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Dissecting the Obesity Paradox in Patients With Obesity and CKD

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Obesity is a multidimensional risk factor for developing chronic kidney disease (CKD) and CKD progression.[1] Overweight patients living with advanced CKD are incentivized to lose weight to improve their health, mobility, and access to kidney transplantation.[2] However, a phenomenon known as the "obesity paradox" complicates the relationship between obesity and mortality in patients with advanced CKD and end-stage kidney disease. This paradox is defined by findings from observational epidemiologic studies demonstrating an inverse relationship between body mass index (BMI) and mortality.[3] This has led to a more nuanced understanding of how adipose tissue and fat-free mass (FFM) could mediate obesity's effect on patients with advanced CKD.[4,5] Indeed, prior studies in CKD studies have linked surrogates of muscle mass with worse quality of life, depression, malnutrition, and higher risk of hospitalizations and death in CKD populations.[6] However, it remains unclear to what extent the association of change in BMI or body weight with mortality is influenced by changes in lean mass and other nutritional and clinical characteristics.

In this issue of KI reports, Harhay *et al.*[7] used data from the longitudinal Chronic Renal Insufficiency Cohort Study to identify distinct, multidimensional weight loss phenotypes in CKD and end-stage kidney disease. They identified distinct trajectories of change in BMI, systolic blood pressure, and serum albumin levels among patients with CKD and obesity associated with increased risk of all-cause mortality. This was done using a joint multivariate longitudinal latent class model that considers the probability of belonging to a particular phenotypic class depending on the changes in these 3 variables over time. The second component of this model was to estimate the association between the identified clinical trajectory and mortality after adjusting for covariates using a proportional hazards regression model. Furthermore, they have conducted a secondary analysis to identify BMI and lean body mass trajectories associated with increased mortality risk.

The study identified 2831 Chronic Renal Insufficiency Cohort Study participants with obesity (BMI $\geq$30 kg/m^2) with a median age of 61 years, 47% prevalence of females, 50% non-Hispanic Black, and a median BMI of 35.6 kg/m^2. The median follow-up period was 6.8 years, with 26% initiating dialysis, 15% being waitlisted for a kidney transplant, and 5% receiving a transplant. At the end of the follow-up, 34% of the cohort had died. The authors characterized 6 latent classes in their model, with class 6 associated with the highest 5-year cumulative incidence of mortality of 6.8%, corresponding to an adjusted hazard ratio of 1.90 (95% confidence interval: 1.45, 2.50). Class 6 was characterized by steep and early BMI loss of >20%, initially stable then rising systolic blood pressure, and early decline in serum albumin followed by increasing levels. The secondary analysis evaluated another 6-class BMI and FFM model associated with mortality. This model revealed that class 1, characterized by early substantial BMI decline followed by BMI gain with a steep FFM decline over time, was associated with the highest level of mortality.

The current study underscores the heterogeneity in weight loss phenotypes and their differential association with risk of mortality. It distinguishes high-risk weight loss patterns as a phenotype of rapid weight loss, increasing systolic blood pressure, and declining serum albumin. Direct and indirect measures of FFM are also important for assessment of nutritional status and sarcopenia, or reduced muscle

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mass and function. Sarcopenia has been linked to poor outcomes independent of BMI across multiple populations, including patients with kidney disease.[5,8] The study also emphasizes the clinical relevance of measured FFM in interpreting risks associated with weight and BMI trajectories. Specifically, it demonstrates that patients with obesity and CKD experiencing a greater increase in BMI relative to their increase in FFM have a higher risk of death compared to those with a proportional gain of both values.

The strength of the current investigation by Harhay *et al*.[7] included the use of a sophisticated multivariate latent trajectory modeling strategy in a racially representative group of participants with CKD and obesity, with adjustments of important confounders including whether the weight loss was unintended. Limitations included an inability to distinguish specific weight loss strategies used by the participants in the Chronic Renal Insufficiency Cohort Study cohort. Second, it is unclear if the mortality risk associated with these weight loss phenotypes applies to populations with end-stage kidney disease treated with dialysis where higher muscle mass has been associated with greater survival.[9] Third, it is unclear how changes in tissue hydration status may influence the accuracy of FFM measures from bioelectrical impedance analysis in CKD.[8] Furthermore, reliance on bioelectrical impedance analysis may not be feasible in clinical practice, and more practical bedside measures of assessing muscle function such as physical performance testing should be evaluated. Future studies should investigate if longitudinal change in physical performance measures assessing functional muscle mass further distinguishes the risk associated with these trajectories independent of BMI, weight loss, and FFM.

Weight loss strategies preserving or improving muscle mass and function through healthy diet and exercise training are foundational to improving health in overweight and obese patients living with CKD. Indeed, previous randomized controlled trials had demonstrated that a low-intensity, home-based walking program has been shown to improve patients' functional capacity and cognitive function,[S1] and adding endurance training to a strengthening or balancing training regimen has been shown to improve muscle mass and physical performance in patients with advanced CKD.[S2] More research is needed to determine the optimal interventions for achieving a healthy weight loss pattern in patients with CKD while preserving or improving their muscle mass, strength, and endurance. These interventions have implications for reducing the burden of frailty and improving the quality of life in patients living with CKD.

DISCLOSURE

All the authors declared no competing interests.

SUPPLEMENTARY MATERIAL

Supplemental File (PDF)

Supplemental References.

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