Misclassification of Obesity in CKD: Appearances Are Deceptive

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In the short span of a century, obesity has transitioned from being viewed as a sign of good health to becoming one of the major health challenges of modern society. In 1832, the Belgian astronomer and statistician Adolphe Quetelet (1796–1874) noted that “other than the spurts of growth after birth and during puberty, the weight increases as the square of the height” (1). The Quetelet index of body weight remained buried in oblivion until Ancel Keys (1904–2004), under the new name of body mass index (BMI), proposed it in 1972 as an attainable community screening tool of fatness (2). Little did Quetelet anticipate the effect that his metric would have in public health. BMI and the World Health Organization BMI categories serve nowadays as protruding variables in population research addressing relationships between adiposity, health, and disease. The current widespread use of BMI as a measure of adiposity in the community and a predictor of health risk requires, however, an understanding of its limitations both on an individual basis and especially, in the clinical setting. These limitations are well known by nephrologists and include the inability of BMI to differentiate between body composition compartments (fat, muscle, and bone) or body fat distribution (abdominal versus peripheral), and to account for differences related to age, sex, ethnicity, and physical fitness. Of importance in our setting is the fact that BMI is confounded by fluid retention (3).

Meta-analyses consistently relate overweight and obesity compared with normal BMI with 1.5- to 2.0-fold increased risk of ESRD progression and death before RRT (4). However, a recent report including half a million United States veterans with CKD showed that low BMI categories equally associate with those risks (5). A recurrent discussion in such association studies is that BMI, when used in isolation, gives distorted prognostic information. Although high BMI categories likely represent fatness, diabetes, or dehydration, low BMI categories may indicate wasting and cachexia, deficient energy reserves, infection, or cancer (6,7). Although the effect of excess fatness on hyperfiltration, glomerular damage, and CKD progression is a matter of great concern, what happens to muscle tissue in the context of moderate advanced CKD has received less attention so far.

In this issue of CJASN, Sharma et al. (8) report on the largest study to date addressing body composition in community-dwelling adults with differing degrees of renal function. Using the 1994–2004 US National Health and Nutrition Examination Survey (NHANES), Sharma et al. (8) included 11,643 individuals who underwent dual-energy x-ray absorptiometry (DEXA) measurements and also had plasma creatinine or cystatin C values. On the basis of these results in a nationally representative population, Sharma et al. (8) showed that, throughout every eGFR strata considered, the true prevalence of obesity, as correctly assessed by DEXA body fat percentage, is much larger than that assessed by BMI. The proportion of BMI obese individuals with CKD stages 3 and 4 was 30%–35%, a figure similar to that of United States patients on incident dialysis in the classic report by Kramer et al. (9). However, obesity as measured by DEXA fatness was present in 50%–70% of the individuals. It is, therefore, possible that there is more obesity than meets the eye when looking at BMI only. These figures are intriguingly similar to our report on Swedish patients on dialysis (10): excess fatness was present in up to 65% of our patients, and the majority (>50%) of them was misclassified by BMI cutoffs. The reason for this considerable misclassification in both studies was, by subtraction, reduced muscle mass (sarcopenia), which in the study by Sharma et al. (8), increased almost linearly across worsening CKD strata and conveyed the extreme situation that 98% of obese individuals with sarcopenia were not correctly diagnosed by BMI.

This descriptive cross-sectional study leaves many questions unanswered. For instance, obese sarcopenia has been linked to increased risk of mortality in patients on dialysis (11), but what are the outcome consequences of sarcopenia and obese sarcopenia in nondialyzed CKD? Given that pre-ESRD body weight changes associate with postdialysis mortality risk (12) and that muscle mass loss is greater in elderly individuals with low eGFR (13), could this risk be attributed to specific changes in body composition? Furthermore, is the increase in sarcopenia prevalence explained by muscle disuse or uremia-induced muscle catabolism? Because available data—albeit limited—describe a rather low prevalence of malnutrition in nondialyzed CKD (14), I am more inclined to imply physical inactivity as a likely cause. Nevertheless, such body compositional changes (reduced muscle mass and increased fat mass, mostly in the abdominal region) are a prodromal feature of the normal aging process (15). Therefore, differences in the

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prevalence of sarcopenia in this study might just reflect differences in the age distribution of patients with and without CKD. It is noteworthy that, in the work by Sharma et al. (8), the linear increase in patients with sarcopenia across worsening CKD strata flattened out after standardization by age, and although Foley et al. (16) reported a higher prevalence of sarcopenia in individuals with CKD stage ≥3 in the NHANES than in those with normal renal function, simple adjustment for age abrogated this difference. Both aging and the abovementioned body compositional changes lead to frailty. In fact, changes in fat mass and muscle mass have been oppositely and independently correlated with frailty in patients on prevalent hemodialysis (17). Does CKD as such induce sarcopenia or—considering that CKD is a disease that appears in the elderly and frail (18)—are these sarcopenic conditions the main reason for sarcopenia and obese sarcopenia in CKD? To this already complex scenario, we must also consider the contribution of bone tissue given that sarcopenia in CKD stages 3 and 4 has been shown to be accompanied by higher odds of osteoporosis, osteopenia, and vitamin D deficiency (19).

Methodological challenges when defining the exposures in the study by Sharma et al. (8) limit its applicability in the clinical setting. First, Sharma et al. (8) based their findings on a cohort-based cutoff of fatness (>60% of the study population distribution). Because cutoffs of percentages of body fat that correspond to BMI categories substantially vary depending on age, sex, and race-ethnicity, the recent NHANES-derived classification (20) taking these demographic factors into account may have been more appropriate. Second, Sharma et al. (8) used a United States reference population for the diagnosis of sarcopenia, but appropriate country-, age-, sex-, and ethnic-specific cutoffs for other countries are usually lacking. The choices of cutoffs and reference populations are not inconsequential, because the prevalence of sarcopenic obesity in adults in the NHANES varied up to 26-fold depending on the many research definitions available in the literature (21), reflecting overall a profound lack of agreement among scientific societies. Our own attempts to accurately classify sarcopenia in patients on dialysis yielded a similar wide variability (22). There is certainly a need to establish consensus criteria that can be reliably applied across clinical and research settings.

However, although the scientific community continues to debate the reference limits of fat and muscle, the important take-home message of this study is that body composition assessment offers much more clinical information than simple measures of body size (8). This has implications for both researchers deciphering the risk associated to obesity and frailty and also, clinicians and renal dietitians assessing nutritional status. Hopefully, the study of Sharma et al. (8) may awaken renewed interest in the need for body composition monitoring in earlier stages of CKD. Given that the misclassification of obesity by BMI in CKD is so large, one must be cautious in assuming that the ideal BMI for this patient population can be derived by simple extrapolation from community-based cutoffs. A better understanding of the nature of body compositional derangements offers, as a next step, better opportunities to tailor effective nutritional therapies that would result in sought-after improvements in body composition and nutritional status. Such results could be achieved by implementing adequately composed diets, administering anabolic agents, implementing controlled exercise programs, or likely, using a combination of all three (23). Evidence in this regard, albeit positive (24–27), is mainly confined to healthier younger patients and otherwise, currently rather scarce in patients with CKD not on dialysis. Rosenberg (28) first highlighted in 1997 the functional significance of the age-related loss of muscle mass by naming it sarcopenia. Many investigations thereafter have followed into the functional consequences of low lean mass. Although it is becoming apparent that low muscle mass, by itself, is a poorer predictor of functional outcomes than low muscle strength (29,30) and that sarcopenia and obesity exert a synergistic effect on physical performance in the elderly (31), studies investigating how sarcopenia and, especially, obese sarcopenia along the wider CKD spectrum may affect frailty, functional mobility, and outcomes are warranted.

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Disclosures

None.

References


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See related article, “Association of Sarcopenia with eGFR and Misclassification of Obesity in Adults with CKD in the United States,” on pages 2079–2088.