Association of Body Composition with Survival Among Patients on Hemodialysis

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Several years ago, an "obesity paradox" was reported among several different cohorts of patients who were on dialysis (1–4). It soon became apparent that patients with high body mass index (BMI), even at levels considered obese and morbidly obese, had better survival than patients whose BMI was in the normal range (5). Although BMI is strongly correlated with percentage of body fat, including among patients who are on dialysis, it does not allow for the separation of fat and lean in an individual because it is calculated only from height and weight. Nevertheless, the improved survival among even those with extremely high BMI suggested that being fatter was truly advantageous. Individuals with higher BMI and higher body fat usually also have higher lean body mass than those with low BMI, so the question of which component of body composition—fat or lean—is associated (or is more associated) with the observed obesity paradox became a point of debate, contention, and, of course, further research.

Initial attempts to use creatinine generation, calculated from 24-hour creatinine data reported on the Centers for Medicare and Medicaid Medical Evidence Form 2728, yielded contradictory results (5,6). One analysis showed that adjustment for creatinine generation did not mitigate the high BMI survival advantage (5), but another showed that patients with high BMI but creatinine generation (as a proxy for muscle mass) in the lowest quartile did not have a survival advantage and argued that the survival advantage of high BMI was limited to patients with normal or high muscle mass (6). Still other investigators called into question the use of these data on the basis that the quality may be low, with some providers reporting a creatinine-based estimated GFR rather than a measured creatinine clearance (7). Furthermore, even with reporting of true creatinine clearance, incomplete urine collections could lead to underestimation of creatinine generation and, thus, underestimation of muscle mass.

More sophisticated measures of body composition or parameters that can be used to estimate body composition are needed to address whether higher muscle mass, body fat, or both are associated with longer survival among patients who are on dialysis. However, direct measurement of body composition is resource intensive, and it is unlikely that these measures will ever be available on cohorts of tens or hundreds of thousands similar to those that have been assembled with BMI data. Nevertheless, several recent studies, including one by Noori *et al.* (8) in this issue of the *CJASN* and one by Huang *et al.* (9) in the April 2010 issue of *Kidney International*, have gone beyond height and weight, using anthropometry to assess the relative contribution of fat and muscle to survival of patients who are on hemodialysis (HD).

Noori *et al.* (8) validated mid-arm muscle circumference (MAMC) of the nonvascular access–containing arm as a correlate of lean body mass using dual-energy x-ray absorptiometry (DEXA) as a gold standard in a subset of 118 of their cohort and found a correlation of 0.72. Similarly, triceps skin-fold thickness (TSF) was correlated with fat mass measured by DEXA (r = 0.74). They then went on to assess the associations of MAMC and TSF with survival for up to 63 months (median follow-up 2 years) in a cohort of 792 patients who were undergoing maintenance HD. Patients were divided into quartiles of MAMC and of TSF in multivariable Cox proportional hazards models. Neither MAMC nor TSF showed a statistically significant trend for better survival with successive quartiles in unadjusted models, but both were significantly associated with better survival after case-mix adjustment. Higher MAMC remained significantly associated with better survival after additional adjustment for laboratory measures related to nutrition, dialysis management, and inflammation, but these adjustments rendered the association between higher TSF and survival NS. Unfortunately, they did not perform an analysis in which both quartiles of MAMC and TSF were included. Instead, they dichotomized the cohort at the medians of MAMC and TSF and created four groups on the basis of these categories. In this analysis, having high MAMC, high TSF, or both high MAMC and high TSF was associated with better survival than having low MAMC and low TSF. Because low MAMC and low TSF was the reference category, it is not possible to determine whether any of the other categories was more advantageous than any other or to determine whether fat mass or muscle mass is the "more important" predictor of survival. However, compared with having both low fat and low muscle, it seemed to be equally protective to have higher fat mass or higher muscle mass, and having both higher fat and muscle did not seem to be "best."

Huang *et al.* (9) recently reported results of anthropometry

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performed on participants in the Hemodialysis (HEMO) study. Again, MAMC was used as a surrogate for muscle mass and TSF as a surrogate for body fat, and, again, MAMC and TSF were divided into quartiles for analysis. What was different, however, was that both were included in the same multivariable-adjusted model, and both were found to be associated with all-cause mortality. Unlike the results reported by Noori *et al.* (8), the negative association between TSF and all-cause mortality became stronger after adjusting for demographics, comorbid conditions, nutritional status, laboratory tests, and dialysis characteristics. To compare the strength of association of muscle and fat, they assessed the hazard ratio of a 1-SD increase in each, which was 0.83 (95% confidence interval 0.75 to 0.91) for TSF and 0.90 (95% confidence interval 0.83 to 0.97) for MAMC. The authors noted that although the relationship between TSF and mortality was linear, the risk associated with MAMC was particularly evident in the lowest quartile.

The data from these two studies support an important association of both body fat and muscle mass with survival among patients who are on HD. Certainly, one could argue that anthropometry is not a perfect means of measuring body composition in the dialysis population. However, it seems unlikely that TSF and MAMC are so flawed as to produce false associations. On the basis of these studies, we can be relatively confident that the association of high BMI with improved survival among HD patients is more complex than a simple association with greater body fat. The next challenge will be to address the mechanisms underlying the associations between body composition and survival so that we can consider strategies to change body composition and determine whether such intervention can improve outcomes, and this challenge may require more precise measures of body composition than BMI or anthropometry.

Disclosures

None.

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See related article, "Mid-Arm Muscle Circumference and Quality of Life and Survival in Maintenance Hemodialysis Patients," on pages 2258–2268.