Associations of Body Size and Body Composition with Functional Ability and Quality of Life in Hemodialysis Patients

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Abstract

**Background and objectives** Modifiable factors, such as body size and body composition, could influence physical function and quality of life in patients undergoing maintenance hemodialysis (MHD).

**Design, setting, participants, & measurements** From January 2008 to June 2012, in body mass index (BMI), waist circumference (WC), and magnetic resonance imaging measurements of midthigh muscle area (MTMA) and intra-abdominal fat area (IAFA) were obtained at baseline in 105 MHD patients. Six-minute walk distances and physical and mental component scores (PCS and MCS) from the Short Form-12 questionnaire were obtained at baseline and 6 and 12 months. Separate mixed-effects regression models were used to relate baseline BMI, WC, and IAFA with baseline and the average of follow-up 6-minute walk distances and PCS and MCS after adjustment for baseline covariates and MTMA.

**Results** For baseline covariates and baseline MTMA, each SD increase in baseline BMI was inversely associated with baseline (−31.5 m; 95% confidence interval [95% CI], −53.0 to −10.0 m) and follow-up (−36.9 m; 95% CI, −54.6 to −19.2 m) 6-minute walk distances. Results were similar for WC and IAFA. In each of these models, each SD increase in MTMA had a strong positive association with 6-minute walk distance. Adiposity measures were not associated with baseline or follow-up PCS and MCS. After adjustment for baseline BMI, each SD increase in baseline MTMA was associated with higher baseline PCS score (3.78; 95% CI, 0.73 to 6.82) and MCS (3.75; 95% CI, 0.44 to 7.05) but had weaker associations with follow-up PCS and MCS.

**Conclusions** Body size and composition are significantly associated with physical functioning and quality of life. Interventions that improve muscle mass and decrease obesity might improve these measures in patients undergoing MHD.

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**Materials and Methods**

**Study Population and Baseline Characteristics**

This ongoing longitudinal study includes adults (≥18 years) who have been receiving MHD for at least 3 months at the University of Utah and Vanderbilt University Medical Center (VUMC) outpatient dialysis units. Exclusion criteria were medical conditions with increased short-term mortality, such as cancer, uncontrolled infection, or congestive heart failure.

Introduction

Physical functional ability is significantly impaired in patients undergoing maintenance hemodialysis (MHD), as evidenced by both objective and subjective measures of physical performance (1–8). Health-related quality of life (QOL) as evaluated by validated self-reported questionnaires is also markedly diminished in this population (9). Identification of reversible factors that are associated with poor physical function and QOL in MHD patients may provide targets for therapeutic interventions. Previous studies have evaluated the association of kidney disease and other comorbid conditions with measures of physical function (2), as well as dialysis frequency, with self-reported physical health (3). There is a paucity of data examining the specifics of body composition (i.e., body size and fat and muscle content) as it relates to functional capacity and QOL in MHD patients.

PICNIC (Protein Intake, Cardiovascular Disease, and Nutrition In Stage V CKD) is a prospective observational study with the primary goal of examining the effect of nutrient intake on vascular health, body composition, and physical functioning in MHD patients. In the current analyses, we used PICNIC data to examine the hypothesis that adiposity is associated with worse physical function and QOL, whereas higher muscle mass is associated with better physical function and QOL in MHD patients. We also hypothesized that larger body size is associated with worse physical function and QOL despite the known associations of larger body size with better survival in MHD patients (10–12).
as symptomatic heart failure; active malignancy (excluding squamous and basal cell skin cancers); inability to walk or use of a wheelchair; contraindications to magnetic resonance imaging, such as pacemakers; and atrial fibrillation due to possible interference with measurement of pulse-wave velocity.

Study Visits
Participants were scheduled for study visits after overnight fasting at the University of Utah and VUMC on midweek nondialysis days. The study visits were conducted at clinical research centers at each institution at baseline and 6 and 12 months by trained study coordinators. A standardized questionnaire was used to obtain demographic characteristics, medical history, past/current smoking/alcohol use, medications, and socioeconomic data. Height was measured to the nearest centimeter using a metal rule (200 cm, aluminum model #733; Radiation Products Design, Buffalo, NY) attached to a wall and a standard triangular headboard. The average of three postdialysis weights the week before the study visit was obtained from the dialysis records. Body mass index (BMI) was calculated using the baseline, 6-month, and 12-month weights. Body mass index (BMI) was calculated as postdialysis weight in kilograms divided by height in meters squared. Fasting blood was drawn in lithium heparin tubes. The blood sample was centrifuged within 15 minutes; plasma was divided into multiple aliquots of heparin tubes. The blood sample was centrifuged within 15 minutes; plasma was divided into multiple aliquots of 1 ml each and frozen immediately with dry ice and stored at −80°C freezer.

Magnetic resonance imaging of the legs and abdomen was performed at both University of Utah and VUMC sites on a nondialysis day at the baseline visit following a standardized protocol (described in the Supplemental Appendix). Typical examples of images used to measure mid-thigh muscle area (MTMA) and intra-abdominal fat area (IAFA) are also presented in the Supplemental Appendix.

Six-Minute Walk Distance
Physical function was measured using the 6-minute walk test per American Thoracic Society standards using a flat surface on an indoor walking course (13). The details of the protocol are presented in the Supplemental Appendix.

Short Form-12
Health related QOL was assessed at baseline and the 6- and 12-month follow-up visits using the Short Form (SF)-12 questionnaire, a short-form survey with questions selected from the SF-36 Health Survey, a standard outcomes measure tool (14,15). The SF-12 has been validated as an abbreviated alternative to the lengthy SF-36 questionnaire (16,17). The questions of the SF-12 are scored and weighted to create two scales that measure mental and physical functioning and overall health-related QOL. Physical and mental health component scores (PCS and MCS) are computed using the scores of 12 questions. The scores range from 0 to 100, where a 0 score indicates the lowest level of health and 100 indicates the highest level of health.

Statistical Analyses
Baseline characteristics were summarized for subgroups defined by levels of baseline IAFA and MTMA above and below their respective median values in the cohort, using means±SDs or medians (interquartile ranges) for continuous variables, and frequencies and percentages for categorical variables.

Initial univariate descriptive summaries and histograms demonstrated approximate normality for each outcome variable, so that all outcomes were analyzed without transformation in subsequent statistical analyses. Scatter plots with nonparametric regression curves were examined for each of the pairwise relationships between the 6-minute walk, PCS and MCS outcomes, and body size and body composition predictor variables to check for possible nonlinear relationships. No deviations from linearity were detected.

Separate mixed-effects longitudinal regression analyses were used to relate the 6-minute walk measurements at baseline, 6 months, and 12 months to each SD increase in baseline BMI, waist circumference, and IAFA as individual exposure variables. Use of SD provides a standardized method of comparing effect sizes between various explanatory variables that have different units. This also avoids arbitrary choice of increments for different parameters. For instance, a 1-kg/m² increase in BMI is very different from a 1-cm increase in waist circumference or a 1-cm² increase in MTMA or IAFA because the distribution of these variables is quite different. Each of the mixed models also included age; sex; race; study site; and baseline assessments of duration of ESRD, vascular access type, coronary artery disease, cerebrovascular disease, peripheral vascular disease, congestive heart failure, diabetes, lung disease, and malignancy as baseline covariates. Each model produced one coefficient to characterize the cross-sectional association of that model’s body size or body composition measure with the baseline 6-minute walk, and a second coefficient to characterize the association of the baseline body size or composition measure with the average of the 6-minute walk measurements at 6 and 12 months. These three mixed-effects analyses were repeated after adding MTMA as an additional covariate and were repeated again using the baseline, 6-month, and 12-month PCS and MCS as the outcome variable.

In additional sensitivity analyses, the preceding models were repeated with further adjustment for baseline hemoglobin, dialysis dose, plasma C-reactive protein, and albumin. These results are presented in the Supplemental Material. The details of the mixed models are also provided in the Supplemental Material.

In additional analyses using normal BMI (BMI, 22–24.9 kg/m²) as the reference category, the associations of underweight (BMI<22 kg/m²), overweight (BMI, 25–29.9 kg/m²), and obese (BMI≥30 kg/m²) categories with 6-minute walk distances were examined. These results are also presented in the Supplemental Material. We performed analyses using Stata12 and SAS version 9.2.

All participants gave informed consent, and the study was approved by the University of Utah and the Vanderbilt University institutional review boards. The study is registered at clinicaltrials.gov (NCT00566670).

Results
The study population consisted of 105 adult participants with baseline MRI measurements of both MTMA and IAFA. The mean age was 50.8±16.8 years, 56% were men.
and 21% were African Americans. Eighty-eight were from the Utah site and 17 were from the Vanderbilt site.

Baseline characteristics of study participants are reported in Table 1 by subgroups defined by median levels of IAFA and MTMA. Older age, male gender and Caucasian race were associated with higher IAFA. There was also a greater prevalence of diabetes along with higher BMI and waist circumference in those with higher IAFA. Male gender and African American race were associated with higher MTMA (Table 1). Those with higher MTMA also had higher BMI and waist circumference.

Correlation matrix of baseline BMI, waist circumference, IAFA and MTMA are presented in Table 2. Body size and measures of adiposity were strongly correlated with one another. There was a moderate correlation of muscle area with body size and measures of adiposity.

Supplemental Table 1 summarizes the 6-minute walk distances, PCS and MCS at baseline, 6 and 12 months. The 15 participants who chose not to perform the 6-minute walk test at baseline had higher baseline IAFA (160±17 versus 124±8 cm², \( P=0.08 \)) and lower baseline MTMA (91±7 versus 106±3 cm², \( P<0.05 \)) than the 90 patients who did complete the 6-minute walk.

Figure 1 summarizes the flow of study participants. Ninety-one (86.7%) of the participants completed the 6-month and 74 (70.5%) completed the 12-month visits. The reasons for dropout of 14 participants at 6 months were death (\( n=3 \)), transplantation (\( n=3 \)), nonadherence (\( n=4 \)), and loss to follow-up (4). The reasons for dropout of 31 participants at 12 months were also death (\( n=7 \)), transplantation (\( n=4 \)), nonadherence (\( n=7 \)), and loss to follow-up (\( n=13 \)). Baseline clinical characteristics of those who completed the 12-month follow-up versus those who dropped out early are summarized in Supplemental Table 1.

### Table 1. Baseline characteristics by intra-abdominal fat area and midthigh muscle area groups

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Intra-Abdominal Fat Area (cm²)</th>
<th>Midhigh Muscle Area (cm²)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>( \leq 118.7 \text{ cm}^2 ) (n=53)</td>
<td>Muscle( \leq 99.2 \text{ cm}^2 ) (n=53)</td>
</tr>
<tr>
<td>Intra-abdominal fat area (cm²)</td>
<td>70.9±28.3</td>
<td>123.6±79.9</td>
</tr>
<tr>
<td>Midhigh muscle area (cm²)</td>
<td>97.6±26.8</td>
<td>82.0±11.8</td>
</tr>
<tr>
<td>Demographics and dialysis characteristics</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age (yr)</td>
<td>48.2±17.0</td>
<td>52.8±16.2</td>
</tr>
<tr>
<td>Men (%)\textsuperscript{a}</td>
<td>55</td>
<td>62</td>
</tr>
<tr>
<td>Black (%)\textsuperscript{b}</td>
<td>26</td>
<td>13</td>
</tr>
<tr>
<td>White (%)\textsuperscript{c}</td>
<td>55</td>
<td>79</td>
</tr>
<tr>
<td>AV fistula (%)</td>
<td>66</td>
<td>73</td>
</tr>
<tr>
<td>Duration of ESRD (yr)</td>
<td>3.1 (0.8, 4.8)</td>
<td>2.3 (1.0, 3.7)</td>
</tr>
<tr>
<td>Clinical characteristics</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Coronary artery disease (%)</td>
<td>21</td>
<td>29</td>
</tr>
<tr>
<td>Cerebrovascular disease (%)\textsuperscript{b}</td>
<td>17</td>
<td>17</td>
</tr>
<tr>
<td>Peripheral vascular disease (%)</td>
<td>11</td>
<td>29</td>
</tr>
<tr>
<td>Congestive heart failure (%)</td>
<td>17</td>
<td>21</td>
</tr>
<tr>
<td>Diabetes mellitus (%)\textsuperscript{c}</td>
<td>26</td>
<td>58</td>
</tr>
<tr>
<td>Lung disease (%)</td>
<td>12</td>
<td>19</td>
</tr>
<tr>
<td>Malignancy (%)</td>
<td>8</td>
<td>6</td>
</tr>
<tr>
<td>Past/current smoking (%)</td>
<td>57</td>
<td>40</td>
</tr>
<tr>
<td>Past/current alcohol use (%)</td>
<td>60</td>
<td>52</td>
</tr>
<tr>
<td>Body mass index (kg/m²)\textsuperscript{b,d}</td>
<td>24.2±3.8</td>
<td>32.7±6.0</td>
</tr>
<tr>
<td>Waist circumference (cm)\textsuperscript{b,d}</td>
<td>87.9±10.1</td>
<td>110.5±12.6</td>
</tr>
<tr>
<td>Laboratory measures</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hemoglobin (g/dl)</td>
<td>11.6±1.2</td>
<td>12.0±1.4</td>
</tr>
<tr>
<td>Serum calcium (mg/dl)\textsuperscript{f}</td>
<td>9.2±0.6</td>
<td>8.9±0.7</td>
</tr>
<tr>
<td>Serum phosphorus (mg/dl)</td>
<td>5.8±1.5</td>
<td>6.2±1.9</td>
</tr>
<tr>
<td>Urea reduction ratio</td>
<td>0.74±0.09</td>
<td>0.70±0.15</td>
</tr>
</tbody>
</table>

Values expressed with a plus/minus sign are the mean±SD. Duration of ESRD is expressed as median (interquartile range). AV, arteriovenous.

\( ^{a} P<0.001 \) for midthigh muscle area.

\( ^{b} P<0.05 \) for midthigh muscle area.

\( ^{c} P<0.05 \) for intra-abdominal fat area.

\( ^{d} P<0.001 \) for intra-abdominal fat area.
follow-up (−24.5; 95% CI, −40.8 to −8.2 m) 6-minute walk distances (Figure 2A). The negative association of baseline BMI with 6-minute walk distances were more pronounced at baseline (−31.5; 95% CI, −53.0 to −10.0) and follow-up (−36.9; 95% CI, −54.6 to −19.2) after adjustment for baseline MTMA. In the model that included both baseline BMI and MTMA, each SD increase in baseline MTMA was strongly associated with higher 6-minute walk distances at baseline (46.6; 95% CI, 16.6 to 76.6 m) and follow-up (41.3; 95% CI, 13.6 to 69.1 m).

Each SD increase in waist circumference and IAFA were also negatively associated with 6-minute walk distances at baseline and follow-up (Figure 2, B and C). Again, these associations were stronger when adjusted for baseline muscle mass.

As shown in Supplemental Figure 2, compared with the normal BMI group, both underweight and obese groups showed a negative association with 6-minute walk distances. However, these relationships were stronger in the obese group.

Associations of Body Size and Body Composition Measures with Baseline and Follow-Up PCS

Neither baseline body size nor baseline body fat measures were associated with the PCS at baseline or follow-up (Figure 3), with or without adjustment for MTMA. On the other hand, in the model that included both BMI and MTMA, each SD increase in baseline MTMA was associated with 3.78-point (95% CI, 0.73 to 6.82) higher score on baseline PCS. The association of baseline MTMA with the 6- and 12-month average PCS was weaker and nonsignificant.

Associations of Body Size and Body Composition Measures with Baseline and Follow-Up MCS

The associations of body size and body composition measures with baseline and follow-up MCS were similar to those described for PCS and are summarized in Figure 4. Sensitivity analyses results are reported in Supplemental Tables 3–5. Additional adjustment for baseline plasma albumin, plasma C-reactive protein, hemoglobin, and urea reduction ratio attenuated the associations of IAFA with 6-minute walk distances only by about 5% in the baseline as well as follow-up models (Figure 2C, Supplemental Table 3). On the other hand, when adjusted for these variables, the contemporaneous association of MTMA with 6-minute walk distances is attenuated by about 20% and remains significant but attenuated by 40% and reaches nonsignificance for the follow-up measurements.

Discussion

Patients undergoing MHD have poor functional status and debilitation (1–5). Poorer physical function is also a strong predictor of mortality in these patients (5). The relationship between body composition and debility, however, is unclear because few studies have used detailed measures of body composition. Hence, in this study we used MRI to measure body composition and examined the associations of physical functioning and QOL. The results of this study suggest that higher adiposity (BMI, waist circumference, and IAFA) are associated with better physical functioning and QOL. Clinical implications of these findings are such that strategies targeted at improving muscle mass in MHD patients, such as nutritional supplementation, exercise, or pharmacologic intervention, could potentially improve their physical functioning and QOL.

In a cross-sectional analysis of 375 hemodialysis patients enrolled in the Frequent Hemodialysis Network Study, bioimpedance analysis was used to indirectly estimate adiposity (3). The results of that study suggested a negative association of adiposity with physical performance, as measured by the Short Physical Performance Battery, a test consisting of 4-m walk for gait speed, chair raise, and balance ability. In the current study, we used MRI to directly measure metabolically active intra-abdominal fat and examined the associations of adiposity with baseline and follow-up 6-minute walk distances. There is a clear inverse relationship between baseline BMI, waist circumference, and IAFA with baseline as well as the average of 6-minute walk distances (Figure 2). It should be noted that BMI is

<p>| Table 2. Correlation matrix of baseline body size and body composition measures |
|---------------------------------|---------------------------------|---------------------------------|---------------------------------|---------------------------------|</p>
<table>
<thead>
<tr>
<th>Variable</th>
<th>BMI (kg/m²)</th>
<th>Waist (cm)</th>
<th>IAFA (cm²)</th>
<th>MTMA (cm²)</th>
</tr>
</thead>
<tbody>
<tr>
<td>BMI</td>
<td>1</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Waist</td>
<td>0.87, P&lt;0.001</td>
<td>1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>IAFA</td>
<td>0.73, P&lt;0.001</td>
<td>0.83, P&lt;0.001</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>MTMA</td>
<td>0.29, P=0.001</td>
<td>0.39, P&lt;0.001</td>
<td>0.22, P=0.002</td>
<td>1</td>
</tr>
</tbody>
</table>

Presented as Rho values with P values. BMI, body mass index; IAFA, intra-abdominal fat area; MTMA, mid-thigh muscle area.

Figure 1. | Flowchart of study participants.
Figure 2. Associations of baseline body size and body composition measures with baseline and average follow-up 6-minute walk distances in mixed-effects models. BMI, body mass index.
Figure 3. | Associations of baseline body size and body composition* measures with baseline and average follow-up physical component scores in mixed-effects models.

* For each SD increase of explanatory variable.
* SDBMI=0.6(kg/m²), SDwaist=27.9(cm), SDintra=16.1(cm), SDMV=73.4(cm²).
* BMI, waist circumference and IAFA were evaluated in separate models and not jointly.
** Adjusted for age, gender, race, duration of ESRD, vascular access type, study site, CAD, CVD, PVD, CHF, diabetes, lung disease and malignancy.
Figure 4. Associations of baseline body size and body composition* measures with baseline and average follow-up mental component scores in mixed-effects models.

* For each SD increase of explanatory variable
* $SD_{BMI}=6.6(kg/m^2)$, $SD_{Mid-thigh muscle area}=14.9(cm^2)$, $SD_{Waist}=73.4(cm)$
** BMI, waist circumference and IFMA were evaluated in separate models and not jointly
*** Adjusted for age, gender, race, duration of ESRD, vascular access type, study site, CAD, CVD, PVD, CHF, diabetes, lung disease and malignancy
simply a measurement of body size alone and does not consider body composition. People who are obese also have a higher muscle mass. Therefore, adjustment for MTMA increased the negative association of BMI with 6-minute walk distances (Figure 2). It also should be noted that waist circumference, a simple measure of abdominal obesity, had similar associations with 6-minute walk distances, as did the more detailed MRI-measured IAFA.

In an earlier cross-sectional study of 46 hemodialysis patients, higher serum creatinine, a surrogate marker of muscle mass, was associated with faster stair-climbing and chair-rising time (2). The current study confirms these findings with more precise measures, such as MTMA measured by MRI. Of note, MTMA had a strong positive relationship not only with baseline but also with the average of 6- and 12-month follow-up 6-minute walk distances (Figure 2). These data indicate that these associations persist over time in MHD patients. Accordingly, interventions that increase muscle mass or prevent its loss over time could potentially improve physical functioning in this debilitated population. Because measures of adiposity have a strong negative association with 6-minute walk distances (Figure 2), interventions that decrease fat mass while preserving muscle mass might also lead to improved physical functioning.

Compared with the general population, MHD patients have lower QOL. Lower PCS are associated with increased mortality in MHD patients (9). There has been a paucity of data on the associations of body composition, a potentially modifiable factor, with QOL in MHD patients. In the current study, baseline measures of adiposity were not associated with baseline or follow-up measures of QOL. On the other hand, baseline MTMA was positively associated with better QOL at baseline as measured by PCS and MCS (Figures 3 and 4). However, the associations of baseline MTMA with 6- and 12-month follow-up PCS and MCS were weaker. This suggests a contemporaneous association of muscle mass with well-being and indicates that interventions that increase muscle mass could potentially improve QOL in MHD patients.

Higher BMI (10–12,18–21) and higher fat mass (22) have been associated with better survival in hemodialysis patients. Poorer physical function is also a strong predictor of mortality in dialysis patients (5). Thus, it appears counterintuitive that higher BMI, waist circumference, and intra-abdominal fat are associated with poorer physical function. This apparent paradox of the association of adiposity with better survival but lower physical function in dialysis patients is probably due to the fact that adiposity confers a survival advantage independent of physical functioning. Nonetheless, while higher fat mass may confer a survival advantage, higher muscle mass is even more protective (10). Because this study shows that higher muscle mass is also associated with better physical function and QOL, interventions, such as increased physical activity, that decrease fat mass and increase muscle mass are likely to improve physical function, QOL, and survival in dialysis patients. Such interventions need to be tested in clinical trials.

Although the most accurate technique for body composition measurement is debatable, MRI has been considered by some to be the gold standard (23). The strength of this study, in addition to the use of MRI, is the use of 6-minute walk for objective measurement of physical functioning. As 6-minute walk is self-paced, it may better reflect the functional exercise level for daily physical activities (13). Unlike the Short Physical Performance Battery used in previous studies (3), 6-minute walk distance is also a measure of endurance. The SF-12 is a validated tool for measurement of QOL and, compared with SF-36 (16,17), has the advantage of fewer questions and administrative ease.

Although the associations of adiposity with physical functioning appear independent of inflammation (Supplemental Table 3), the associations of muscle mass with follow-up 6-minute walk distances were attenuated by adjusting for C-reactive protein. It is unclear whether inflammation is a confounder or is in the causal pathway between muscle mass and physical function. Further studies are warranted to examine these in further detail.

There are inherent limitations in this study, as in any study attempting to assess performance status. Not all participants enrolled in the study participated in the 6-minute walk test. The participants who were more likely to not walk were also more likely to be obese and have low muscle area and high fat area. Hence, this study probably underestimates the effect of measures of adiposity and muscle mass on physical functioning in MHD patients. Because MHD patients have a high burden of comorbid illnesses, there was also a high dropout at 6 and 12 months. This might also underestimate the effect of the body composition on physical functioning and QOL.

In summary, in this predominantly white dialysis population, our results show that measures of adiposity are associated with lower functional ability, whereas higher muscle mass is associated with better physical function and QOL. Interventional trials are needed to test whether decreasing fat mass and increasing muscle mass improve physical function and QOL in this frail population.

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Disclosures
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