CKD progression: a risky business

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In 2006, the very strong association between obesity and end-stage kidney disease (ESKD) risk was demonstrated among 320,252 adults enrolled in the Kaiser Permanente health system. These individuals volunteered for a screening health checkup between 1964 and 1985 and were followed until death, dialysis initiation or until 31 December 2000. Class III obesity or body mass index (BMI) ≥40 kg/m2 were associated with ~600% higher risk of ESKD compared to an ideal BMI (18.5–24.9 kg/m2) [1]. In the 21st century, morbid obesity emerged as one of the strongest and most important modifiable risk factors for ESKD. These findings dramatically redirected attention to nutrition and lifestyle factors as mediators for chronic kidney disease (CKD) risk. However, it still remains unclear whether obesity merely heightens Stage 1–3 CKD incidence or accelerates CKD progression among individuals with established CKD or both.

Excess weight is one of the strongest risk factors for ESKD [2] but associations between obesity and incident CKD are quite modest [3, 4]. Clearly, obesity itself is not a sufficient risk factor for the development of ESKD, given that over one-third of adults in many industrialized countries are obese while kidney disease prevalence is substantially lower. Less quantified is the impact of obesity on kidney disease progression among individuals with established CKD. This discrepancy may be explained by amplification of obesity’s deleterious effects in the setting of decreased glomerular filtration rate (GFR). The increased metabolic needs in the obese state translate in to an increased absolute GFR [5], which may result in heightened intra-capillary glomerular pressure and subsequent glomerulosclerosis depending on nephron number [6]. The glomerular hypertrophy that frequently accompanies obesity may accelerate kidney injury by increasing glomerular capillary wall tension and susceptibility to barotrauma [7] and decreasing podocyte density [8]. Thus, biologic plausibility exists to support a causal relationship between excess weight and rapid kidney function decline in the setting of established CKD. However, clinical data supporting this theory remain limited.

In this issue of Nephrology Dialysis Transplantation, Brown et al. [9] examine the association between BMI and kidney disease progression among 499 adults with established Stage 3–5 CKD in the absence of diabetes [9]. Using serum creatinine measured annually, GFR was estimated (eGFR) using the Modification of Diet in Renal disease Formula. Change in eGFR was then assessed by obesity presence defined as a BMI >30 kg/m2. A total of 131 patients with BMI ≥30 kg/m2 were included and BMI in this group ranged from 30.0 to 52.4 kg/m2. Among the 368 patients with BMI <30 kg/m2, BMI ranged from 13.2 to 29.9 kg/m2. The mean follow-up period was ~3 years but this varied substantially with some individuals being followed for <1 year while others were followed as long as 84 months. An average of three eGFR measurements was available for each individual. Overall, the analysis showed no significant difference in annual eGFR decline by obesity status with eGFR in the non-obese declining by 1.77 versus 1.28 mL/min/1.73 m2/year in the obese group. The authors suggested that the null findings reflect the indolent course of obesity-associated kidney disease. It is also possible that the null effects were due to methodological issues of the study, which demonstrates the difficulties in quantifying kidney disease progression.

In the study by Brown et al., obesity was defined by BMI, a function of both muscle and fat, which does not quantify regional adiposity [9]. Unlike BMI, abdominal obesity does not correlate with muscle mass and is tightly linked with traditional CKD risk factors, cardiovascular disease and mortality even after adjustment for BMI [10–13]. The use of serum creatinine-based GFR measures influenced by muscle mass likely confounds the issue, but few studies have examined the effect of BMI on creatinine-based GFR-estimating equations [14]. This confounding could be curtailed with the use of direct or cystatin C-based GFR measurements but investigators still face other complex issues when quantifying kidney disease progression. Another limitation of the study was the lack of important clinical data such as urine protein excretion as well as kidney disease etiology, which may be difficult to ascertain in a clinical cohort. Urine protein excretion in conjunction with GFR has important prognostic implications for progression of CKD as well as cardiovascular disease and mortality [15–17].

Plotting repeated GFR measurements over time will demonstrate a sawtooth pattern in most patients. The substantial intra-individual variation is due to the multiple...
nutritional and demographic factors that influence GFR and vary over time. Thus, progression of kidney disease as assessed by change in GFR is frequently non-linear. An analysis of the African American Study of Kidney Disease and Hypertension (AASK) examined longitudinal GFR trajectories and found that 41.6% in that cohort had an >90% probability of having either a GFR trajectory that was non-linear or a prolonged period of non-progression. Non-linear GFR progression, defined as a difference in mean GFR slope between the first half of the follow-up period versus the last half of the follow-up period $>3$ mL/min/1.73 m$^2$/year, was present in approximately one-third of AASK participants (1), a group without diabetes at baseline [18]. Thus, discerning GFR progression without adequate follow-up time is extremely problematic. In fact, the follow-up period likely needs to be at least 5 years even within a cohort with an average GFR decline $>4$ mL/min/year [19, 20]. Repeated measures of any biomarker are subject to random error and change in eGFR can simply be due to random error and not due to kidney disease progression. Individuals with extreme values (high or low eGFR) will be most likely to demonstrate the largest changes in GFR when measured at a subsequent time point. This phenomenon is called regression to the mean and can be assessed by plotting change in eGFR by baseline eGFR values. Thus, it is important to adjust for baseline values when assessing change in any biomarker. Once an individual dies or initiates dialysis, he is excluded from subsequent follow-up in studies that examine GFR slope or change. Such individuals may have lower baseline eGFR and/or demonstrate rapid kidney disease progression. These persons will have the least number of eGFR measurements and shortest follow-up time. Standard regression techniques for assessing GFR slope weigh heavily on individuals with the most data points. Differences in GFR slope estimates between two groups are then closer to zero compared to methods that account for the differing follow-up times such as mixed models [20]. What may be more useful is to utilize a dichotomous outcome to define CKD progression such as a $\geq5\%$ decline in eGFR compared to baseline values [21] or a $>3$ mL/min/1.73 m$^2$/year annual eGFR decline [22].

Another method to assess kidney disease progression is to examine differences in the initiation of renal replacement therapy (RRT) by obesity group. Risk is simply defined as the number of patients who reach the end point (RRT) divided by the total number at risk in that group during the follow-up period. So for the non-obese group, this would be 72/368 or 19.6% and for the non-obese group, this would be 20/131 or 15.2%. Thus, the overall risk for RRT was very similar between the obese and non-obese groups. However, risk does not gauge the time it takes for disease to occur. The rate or incidence density of a disease does provide information on how fast disease occurs. A rate may be defined by the number of events (such as number who initiate RRT) during the follow-up period divided by the total number of person-years of follow-up which is often reported as 100, 1000 or even 100,000 person-years depending on the length of the study. The inverse of a rate provides information on how fast disease is occurring (number of person-years of follow-up needed to see one event). Although differences in mean eGFR decline did not differ substantially between the non-obese and obese group, the crude rate of RRT was $\sim$2-fold higher in the obese group versus the non-obese group in this study. Among patients with Stage 4 CKD at baseline, rate of RRT was over 3-fold higher among the obese group compared to the non-obese group. Unfortunately, 95% confidence intervals were not provided. These findings were noted despite the inclusion of individuals with BMI $<18.5$ kg/m$^2$ in the non-obese group. Individuals with BMI below the ideal range may have comorbid conditions that impact outcomes including need for RRT and mortality.

Since the 1970s, obesity has been linked with progressive kidney disease and some suggest an emerging epidemic of obesity-related glomerulopathy [23–25]. Over 20 years ago, several independent groups demonstrated the protective effects of caloric restriction for retarding

Fig 1. Probability of non-linear progression of GFR by baseline characteristic among 846 participants of the AASK with at least 3 years of follow-up. Non-linear GFR progression defined as mean GFR slope differing by $>3$ mL/min/1.73 m$^2$/year between the first half of the follow-up period compared to the second half of the follow-up period [18].

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kidney injury in subtotal nephrectomy animal models such as the spontaneously hypertensive rat with uninephrectomy regardless of liberal protein intake [26–29]. Caloric restriction and other lifestyle interventions have been the most poorly utilized interventions for prevention of CKD and CKD progression. Although this study showed no association between obesity and eGFR progression, readers must be cognizant of the substantial difficulties in analyzing kidney disease progression. Another similar study of 125 individuals with CKD in the absence of diabetes found that baseline BMI was strongly associated with faster CKD progression [30]. This study was smaller than Brown’s study but included information on proteinuria and individuals were followed at least 5 years.

These conflicting observational studies add to the large body of literature on obesity and kidney disease that now spans 40 years. Observational data show that intentional weight loss among overweight and obese individuals with overt proteinuria leads to substantial reductions in urine protein excretion [31]. Weight loss after bariatric surgery in morbidly obese individuals without kidney disease dramatically improves kidney disease risk factors including systolic blood pressure and insulin resistance [32]. While we applaud the efforts of Brown and others to disentangle systolic blood pressure and insulin resistance [32], we remain enthusiastic about the efforts that focus on well-designed randomized controlled trials of weight loss for obese individuals with CKD. We believe such efforts are urgently needed.

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References


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