Obesity and kidney disease: from population to basic science and the search for new therapeutic targets

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The global burden of kidney disease is increasing strikingly in parallel with increases in obesity and diabetes. Indeed, chronic kidney disease (CKD) and end-stage renal disease (ESRD) coupled with comorbidities such as obesity, diabetes, and hypertension cost the health care system hundreds of billions of dollars in the US alone. The progression to ESRD in patients with obesity and diabetes continues despite widespread use of inhibitors of the renin-angiotensin-aldosterone system (RAAS) along with aggressive blood pressure and glycemic control in these high-risk populations. Thereby, it is increasingly important to better understand the underlying mechanisms involved in obesity-related CKD in order to develop new strategies that prevent or interrupt the progression of this costly disease. In this context, a key mechanism that drives development and progression of kidney disease in obesity is endothelial dysfunction and associated tubulointerstitial fibrosis. However, the precise interactive mechanisms in the development of aortic and kidney endothelial dysfunction and tubulointerstitial fibrosis remain unclear. Further, strategies specifically targeting kidney fibrosis have yielded inconclusive benefits in human studies. While clinical data support the benefits derived from inhibition of the RAAS, there is a tremendous amount of residual risk for the progression of kidney disease in individuals with obesity and diabetes. There is promising experimental data to suggest that exercise, targeting inflammation and oxidative stress, lowering uric acid, and targeting the mineralocorticoid receptor signaling and/or sodium channel inhibition could improve tubulointerstitial fibrosis and mitigate progression of kidney disease in persons with obesity and diabetes.

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Chronic kidney disease (CKD) is a global public health concern. Recent data highlight that roughly 10% of the world's population has CKD,[1] similar to the 10% of the population in the United States reported to have CKD.[2,3] Recently in the US, rates of CKD, including end-stage renal disease (ESRD), which had substantially increased in the late 1990s and early 2000s, have plateaued, with increases observed only in the aging population.[4] CKD rates in the US may have stabilized partly due to improved awareness and treatment of diabetes; however, this is in contradistinction to the global increases in diabetes such as in Asian countries, where diabetic kidney disease appears to have increased.[4,5] Further, global trends suggest that CKD continues to rise in lower- to middle-income countries that are experiencing a transition of noncommunicable diseases such as obesity, diabetes, hypertension, and CKD,[6–8] where the provisions for renal replacement therapy are limited and the presence of CKD contributes to 1 million deaths annually.[9]

Recent data from the Global Burden of Disease, Injuries and Risk Factors study (GBD) suggest that global morbidity and mortality related to CKD are rising,[9–11] from the 27th leading cause of global morbidity and mortality in 1990 to the 18th in 2010,[9] and CKD is thought to be the 1 non-communicable disease that contributed the most to global morbidity and mortality increases in the past 20 years.[12] More specifically, CKD-related disability is 1 of the more prominent causes of global morbidity, ranking 15th and then 20th for disability and disability-adjusted life years.[10,11] Care for management of ESRD alone in the US is 1 of the leading expenditures (roughly 49 billion USD), and this cost does not include associated expenditures for managing comorbid diabetes, hypertension, and cardiovascular disease, which can equate to an additional 150 billion USD.[13,14] Thus, the clinical dilemma regarding CKD is the disproportionate use of resources for the care of patients with CKD that often still progresses to ESRD and associated cardiovascular mortality.

The obesity epidemic is increasingly recognized as the driving force behind the global expansion of diabetes and CKD.[15] Data from the World Health Organization's Global Health Observatory suggest that obesity prevalence has more than doubled in the past 3 decades and includes almost 500 million individuals.[16] In this context, the increase in obesity rates over the past several decades, along with a shift in the availability of inexpensive, energy-rich food stores and improved global distribution systems, have contributed much to the current pandemic.[17] These Global Health Observatory data suggest that the greatest increases occurred in the Americas and in China, while the lowest increases occurred in Southeast Asia. The increase in the Americas is thought to be related to altered energy intake, with the increased consumption of diets high in fat and refined carbohydrates, and sedentary lifestyles[18,19] Given the rising incidence of global obesity, diabetes, and associated kidney disease—albeit at differential rates across cultures—it is important to understand the relationship between obesity and kidney disease. Understanding the underlying mechanisms by which obesity promotes kidney injury and development of CKD is critical to the development of interventions that prevent the progression of early obesity and kidney disease.

Obesity and risk for CKD and ESRD: population-level evidence

As discussed, there has been much interest in the CKD and ESRD trends not only in Western countries but across the globe. While CKD trends in Western countries such as the US may have stabilized in recent years, global trends continue to rise and mirror obesity trends. This global expansion of obesity has been linked to CKD in many populations. Annual data from the United States Renal Data System indicate continued increases over time in mean weight and body mass index (BMI) that strongly correlate to incident cases of ESRD.[20,21] These findings suggest a rise in obesity among individuals with ESRD, and similar data in Japan support a rise in obesity among individuals with CKD and ESRD.[22] There are few data from national-level registries in other countries or population-level data to draw upon. However, there are 2 studies that report a link between increases in body size and incident ESRD, 1 from Japan and 1 from the US.[23,24] In a study of more than 100,000 screened individuals in Japan, the risk for incident ESRD rose for those with a BMI > 25 kg/m^2 even after adjusting for clinical confounders such as age, sex, hypertension, and proteinuria.[23] In a US population, a similar observation indicated a graded relationship whereby increasing BMI (<25, 25–29.9, 30–34.9, and >35 kg/m^2) led to a proportional increase in incident ESRD over a median follow-up of 21 years that persisted after accounting for baseline diabetes and hypertension.[24] These data offer clear evidence of the rise of obesity among the CKD and ESRD population in the US and the risk for incident ESRD in 2 regions of the world that collect data of this nature.

However, there have also been cohort studies from various cultures, both Western and Eastern, derived from registry data of community-based screenings that establish the relationship between increases in BMI and new-onset CKD.[25–27] For example, a population-based study from Western Europe using a case-control cohort examining the relative risk for incident CKD (estimated glomerular filtration rate [GFR] $<$ 60 ml/minute [min]/1.73 m^2) and BMI demonstrated a greater risk in those with a BMI ≥ 25 kg/m^2 relative to those with a BMI ≤ 25 kg/m^2.[25] Further, in men with a BMI ≥ 30 kg/m^2 (i.e., obese) and women with BMI ≥ 35 kg/m^2 (i.e., morbidly obese), the risk for CKD was similar. Even after controlling for the confounding presence of diabetes and hypertension, the association between increased BMI at age 20 years and lifetime risk for incident CKD persisted. Data from 2 other studies conducted in the US, the Framingham Offspring cohort and the Hypertension Detection and Follow-Up Program, demonstrate that a higher BMI led to a higher incidence of new-onset CKD (an estimated GFR $<$ 60 ml/min/1.73 m^2 or proteinuria).[26,27] Results from 2 Japanese cohort studies similarly demonstrated that increases in BMI lead to increases in incident, new-onset CKD.[28,29] In both of these community-based Japanese populations, the risk for incident CKD, as defined by an estimated GFR $<$ 60 ml/min/1.73 m^2, was increased in those with obesity, and there was a graded relationship of increasing risk with advancing stage of CKD.

Data from other studies also suggest that obesity contributes directly and independently to the development of microalbuminuria. In a small prospective cohort of individuals monitored for 20 years after unilateral nephrectomy, those with obesity had a higher rate of incident albuminuria relative to nonobese individuals,[30] a finding mirrored in those with IgA nephropathy.[31] In considering the general population, data from a secondary analysis of the Prevention of Renal and Vascular End-stage Disease study (PREVEND) suggest that the majority of all cases of microalbuminuria occur in overweight individuals with BMI $>$ 25 kg/m^2 without diabetes or hypertension.[32,33] In 1 analysis of this Dutch population, the presence of increases in BMI $>$ 25 kg/m^2 enhanced the risk impact of salt intake on the development of albuminuria.[33] These collective data suggest that obesity not only contributes to progressive loss of kidney function and incident ESRD, but also elicits loss of kidney function in healthy individuals, contributing to incident, new-onset CKD.[33,34] Each of these studies from differing regions of the world supports a clear association between obesity and CKD.

However, there is a significant amount of literature examining the relationship between obesity and CKD in the context of other metabolic abnormalities such as insulin resistance, hypertension, and dyslipidemia (e.g., the metabolic syndrome, or cardiorenal metabolic syndrome). It is thought that obesity drives the development of these metabolic derangements, and 2 studies derived from a US population demonstrate this link between obesity, the metabolic syndrome, and CKD independent of the contributions of diabetes and hypertension, both important established risk factors for CKD development.[35,36] Using data from the Third