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Reply to S Beddhu et al

Dear Sir:

Beddhu et al assert that our fundamental assumptions related to the role of “malnutrition–inflammation complex syndrome” in causing a “reverse epidemiology” (ie, an association between obesity and

greater survival in dialysis patients) or “risk factor paradox” (ie, survival advantages of obesity in dialysis patients) are incorrect (1). It is, however, reassuring that Beddhu et al, too, agree that the obesity paradox does indeed exist, no matter what nomenclature one might wish to use to refer to it, and that they say that “effects of nutrition on survival are much stronger than are the effects of atherosclerotic events,” which is consistent with our group’s hypotheses about the central role of nutrition (1–3). The only salient difference among these views appears to be related to the alleged role of inflammation and to the mechanism through which malnutrition exerts its deleterious effect on increasing death risk in dialysis patients. Beddhu et al state that “undernutrition is *not* [emphasis added] associated with inflammation or atherosclerosis but increases the hazard of death from concomitant cardiovascular and noncardiovascular events.” That hypothesis stops short of explaining how undernutrition increases the death risk; it does not offer any new views about or specify any new mechanisms through which the role of undernutrition in worsening survival can be explained in dialysis patients. Similarly, although the authors state that “better nutrition, as evidenced by greater muscle mass, decreases the hazard of death from concomitant cardiovascular and noncardiovascular events, which results in lower cardiovascular and noncardiovascular mortality than is seen in persons with low or moderate muscle mass,” they do not present new information or insight into the pathophysiology of said association. It remains unclear how muscle mass can improve survival, and Beddhu et al do not present any further explanations or hypotheses.

Beddhu et al also state, “Compared with undernutrition, adiposity decreases the hazard of death from concomitant disease processes,” but this statement contradicts their own conclusion in a recent study in which they maintained that “the protective effect conferred by high BMI is *limited* [emphasis added] to those patients with normal or high muscle mass, whereas high BMI patients with inferred high body fat have *increased* [emphasis added] and not decreased mortality” (4). It is reassuring to know that these investigators have now modified their previous conclusion and admit both in the current letter and in another recent letter (5) that the survival advantages of high BMI in dialysis patients are not limited to greater muscle mass. In their current letter, however, they maintain that adiposity is associated with atherosclerosis in dialysis patients, which to our knowledge has not yet been shown in any study of dialysis patients, although it is known in the general population.

As we stated in our recent review (1), the use of urinary creatinine by Beddhu et al as a surrogate of muscle mass to examine the role of body composition in survival advantages of high BMI in dialysis patients (4) was based on assumptions that are not yet proven. Independent of the person’s muscle mass, dietary protein intake, especially the recent intake of meats in the diet, and the level of renal function each affect urinary creatinine excretion (6). Indeed, in the Modification of Diet in Renal Disease (MDRD) study (7), in which the effect of food intake on the progression of renal insufficiency was studied comprehensively, urinary creatinine correlated significantly with dietary protein intake ($r = 0.38$, $P < 0.01$) and with the degree of severity of renal insufficiency. It is interesting that, in the MDRD study, urinary creatinine excretion did not covary closely with the surrogates of muscle mass, including actual and relative body weights, BMI, and arm muscle area (7). Moreover, the MDRD study reported a higher urinary creatinine in African American men and women than in white men and women (7), and African Americans are also known to have better survival on dialysis. Hence, the fundamental assumption of Beddhu et al—ie, that urinary creatinine can be used as a surrogate of muscle mass in patients with severe renal

insufficiency (ie, stage 5 chronic kidney disease) who are not undergoing maintenance dialysis (4)—may not be correct, because a high urinary creatinine concentration may confer better survival as a result of its association with dietary protein intake or other factors not related to muscle mass.

Beddhu et al also criticized the use of the term “reverse epidemiology.” Although we agree that this nomenclature may not be optimal, it is important to note that BMI is not the only conventional cardiovascular disease (CVD) risk factor with a paradoxical association with clinical outcomes in dialysis patients (8). High concentrations of total cholesterol have been associated with both a survival advantage in these patients, as has an inverse relation between blood pressure and outcome (8). These consistent findings across an array of CVD risk factors in dialysis patients support the more inclusive term “reverse epidemiology.” Reverse epidemiology has also been observed in heart failure patients, elderly persons, and patients with advanced malignancies, AIDS, and other chronic diseases (9, 10). This means that >20 million persons—including almost half a million dialysis patients—in the United States alone may be subject to this reverse epidemiology (10). We believe this vulnerability to reverse epidemiology could have very important implications for public advice on health matters, because conventional recommendations for the management of CVD risk factors, such as weight reduction or aggressive treatment of hypercholesterolemia, may not be appropriate.

Whereas such apparently counter-intuitive associations may not necessarily be causal, the possibility of the true protective effect of obesity and hypercholesterolemia in dialysis patients cannot be ruled out. Therefore, we believe that the paradoxically inverse associations that have been consistently observed between conventional risk factors, such as obesity and hypercholesterolemia, and the improved survival in certain chronic disorders, such as chronic renal insufficiency and heart failure, require a more accurate and sophisticated approach to risk factor management. Further studies are clearly needed to elucidate the mechanisms behind this reverse epidemiology affecting obesity and other CVD risk factors so that we offer the best and most effective advice and treatment for our patients. For example, randomized clinical trials of strategies to improve the nutritional and metabolic status of dialysis patients and to ameliorate other chronic disorders are long overdue.

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