

# Time to Look Beyond Obesity Metrics and Mortality in Kidney Disease



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**See Clinical Research on Page 447**

Several studies have linked overweight and obesity to the development of chronic kidney disease (CKD), defined as either estimated glomerular filtration rate <60 ml/min per 1.73 m<sup>2</sup> or increased urinary protein excretion.<sup>1</sup> In the general population, obesity is an independent risk factor for the development of end-stage renal disease.<sup>2</sup> Although obesity is linked to adverse kidney-related outcomes in those with preserved kidney function, similar to the dialysis population, it is paradoxically associated with better survival even in those with non-dependent CKD.<sup>3</sup> Such paradoxical associations can be partly attributed to the study design, as several of the reports have relatively short follow-up, thus underestimating the long-term prognostic implications of obesity as assessed by body mass index (BMI). Further, BMI may misclassify patients with sarcopenia, particularly older adults with CKD,

as it does not differentiate between fat mass and muscle mass.<sup>4</sup> Therefore, studies examining the associations between more specific obesity metrics, such as BMI, waist circumference (proxy for visceral adiposity), whole body fat, and muscle mass and mortality in CKD should help address the obesity-paradox.

In this issue of *Kidney International Reports*, Lin and colleagues<sup>5</sup> studied the associations of BMI and body fat percentage with mortality in those with CKD. They included 326 Taiwanese patients with non-dialysis dependent CKD (mean estimated glomerular filtration rate 29 ± 15 ml/min per 1.73 m<sup>2</sup>) who had BMI and body fat percentage data (assessed using body composition monitor: a bioimpedance device). They were followed for a median duration of 4.9 years, during which 40 of them died (17 cardiovascular deaths and 23 noncardiovascular deaths). Even though BMI >28 kg/m<sup>2</sup> had higher specificity to diagnose obesity, it had low sensitivity (39.6%) to identify those with higher body fat as assessed by the body composition monitor. In the Cox proportional hazards model,

after adjusting for a limited number of covariates, BMI >28 kg/m<sup>2</sup> was associated with lower risk of death (hazard ratio: 0.23; 95% confidence interval: 0.07–0.71), but body fat >25% in men and >35% in women was associated with higher risk of death (hazard ratio: 2.75; 95% confidence interval: 1.28–5.89). In addition, Lin and colleagues<sup>5</sup> studied the associations of BMI and body fat percentage with all-cause death as continuous measures. Although high BMI was associated with decreased mortality, a J-shaped association between body fat percentage and mortality was noted. They further categorized patients into those with high BMI and high body fat, high BMI and low body fat, low BMI and low body fat, and low BMI and high body fat. Interestingly, compared with those who had high BMI and high body fat, those who had low BMI and high body fat had higher risk of all-cause death.

Strengths of this study included a well-defined cohort of population with CKD, use of appropriate BMI cutoff for the Chinese population, assessment of inflammatory markers and adiponectin, and the prospective collection of body composition data. However, several limitations temper our enthusiasm and argue for additional studies in this area and in other ethnic cohorts. Body composition data were assessed using a bioimpedance monitor, which is readily available but subject to limitations, especially in those with abnormal fluid status, such as CKD. This study lacked waist circumference, a proxy for visceral adiposity and a better predictor of mortality than BMI in CKD. More importantly, physical activity data were not available, a

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factor that is associated with mortality in those with and without kidney disease.<sup>6</sup> Given the limited number of events (death), the authors adjusted for 8 covariates, but several important confounding factors, such as malignancy and smoking, were not included. Finally, given the smaller number of events, associations between BMI and body fat with various causes of death were not studied. This is critical, as patients who had lower BMI could have had higher rates of malignancy-related deaths and lower BMI might just reflect their poor health status.<sup>7</sup>

How do these study results advance our knowledge? These results should be considered in the context of another publication from the same group of authors that addressed an important clinical question of whether increased muscle mass or body fat confers survival advantage in the CKD population.<sup>8</sup> This issue has been examined in the general population, and similar to the results of those studies, the authors noted that a high lean tissue index (reflective of muscle mass), but not high BMI or high fat tissue index, predicted a lower risk of both mortality and cardiovascular outcomes in CKD. However, it is important to note that lean body mass was not considered in the current analysis. An analysis of the independent contributions of lean tissue mass and body fat percentage to outcomes such as cardiovascular disease and mortality would be of much value; this can be only indirectly inferred from the group with high BMI and low body fat percentage.

Observational studies tend to analyze the prognostic significance of obesity metrics using baseline values, but availability of these measures at multiple time points during the course of CKD

would help us study the changes in body weight and their impact on cardiovascular disease and mortality in CKD. Recently, Ku *et al.*<sup>9</sup> reported that weight loss starts during the earlier stages of kidney disease and weight changes during the progression of CKD are independently associated with death even after the onset of end-stage renal disease. Due to the nature of this study, intentional and unintentional weight loss were not distinguished. Similarly, whether changes in body composition during the course of CKD affect cardiovascular disease and mortality in CKD merits future studies. Visceral fat is a major determinant of metabolic health and it predicts metabolic abnormalities and mortality better than subcutaneous adipose tissue in those without kidney disease. Visceral fat is metabolically active and secretes adipokines, including adiponectin, leptin, interleukin-6, and vascular endothelial growth factor, that pose cardiac and renal risks.<sup>10</sup> Whether factors associated with visceral adiposity pose the same risk for those with established CKD is unknown. Although the study by Lin *et al.*<sup>5</sup> provide data on total body fat percentage, it did not differentiate visceral and subcutaneous fat. Therefore, we need long-term studies that discriminate total, subcutaneous and visceral adiposity to enhance our understanding about the effect of different adipose tissue types in CKD.

Results of observational studies help us at best develop hypotheses, but cannot provide definitive conclusions to alter clinical practice. Interventional studies of intentional weight loss using diet and exercise or using bariatric procedures in those with morbid obesity on kidney disease progression and cardiovascular disease

are lacking. Recent pilot clinical trials have demonstrated the feasibility and the potential metabolic benefits of lifestyle modifications among the CKD population.<sup>11</sup> But, whether these short-term benefits translate to long-term cardiovascular and kidney benefits is unknown. More than 30% of the non-dialysis-dependent CKD population are obese, and given the dearth of clinical trial data, safety and beneficial effects of intentional weight loss modalities, such as lifestyle interventions, should be tested in large clinical trials for the CKD population.

## DISCLOSURE

All the authors declared no competing interests.

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