01
nPNA, kg/day	1.07 ± 0.24	1.11 ± 0.26	1.11 ± 0.24	1.04 ± 0.19	1.02 ± 0.23	<0.01
EPO dose, ×1000 U/wk[b]	11.2 (6.4 to 18.2)	11.4 (7.0 to 19.9)	10.7 (6.7 to 16.7)	10.3 (5.5 to 17.0)	12.4 (6.2 to 20.5)	0.91
Biochemical measurements						
Serum albumin, mg/dl	3.9 ± 0.4	3.9 ± 0.4	3.9 ± 0.4	3.9 ± 0.3	3.9 ± 0.4	0.55
Prealbumin, mg/dl	28.4 ± 9.5	26.9 ± 9.4	28.4 ± 9.4	29.6 ± 9.6	29.0 ± 9.6	0.01
creatinine, mg/dl	10.2 ± 3.2	9.3 ± 2.8	10.0 ± 3.0	10.6 ± 3.4	10.9 ± 3.5	<0.01
Calcium, mg/dl	9.3 ± 0.7	9.4 ± 0.7	9.3 ± 0.7	9.3 ± 0.6	9.4 ± 0.7	0.80
iron, mg/dl	67 ± 26	67 ± 28	69 ± 27	66 ± 24	64 ± 26	0.17
Phosphorus, mg/dl	5.8 ± 1.5	5.6 ± 1.4	5.7 ± 1.4	5.8 ± 1.5	6.0 ± 1.4	<0.01
Ferritin, ng/ml[b]	481 (231 to 809)	423 (115 to 618)	453 (231 to 755)	505 (254 to 834)	548 (264 to 829)	<0.01
Bicarbonate, mg/dl	22.3 ± 2.8	22.3 ± 3.1	22.3 ± 2.9	22.3 ± 2.7	22.2 ± 2.7	0.93
Homocysteine, μmol/L	23 ± 10	22 ± 8	24 ± 11	23 ± 8	25 ± 12	0.02
CRP, mg/l[b]	3.7 (1.5 to 7.4)	2.4 (1.2 to 5.4)	3.6 (1.2 to 7.7)	3.6 (1.6 to 7.6)	4.9 (2.2 to 8.6)	<0.01
IL-6, pg/ml[b]	7.0 (4.0 to 13.3)	6.8 (3.8 to 13.5)	6.8 (3.8 to 15.8)	6.2 (4.0 to 11.2)	7.7 (4.3 to 13.2)	0.91
TNF-α,pg/ml[b]	5.6 (3.8 to 8.8)	5.8 (3.7 to 9.1)	5.6 (3.7 to 9.0)	5.7 (3.6 to 8.9)	5.5 (4.1 to 8.6)	0.88
Blood hemoglobin, g/dl	12.1 ± 0.9	12.1 ± 1.0	12.1 ± 1.0	12.1 ± 0.9	12.0 ± 0.9	0.52
White blood count, ×1000 cells/μl	7.2 ± 2.3	7.0 ± 2.1	7.2 ± 2.7	7.1 ± 2.1	7.5 ± 2.3	0.07
Lymph., % of white blood count	23 ± 8	23 ± 8	23 ± 7	24 ± 8	22 ± 8	0.41

All values are presented as mean ± SD or percentages except for variables that are not normally distributed (vintage, erythropoietin dose, ferritin, CRP, IL6, and TNF-α), in which we used interquartile range (IQR). Kt/V = dialysis dose.
[a]P values for dialysis dose (vintage), ferritin, erythropoietin dose, CRP, IL-6, and TNF-α are based on the logarithmic values of these measures.
[b]These values are medians with the 25th to 75th percentiles in parentheses.

Table 3. Baseline SF36[a] health-related quality of life scores[b] across quartiles of mid-arm muscle circumference in 792 MHD patients

Variables	Mid-arm Muscle Circumference Quartiles				
	Quartile 1 (n = 199)	Quartile 2 (n = 198)	Quartile 3 (n = 199)	Quartile 4 (n = 196)	P for Trend
SF-36 mental health dimension	50 ± 20	55 ± 22	54 ± 20	53 ± 20	0.17
SF-36 physical health dimension	44 ± 21	47 ± 23	47 ± 21	46 ± 22	0.54
SF-36 scales					
Body pain	56 ± 29	61 ± 29	60 ± 29	56 ± 28	0.99
General health	44 ± 24	47 ± 21	44 ± 21	44 ± 21	0.97
Mental health	62 ± 21	67 ± 21	67 ± 19	69 ± 20	<0.01
Physical function	44 ± 28	46 ± 31	48 ± 29	47 ± 30	0.36
Role emotional	42 ± 43	52 ± 44	48 ± 43	47 ± 42	0.42
Role physical	31 ± 39	37 ± 41	36 ± 42	36 ± 42	0.19
Functionality	57 ± 27	62 ± 29	63 ± 28	63 ± 27	0.08
Vitality	48 ± 21	50 ± 24	49 ± 21	47 ± 22	0.52

[a]Short form quality of life score with 36 questions.
[b]Of all the 792 patients under study, data of quality of life were available for 690 patients.

lowest MAMC in those with BMI <25 kg/m^2 was 0.14 (0.04 to 0.71), whereas for BMI ≥25 kg/m^2, it was not significant, *i.e.,* 0.99 (0.70 to 1.26).

Survival Predictability of Combinations of MAMC and TSF

We dichotomized the MAMC and TSF using their median values (high *versus* low) and created four (2 × 2) combined groups. As shown in Table 5, using the concordant low MAMC/low TSF as the reference group, combined high MAMC with either high or low TSF exhibited the greatest survival, in that the death hazard ratios (and 95% confidence interval) for both high and combined high MAMC and low TSF were 0.52 (0.36 to 0.77) and 0.59 (0.39 to 0.88), respectively.

Discussion

We examined the associations of DEXA-measured LBM with several anthropometric and biochemical measures in 118 MHD patients and found that MAMC and, to a lesser extent serum creatinine, correlated with LBM. The TSF correlated with DEXA-measured fat mass. We examined the larger cohort of 792 MHD patients and found that higher MAMC tended to be associated with better short form 36 measured mental health score at baseline. It was also associated with greater 5-year survival even after adjustment for demographics, comorbid conditions, and measures of nutritional status and inflammation including BMI and serum levels of albumin, prealbumin, CRP, and inflammatory cytokines. The association was particularly strong among low BMI (<25 kg/m^2) patients. Serum creatinine concentration showed a similar, although somewhat less consistent, survival association, especially after adjustment for nutritional and inflammatory markers. Higher TSF, a surrogate of body fat, also exhibited a trend toward greater survival, but it was a weaker survival predictor than MAMC or serum creatinine concentration. Combined high MAMC with either low (compared with both low) exhibited the

greatest survival. These findings suggest that quality and quantity of body compositions might have a bearing on MHD patient survival.

In MHD patients, lower BMI is consistently a predictor of higher mortality, whereas higher BMI even in the ranges of obesity and morbid obesity seems to confer survival benefits (5–6,35–39). Kopple *et al.* (7) found similar seemingly counterintuitive associations using body weight adjusted for height, as did several other studies (10,36,40–42). The only exceptions to this so-called obesity paradox (43) or reverse epidemiology (44) seem to be Asian-American MHD patients (45), in whom obesity does not consistently seem protective. Although BMI is most frequently used in nutritional assessment surveys as a surrogate of body size and nutritional status, it does not precisely reflect body composition, nor does it differentiate between muscle and fat mass (12). MAMC, which was a better surrogate of DEXA-measured LBM in our validation substudy, may reflect both muscle mass and caloric and protein adequacy (46). Hence, it can serve as a general index of appropriate nutritional status, whereas its reduction, known as sarcopenia (47), may be a sign of malnutrition or wasting (46).

We also found an association between higher TSF, a surrogate of body fat, and greater survival in MHD patients. In a previous 30-month longitudinal prospective study of 535 MHD patients, low total body fat percentage was an independent risk factor for poor survival, although the more obese patients had a higher prevalence of diabetes mellitus (20). More importantly, a decline in body fat over a 6-month period was associated with twice the death risk of those patients who had an increase in body fat (20). Thus, in contrast to the general population, fat mass seems to be protective in dialysis patients. However, it is not clear whether fat confers better survival benefits compared with muscle mass. In this study, we found that the association of high MAMC with greater survival is seen with both low and
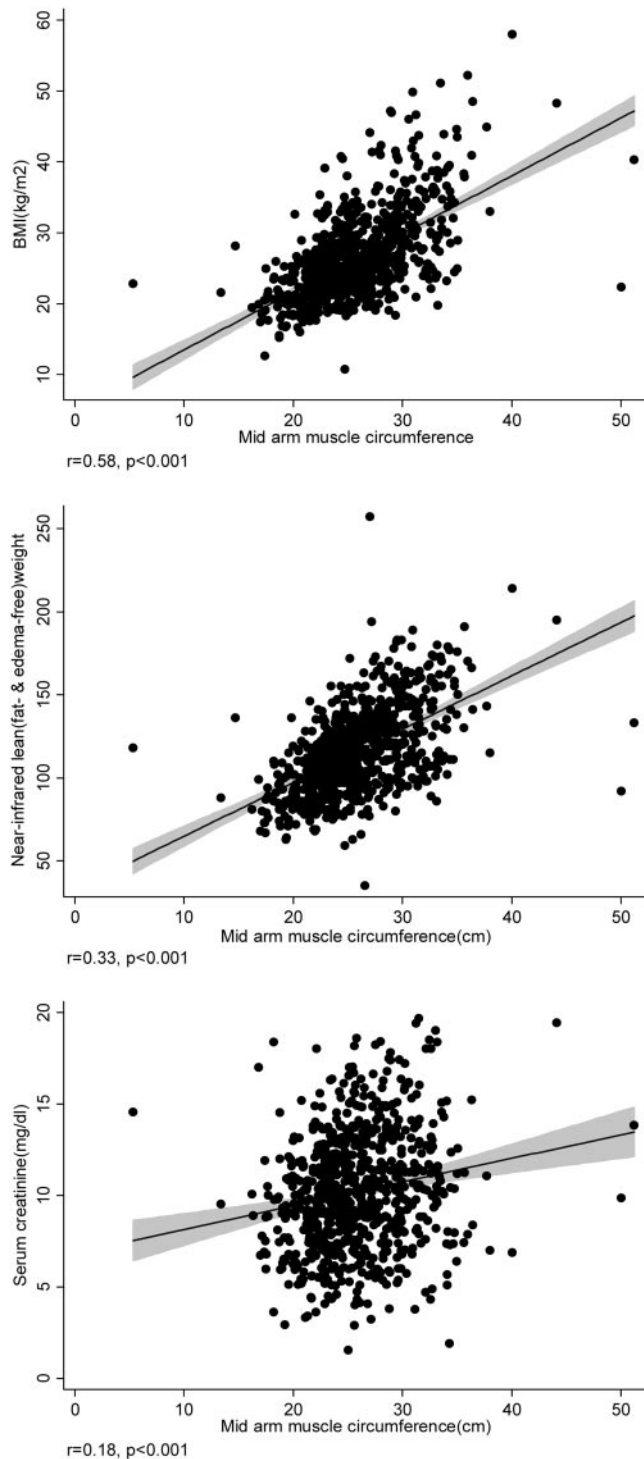
r=0.58, p<0.001

r=0.33, p<0.001

r=0.18, p<0.001

Figure 1. Scatter plots, regression line, and 95% CI, reflecting the correlations between MAMC with BMI (top), NIR lean weight (middle), and serum creatinine concentration (bottom) in 792 MHD patients. Shaded areas reflect the 95% CIs.
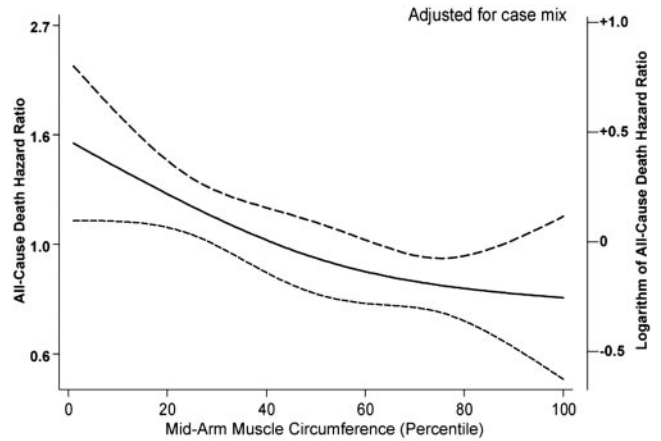

Figure 2. Spline model with 95% CIs reflecting adjusted mortality predictability of MAMC, expressed as a fraction of the average MAMC in the 792 MHD patients (from October 2001 to January 2007). Case-mix variables include age, gender, race/ethnicity, diabetes, dialysis vintage, insurance (Medicare), marital status, modified Charlson comorbidity score, dialysis dose (Kt/V), and kidney residual urine.
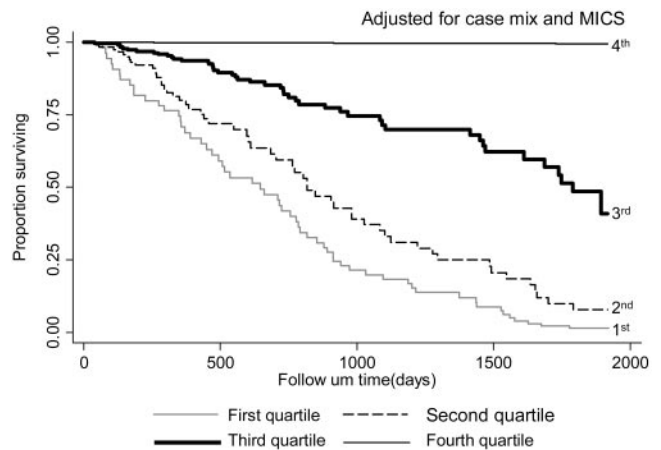

Figure 3. Kaplan-Meier proportion of surviving MHD patients after 5 years of observation according to the quartiles of MAMC in 792 MHD patients (adjusted for case-mix and MICS). Case-mix variables: age, gender, race/ethnicity, diabetes mellitus, dialysis vintage, primary insurance, marital status, Charlson comorbidity score, dialysis dose (Kt/V), and kidney residual urine. MICS variables included serum phosphorus, albumin, creatinine, bicarbonate, calcium, ferritin, blood hemoglobin, white blood count, and lymphocyte percent; prescribed erythropoietin; normalized protein catabolic rate (nPCR), also known as normalized protein nitrogen appearance; and BMI.

high TSF, as shown in Table 5. Hence, muscle mass may possibly be more important than peripheral body fat mass in predicting survival, consistent with the hypothesis by Beddhu *et al.* (11) that "if fat is good, muscle is better."

A previous study indicated a stronger and more significant

correlation between BMI and fat mass than between BMI and LBM in CKD patients at stages 3 to 5 (48). Hence, many previous studies assumed that the protective effect of BMI on mortality in MHD patients is related to fat mass and not LBM or muscle (20,48,49). We found a trend between higher peripheral fat mass, reflected by higher TSF and lower mortality, whereas we found a relatively consistent and graded association be-

Table 4. Hazard ratios (HR) and 95% confidence interval (CI) of 5-year mortality according to quartiles of mid-arm muscle circumference, serum creatinine, and triceps skinfold in 792 MHD patients (October 2001 to January 2007)

Variables	Quartile 1	Quartile 2	Quartile 3	Quartile 4	P for Trend
Mid-arm muscle circumference quartiles					
n	(n = 199)	(n = 198)	(n = 199)	(n = 196)	
Unadjusted	1.00	0.86 (0.61, 1.23) [P = 0.42]	0.68 (0.47, 0.99) [P = 0.04]	0.79 (0.55, 1.14) [P = 0.21]	0.10
Case-mix[a] adjusted	1.00	0.70 (0.49, 1.02) [P = 0.06]	0.59 (0.40, 0.87) [P < 0.01]	0.55 (0.37, 0.82) [P < 0.01]	<0.01
Case-mix MICS[b] adjusted	1.00	0.92 (0.62, 1.36) [P = 0.68]	0.73 (0.47, 1.13) [P = 0.16]	0.63 (0.37, 1.05) [P = 0.07]	0.04
Case-mix + MICS + inflammation[c] adjusted	1.00	0.86 (0.58, 1.29) [P = 0.48]	0.69 (0.45, 1.08) [P = 0.10]	0.63 (0.38, 1.06) [P = 0.08]	0.04
Serum creatinine quartiles					
n	(n = 186)	(n = 182)	(n = 184)	(n = 184)	
Unadjusted	1.00	1.13 (0.80, 1.59) [P = 0.46]	0.71 (0.49, 1.02) [P = 0.07]	0.36 (0.23, 0.56) [P < 0.01]	<0.01
Case-mix[a] adjusted	1.00	1.16 (0.82, 1.67) [P = 0.39]	0.74 (0.49, 1.12) [P = 0.15]	0.53 (0.31, 0.92) [P = 0.02]	<0.01
Case-mix MICS[b] adjusted	1.00	1.08 (0.73, 1.61) [P = 0.67]	0.80 (0.51, 1.26) [P = 0.33]	0.58 (0.32, 1.06) [P = 0.07]	0.04
Case-mix + MICS + inflammation[c] adjusted	1.00	1.10 (0.74, 1.65) [P = 0.61]	0.81 (0.51, 1.29) [P = 0.38]	0.61 (0.33, 1.12) [P = 0.11]	0.07
Triceps skinfold quartiles					
n	(n = 211)	(n = 188)	(n = 195)	(n = 198)	
Unadjusted	1.00	1.24 (0.86, 1.79) [P = 0.24]	0.86 (0.59, 1.28) [P = 0.48]	1.05 (0.73, 1.53) [P = 0.76]	0.77
Case-mix[a] adjusted	1.00	0.91 (0.62, 1.35) [P = 0.66]	0.64 (0.42, 0.97) [P = 0.03]	0.69 (0.45, 1.07) [P = 0.10]	0.03
Case-mix MICS[b] adjusted	1.00	1.03 (0.66, 1.59) [P = 0.82]	0.70 (0.43, 1.16) [P = 0.91]	0.78 (0.44, 1.39) [P = 0.55]	0.20
Case-mix + MICS + inflammation[c] adjusted	1.00	0.94 (0.60, 1.47) [P = 0.79]	0.66 (0.39, 1.09) [P = 0.10]	0.73 (0.41, 1.30) [P = 0.29]	0.15

[a]Case-mix variables include age, gender, race/ethnicity, diabetes, dialysis vintage, insurance (Medicare), marital status, modified Charlson comorbidity score, dialysis dose (Kt/V), and kidney residual urine.
[b]MICS variables include albumin, log erythropoietin dose, creatinine, hemoglobin, serum phosphorus, normalized protein catabolic rate (nPCR), bicarbonate, calcium, log ferritin, white blood count, lymphocyte percent, and body mass index.
[c]Inflammatory markers include C-reactive protein, IL-6, TNF-α.

Table 5. Hazard ratios and 95% confidence interval of 5-year mortality across four groups (2 × 2) of high *versus* low MAMC or TSF in 792 MHD patients (October 2001 to January 2007)

	Low MAMC and Low TSF	Low MAMC and High TSF	High MAMC and Low TSF	High MAMC and High TSF
Number of subjects	194	202	205	191
Number of deaths	70	51	46	55
Crude mortality	36%	25%	22%	28%
Unadjusted death HR	1	0.66 (0.46 to 0.95)	0.60 (0.41 to 0.87)	0.71 (0.49 to 1.00)
P value	n/a	0.02	<0.01	0.05
case-mix adj. death HR	1	0.61 (0.41 to 0.89)	0.59 (0.39 to 0.88)	0.52 (0.36 to 0.77)
P value	n/a	0.01	<0.001	<0.001

tween higher muscle mass, reflected by MAMC and greater survival, as shown in Figure 2. In agreement with these findings, Marckmann (50) scored MHD patients according to relative body weight, serum transferrin, MAMC, and TSF and found that dialysis patients with a poor nutritional status had increased mortality. Beddhu *et al.* (11) found that the protective effect of BMI in the MHD population is conferred to those patients with elevated muscle mass, reflected by higher urinary creatinine before the initiation of dialysis therapy. Araujo *et al.* (51) found that higher MAMC is predictive of a lower death hazard ratio in MHD patients. Honda *et al.* (52) showed that protein energy wasting, even in overweight dialysis patients, was associated with higher mortality. Finally, Huang *et al.* (53) recently examined the Hemodialysis Study data and found that lower MAMC and low peripheral fat mass were associated with higher all-cause mortality in MHD patients. However, inflammatory cytokines were not measured and hence were not adjusted for in the Hemodialysis Study analyses, nor was the MAMC validated against DEXA. To our knowledge, our study is the only large cohort study with such comprehensive measures of nutritional status and inflammation indicating survival benefits of muscle mass, which is also associated with greater QoL.

There are several potential reasons why muscle mass may be associated with survival (53). First, lower muscle mass may reflect poor nutritional status (54). In our study, MHD patients with lower MAMC exhibited lower values of nutritional markers such as BMI, biceps and triceps skinfolds, total fat mass, and serum concentrations of prealbumin and creatinine (Table 1). Second, low muscle mass may reflect higher levels of or unopposed inflammation, because muscle may confer anti-inflammatory effects in MHD patients (52). However, in our study, low muscle mass was not correlated with lower inflammatory markers (Table 1), and the association of MAMC and mortality was largely independent of MICS including its inflammatory components, whereas the survival advantage of higher peripheral fat or TSF was mitigated after adjustment for MICS. Third, uremic toxins may distribute in the muscle mass compartment (53). Higher muscle mass is correlated with higher non–edema-related body water (55), which can dilute the circulating toxins and cytokines, so that patients with lower muscle mass may have a higher concentration of uremic toxins. Fourth, an in-

creased muscle mass is associated with physical activity and exercise training (56). Exercise can improve arterial stiffness in MHD patients (57), and arterial stiffness is an independent predictor of cardiovascular disease and death in MHD patients (58,59). Higher muscle mass associated with exercise may improve insulin resistance, which is another independent predictor of mortality in dialysis patients (60).

Among the potential limitations of our study is the selection bias during enrollment, but without this bias our associations may have actually been even greater given the relatively low mortality rate of our cohort. Detailed information about hemodialysis treatment and technique such as dialysis membrane did not exist. Skinfold measurements in our study quantified peripheral rather than central fat tissue. Central or visceral fat may be a risk factor for cardiovascular disease and death in both the general population (61) and in CKD patients (62,63), and both human and animal data suggest that there may be fat redistribution in kidney disease (64,65). The methods used for calculation of fat *versus* muscle mass proportions (66) have not been validated in MHD patients. Finally, as in any observational study, we cannot account for unmeasured or residual confounding. There are several strengths to this study including the long follow-up period (up to 63 months), comprehensive laboratory tests, including inflammatory cytokines, concomitant assessments of body composition, and use of DEXA as the reference method to find the best surrogate of LBM, especially because anthropometric measurements may be more closely correlated with DEXA than bioelectrical impedance in dialysis patients (29,67–69). Finally, participants were selected randomly without having prior knowledge of their inflammatory status.

Conclusions

In MHD patients, higher MAMC is a surrogate of larger LBM and a potential predictor of better mental health scale of QoL and greater survival. The survival advantage of MAMC seems more pronounced in lower BMI ranges and may be independent of TSF, which is a surrogate of peripheral fat mass and therefore a predictor of better survival. Larger prospective studies with detailed body composition analyses are needed to verify our findings, and sarcopenia-improving intervention in CKD patients should be evaluated.

Disclosures

None.

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