COMMENT ON ZU ET AL.

Association of Body Weight Time in Target Range With the Risk of Kidney Outcomes in Patients With Overweight/Obesity and Type 2 Diabetes Mellitus. Diabetes Care 2024;47:371–378

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Zu et al. (1) found that a higher body weight time in target range (TTR) was associated with a decreased risk of a composite kidney outcome, which included a decrease in estimated glomerular filtration rate (eGFR) of ≥30% from baseline, progression to <60 mL/min/1.73 m^2 at any follow-up visit, or progression to end-stage kidney disease. Body weight TTR, defined as the proportion of time that body weight is within a specified range, is a novel metric in the management of individuals with overweight or obesity, with or without type 2 diabetes. This metric allows for evaluating the efficacy of weight management strategies, which can be useful for tailoring interventions to better preserve kidney function. However, several crucial considerations must be addressed before adopting this metric in clinical practice to inform decision-making.

The authors used serum creatinine along with the 2009 CKD-EPI estimating equation to derive eGFR (1). Because almost all creatinine stems from muscle tissue, serum creatinine is positively related to muscle mass (2). Estimating equations broadly account for muscle mass–related variability in creatinine by incorporating demographic variables such as age and sex, offering a more refined measure of GFR. An important assumption underpinning the accuracy of these equations is that muscle mass is typical for a given age and sex (2).

This assumption was demonstrably violated in the current study. Gallagher et al. (3) showed that approximately 1 kg of muscle mass was lost 2 years after the start of the Look AHEAD (Action for Health in Diabetes) trial, regardless of whether participants received diabetes support and education or abided by an intensive lifestyle intervention. It is unknown whether body weight TTR is associated with changes in muscle mass, but it is tempting to speculate that an inverse relationship exists; regaining muscle is generally troublesome, as evidenced by the observation that initial loss of trunk muscle in the trial was never regained, not even in the intensive lifestyle intervention group (3). The unfortunate consequence of muscle loss is overestimation of eGFR (2) and, consequently, inadvertently inflated false discovery rates for the current study's primary outcome, with 415 out of 435 events based on creatinine-based eGFR components (1).

More definitive answers may come from evaluation of GFR with endogenous filtration markers insensitive to variations in muscle mass, for which samples are readily available per the trial's design paper. A candidate alternative would be serum cystatin C. As a housekeeping gene product, cystatin C levels are stable amid fluctuating muscle mass (2) but are positively related to C-reactive protein levels (4). Reduced levels of C-reactive protein are among the many benefits of weight reduction (5), suggesting that a higher body weight TTR is associated with lower C-reactive protein levels. Revaluation of the effect of body weight TTR on kidney outcomes is clearly warranted. Part of this revaluation could involve investigating the association between body weight TTR and C-reactive protein levels. The absence of any association would support the reliability of cystatin C-based eGFR, providing an avenue to substantiate the initial findings of Zu et al. (1).

Duality of Interest. No potential conflicts of interest relevant to this article were reported.
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