The Enlarging Body of Evidence: Obesity and Chronic Kidney Disease

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Published online ahead of print. Publication date available at www.jasn.org.

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ISSN: 1046-6673/1706-1501

Obesity is well recognized as a determinant of cardiovascular and other chronic diseases (1–4). More recently, obesity and the metabolic syndrome have been recognized as risk factors for the development and progression of chronic kidney disease (CKD). In this issue of *JASN*, Ejerblad et al. (5) present results from a population-based case-control study conducted in Sweden from 1996 to 1998, examining the association of lifestyle factors with CKD. In this report, the authors compared the likelihood of prevalent CKD, defined as a serum creatinine concentration consistently >3.4 mg/dl in men and >2.8 mg/dl in women, by body size determined using the Quetelet (body mass) index, with separate analyses conducted for current values, highest-ever values, and Quetelet index at age 20 yr. Participation rates were relatively high (78% in cases, 75% in controls). Analyses were adjusted for age, education or income, and the use of tobacco, alcohol, and analgesic medications; stratified analyses by diabetes status and the presumed cause of CKD were also presented.

The current Quetelet index was not associated with the odds of prevalent CKD. When considering the highest ever Quetelet index, the odds of prevalent CKD were increased 1.4-fold among men classified as overweight (Quetelet index 25 to 29.9 kg/m²), 2.7-fold among men classified as obese (Quetelet index 30 to 34.9 kg/m²), corresponding to class I obesity by the National Heart, Lung and Blood Institute [NHLBI] standards [6]), and 4.4-fold among men classified as obese (Quetelet index 35 kg/m²). The odds of CKD among women were significantly increased only among women with NHLBI class II or higher obesity (Quetelet index ≥35 kg/m²). The odds of CKD among women were significantly increased only among women with Quetelet index ≥35 kg/m². When considering Quetelet index ≥25 kg/m² at age 20 yr, the odds of prevalent CKD were increased three-fold in men and women. The association between highest-ever Quetelet index and prevalent CKD was strongest among persons with diabetes; Quetelet index ≥25 kg/m² at age 20 yr was associated with prevalent CKD among all primary disease subgroups.

The results presented by Ejerblad et al. are consistent with several recent reports on the link between obesity (rather, proxies of obesity) and kidney disease. Data from both the Framingham Offspring cohort (7) and the Hypertension Detection and Follow-Up Program (8) showed that higher Quetelet index was associated with an increased risk of new onset CKD (defined in the first study as an estimated GFR [eGFR] <60 ml/min per 1.73 m² in women and <80 ml/min per 1.73 m² in men, and in the second study as eGFR <60 ml/min per 1.73 m² or ≥1+ proteinuria).

Considering the broader criteria for the metabolic syndrome, Chen et al. (9) showed there was a cross-sectional association between prevalent CKD (defined as eGFR <60 ml/min per 1.73 m²) with the metabolic syndrome in the Third National Health and Nutrition Examination Survey. Kurella et al. (10) extended these findings using data from the Atherosclerotic Risk in Communities cohort study, showing an increased risk of incident CKD (defined as eGFR <60 ml/min per 1.73 m²) among patients with metabolic syndrome, even after adjustment for Quetelet index and other factors.

Arguably the strongest evidence linking obesity and kidney disease is derived from two large cohort studies, one in Japan and the other in the United States, linking body size with the development of ESRD. Iseki et al. (11) showed an increased risk of ESRD with higher Quetelet index, although the association was evident only in men. Hsu et al. (12) showed an increased risk of ESRD with higher Quetelet index over a median follow-up of 21 yr. Compared with persons with Quetelet index 18.5 to 24.9 kg/m², persons who were overweight (relative risk [RR] 1.87, 95% confidence interval [CI] 1.64 to 2.14), and those with class I (RR 3.57, 95% CI 3.05 to 4.18), class II (RR 6.12, 95% CI 4.97 to 7.54), and class III obesity (Quetelet index ≥40 kg/m², RR 7.07, 95% CI 5.37 to 9.31) were significantly more likely to develop ESRD. The relation between excess weight and risk of ESRD appeared to persist even after accounting for the presence or absence of baseline diabetes and hypertension.

The study by Ejerblad et al. fills an epidemiologic gap left open by population studies examining either end-stage or early-stage CKD. Based on the sex-specific serum creatinine concentrations selected to define CKD in Ejerblad et al., most of the 926 cases were CKD stage 4 or 5 (eGFR < 30 ml/min per 1.73 m²) based on the National Kidney Foundation’s Kidney Disease Quality Outcomes Initiative (K/DOQI) classification scheme (13). Other findings are noteworthy. The absence of an association between current Quetelet index and CKD might be explained by weight loss as a consequence of advanced CKD, as the authors suggest. However, it may also be a result of competing mortality risks for older persons with longer standing
obesity. While the authors did not identify a statistically significant Quetelet index by sex interaction, the association between Quetelet index and CKD appeared to be stronger in men than in women, as suggested in other studies. Whether this reflects a difference in competing mortality risks, misclassification of adiposity (14), or a true biologic difference is unknown. Finally, while commonly used, the Quetelet index may not be the ideal proxy for adiposity, particularly among persons with CKD. The Quetelet index does not reliably reflect differences in body composition, where higher body weight associated with muscle and fat (or edema) cannot be distinguished. Indeed, studies in the general population have demonstrated higher risks of death and cardiovascular disease associated with larger waist circumference, even after adjusting for Quetelet index (15,16). Studies in ESRD have shown that other proxies of body composition (e.g., phase angle and vector length by bioelectrical impedance analysis) also have prognostic significance (17,18).

In summary, over the past several years, several cross-sectional and longitudinal studies from diverse populations have secured the importance of higher body weight for height as a risk factor for the prevalence and progression of CKD. The nephrology community has been perplexed and somewhat paralyzed by the paradoxical association between higher body weight for height and survival among hemodialysis patients (19–21), a finding almost certainly explained by residual confounding by malnutrition and competing mortality risks in the years preceding ESRD. The Ejerblad et al. study augments the ever-fattening evidence base that obesity is linked to kidney disease. National and international educational efforts on ever-fattening evidence base that obesity is linked to kidney disease. National and international educational efforts on

References


See related article, “Obesity and Risk for Chronic Renal Failure,” on pages 1695–1702.