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Changes in Body Weight and Subsequent Mortality: Are We Any Closer to Knowing How to Deal with Obesity in ESRD?

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Obesity is the bane of modern society: it induces metabolic changes, enhances cardiovascular disease, and increases morbidity (including ESRD) and mortality in the general population (1). The United States is among the most obese nations in the world (2). The situation is dire, and hence discussions about obesity as a national crisis pervade discussions not only in the scientific literature, but also in the lay press and in the mass media (3). It is thus not surprising that any suggestion about obesity not being "bad" (let alone being "good") under certain circumstances is mostly met with incredulity.

It is precisely the nephrology and to some extent the cardiology literature that provides most data about the potential benefits of obesity, having shown that a higher, not lower, body mass index (BMI) is associated with better outcomes in patients with ESRD (4,5) and nondialysis-dependent CKD (6). The scientific discourse about this literature has been at a stalemate, mostly due to the observational nature of the data linking obesity to lower mortality. Proponents point to the consistency of the data, the incredibly large sample sizes of these studies, the strength of the associations, and analogies with other sick populations such as elderly persons or patients with heart failure (7). However, opponents (perhaps rightfully) demand stronger evidence and point to the flaws inherent in observational data, and most importantly to the presence of unmeasured confounders and the inability to conclude that obesity itself may be the cause of the observed better outcomes (8).

Finding the correct answer is a time-sensitive endeavor given the key role of weight reduction recommendations upon transplant wait-listing of obese dialysis patients. Many transplant centers would avoid or suspend the wait-listed status of such candidates. Nevertheless, solving this stalemate is easier said than done: We would need randomized controlled trials showing the effects of weight interventions (loss or gain) that are implemented in a controlled manner. Given the notorious difficulty of performing large randomized controlled trials in dialysis patients, will we experience a continuation of the current entrenchment of opinions, or are there other ways to find certainty about the true effects of obesity?

A potential answer is to design better observational studies, including those that also examine the correlates of change in weight over time, so that they could offer better control of unmeasured confounders and longitudinal changes as well as mimic the effects of randomized controlled trials of weight gain or loss. Most of the literature on obesity has examined the association of static BMI levels with future outcomes, which offers no answer to what might happen if a patient were to lose or gain weight. In this issue of *CJASN*, two excellent articles by Stack *et al.* and Cabezas-Rodriguez *et al.* aim to examine this latter question in more detail (9,10). Stack *et al.* examined the association between changes in BMI in a US-wide nursing home population 3–6 months before starting dialysis and mortality rates after patients' initiation of dialysis (9). The authors show that stable weight was associated with the best outcomes, and those patients who experienced either weight loss or weight gain had higher postdialysis mortality, independent of their baseline BMI levels. These observations may be secondary to regression to the mean phenomenon and are in contradistinction to other recent large observation studies of change in weight over time showing that weight gain, especially in muscle mass, is associated with better survival, whereas weight loss harbors higher death risk (11,12). Nevertheless, a particular strength of this study is that it was able to quantify oral intake, nutritional support, and fluid intake, which are typically not available in most observational studies; this allowed the authors to some extent to control for reasons of weight loss or weight gain.

Notwithstanding the interesting findings of the study by Stack *et al.*, it is unlikely that they will take us closer to determining the effects of voluntary and structured weight-management interventions in CKD, because it is very unlikely that such structured interventions (*e.g.*, diet and/or exercise programs) are being implemented in nursing home residents, especially in the 6 months preceding dialysis initiation. It is much more likely that the changes in weight seen in this study were due to unfavorable conditions such as acute or chronic wasting illnesses (for weight loss) and excess fluid gain and edema formation (for weight gain). Supporting this notion is the fact that serum albumin, a

marker of protein-energy wasting and an extremely potent predictor of outcomes in CKD patients (13,14), was low not only in patients who experienced weight loss but also in those who experienced weight gain; in addition, supplemental fluid intake was higher in patients with weight gain. The principle message of the study by Stack *et al.* appears to be that any change in body weight or BMI is a poor prognostic indicator in a fragile population with a high comorbidity burden and high mortality rate, possibly because it signals an unstable clinical situation including an unfavorable nutritional status.

In this issue of *CJASN*, Cabezas-Rodriguez *et al.* report on their examination of a European prevalent hemodialysis population recruited and followed prospectively over 3 years (10). This study describes a higher risk of mortality associated with weight loss independent of baseline BMI, and lower mortality associated with weight gain, which was more accentuated in those with lower baseline BMI. Although weight gain was not significantly beneficial in patients with baseline obesity (BMI >30 kg/m^2), it was also not detrimental. This study reaffirms in a prospective and well controlled multiethnic cohort the findings from previous observational studies about the detrimental nature of unintentional loss of weight or various determinants of body mass (including muscle or fat mass), and about the lack of adverse effects and potential benefit of unintentional gain of the same parameters (5,11,12,15–17). The reason behind the more subdued benefit associated with weight gain in patients with baseline obesity in the study by Cabezas-Rodriguez *et al.* is not immediately apparent; however, it could be speculated that perhaps weight gain in obese and lean patients may happen for different reasons and it may have different effects on body composition. It is possible that weight gain in an obese individual is more likely to be due to increases in fat mass and/or visceral adiposity, which have negative metabolic effects (18) that could counterbalance to an extent the beneficial effects attributed to higher BMI in this population. Further research in this area using prospective measurements of body composition could be beneficial, because it would give us further indication about the direction in which controlled clinical trials would have to proceed.

One question the study by Cabezas-Rodriguez *et al.* does not provide an answer for (similar to the other observational studies on this topic) is the one about what the effects of intentional, structured weight management programs in this patient population might be. In cohort studies like this, it is likely that the observed weight loss was unintentional and that it happened because of acute or chronic illnesses and worsened protein-energy wasting. In addition, it is likely that weight gain was due to either surreptitious fluid gain, to recovery from protein-energy wasting, or to uncontrolled dietary intake with more fat mass than lean mass gain. It thus remains unclear what would happen if select dialysis patients (*e.g.*, those free of acute or severe chronic illnesses and prone to tolerate the physical, social, and fiscal demands of strict diet and exercise programs) were to submit themselves to a rigorous intervention aimed at optimizing nutritional status and body composition. Nevertheless, in a real-world scenario, such healthy dialysis patients are rare.

Given the preponderance of evidence, there is no question in our mind that weight management in dialysis patients cannot be done safely by merely using general population data and guidelines developed based on them. There are fundamental differences in observational data between the general population and the dialysis and predialysis CKD populations (19), and there are sufficiently plausible explanations for these differences to argue that a weight-management approach tailored to the specifics of the dialysis population is needed (4). Given the strong opinions about obesity that many in the nephrology community (let alone in the wider medical community) espouse, such an approach would have to marry interventions that address the concerns of both those who worry about the deleterious effect of increased visceral obesity as well as those whose main concerns are related to the ill effects of weight loss in this population, such as worsening protein-energy wasting. Several observational studies have suggested that higher muscle mass is associated with beneficial outcomes in dialysis patients (11,20), hence it is plausible to postulate that a program with the goals of increasing BMI while improving body composition (*e.g.*, increasing lean body mass and lowering waist circumference) might be of benefit. Such results could be achieved by implementing properly composed diets (with adequate protein and energy content, and with as-needed restrictions in phosphorus, potassium, and total fluid intake), administering anabolic and/or appetite-inducing medications, implementing a structured exercise program, or using some combination of these (21). Observational studies of dietary supplementation in dialysis patients have suggested a beneficial effect from nutritional interventions in patients with protein-energy wasting (22), but randomized controlled trials seem unavoidable if we want to take the next step toward weight management in this population. After repeated failed attempts to improve mortality in dialysis patients by treating traditional risk factors such as hypercholesterolemia (23), there may just be enough impetus to proceed with a clinical trial of weight management whose design incorporates the wealth of information amassed in observational studies in this field, rather than trying to force the straight jacket of general population goals on this population. Our patients may just be too corpulent for it.

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Disclosures

None.

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See related articles, "Pre-ESRD Changes in Body Weight and Survival in Nursing Home Residents Starting Dialysis," and "Influence of Body Mass Index on the Association of Weight Changes with Mortality in Hemodialysis Patients," on pages 1734–1740 and 1725–1733, respectively.