Editorial Commentary

Body Mass Index-Mortality Paradox in Hemodialysis Patients
Blood Pressure, Blood Volume, and Nutritional Status

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See related article, pp 1014–1020

In the general population, there is a clear association between body mass index (BMI) and mortality. However, in hemodialysis patients, a number of clinical studies have demonstrated that BMI is inversely related to mortality. The explanation for this interesting paradox is unknown.

In this edition of the journal, Agarwal conducted a cross-sectional analysis of 368 dialysis patients in his practice where he determined BMI and gathered demographic and clinical factors. In addition, he used ambulatory blood pressure monitoring after the first or midweek hemodialysis session for 44 hours and measured 2D and M-mode echocardiograms and inferior vena cava diameter. During a total of 1122 patient-years of cumulative follow-up (median: 2.7 years), 119, or 32%, of these patients died. He observed an inverse relationship between the prevalence of hypertension and poor control, with BMI. Moreover, patients with lower BMI had greater left ventricular mass index, and greater evidence of extracellular fluid volume excess. Leaner patients had accelerated mortality in the first 2 years of follow-up, which he noted was not completely explained by blood pressure, left ventricular mass index, or other cardiovascular or dialysis-specific risk factors. Agarwal used appropriate statistical analysis to consider the relationships between the demographic and clinical variables related to the categories of BMI. However, risk adjustment in observational studies may not account for unmeasured confounders. This is particularly important when one considers that a single cross-sectional analysis was used in this study, and there is no opportunity to measure time varying measures of blood pressure, nutrition, and inflammation, which may have a critical influence on longitudinal outcome. Although these new observations are an important addition to the literature on this topic, they do not provide a sufficient answer to the question as to why paradoxically being overweight as a dialysis patient is protective against mortality.

Agarwal suggests that the excess prevalence of hypertension and poor control of blood pressure among lean hemodialysis patients may be attributed to differences in the way overweight patients may sequester extra fluid volume in the extracellular space more effectively than lean people. Although a plausible explanation, this study did not examine this relationship. In his cross-sectional analysis, echocardiographic evidence of volume excess in leaner patients, including increased left atrial diameter and inferior vena cava diameter (both indexed for body surface area), was insufficient to attenuate the inverse relationship between hypertension and BMI. Thus, it is possible that factors other than central circulation volume overload may be a concern for mortality in leaner hemodialysis patients. Agarwal also raised a question as to whether increased muscle mass, as seen in patients with greater BMI, may be associated with increased renalse expression. This enzyme could potentially reduce blood pressure through the reduction of circulating catecholamine levels. However, this theory has never been tested in a clinical trial of human hemodialysis patients.

Another potential mechanism to explain the observed mortality paradox in hemodialysis patients was the possible misclassification of obesity in the participants of his cross-sectional study. He has previously demonstrated the negative predictive value of BMI to detect obesity in patients with kidney disease. Thus, how should we interpret this cross-sectional data, which we know has substantial unmeasured confounders? Although the data from this small clinical study are appropriately analyzed and discussed, it does not make up for the fact that time varying measures would add much to our understanding. The incontrovertible evidence is that leaner patients have greater left ventricular mass index, which indicates long-standing volume excess, greater blood pressure, and greater central blood volume. These markers we know are of critical importance in determining cardiovascular outcome. Although not discussed in this article, the causes of death in these individuals are likely related to progressive heart failure and/or arrhythmia, which would support the hypothesis that inadequate volume control would be an important explanation for the increased risk of death.

In clinical practice, hemodialysis patients, especially those with the malnutrition and inflammation syndrome, often lose weight. If their dialysis prescription is not altered during the course of weight loss, the consequence is volume dependent hypertension (Figure). Longitudinal measures of nutritional and inflammatory parameters, in conjunction with measures of blood pressure, would be very helpful in teasing out whether malnutrition and inflammation, coupled with...
weight loss, are ultimately predictive of higher levels of blood pressure and measures of volume excess, which, in turn, would be associated with greater evidence of cardiac mortality.

The greater earlier mortality rate observed in the leaner patients during the first 2 years of the observational study by Agarwal is of interest. It may well be that those patients who had lost the most weight associated with greater volume excess and blood pressure were selected out of the cohort. An examination of the early causes of death would be helpful to see whether they were predominantly cardiac in nature. With longitudinal follow-up, the mortality rate among the leaner patients matches those with higher BMI. Could it be that, in these individuals who survive the early increase in mortality, more effort was made to adjust the dialysis prescription and to facilitate better control of volume and blood pressure? These understandings can only be answered with prospective longitudinal studies measuring nutritional, inflammatory, and volume status in hemodialysis patients. This contribution to the literature by Agarwal is an important step in the right direction to help explain the mechanistic relationship between low BMI and increased mortality.

Disclosures
None.

References
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