Obesity-Related Glomerulopathy and Single-Nephron GFR

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During the past 2 decades, an epidemic of obesity has emerged, largely in the Western world but also emerging in less developed countries as well. According to the National Health and Nutrition Examination Survey, the prevalence of obesity in the United States was 30.5% in 1999 to 2000 and increased to 42.4% in 2017 to 2018.[1] A seminal study by Hsu and colleagues showed that compared to subjects with normal body weight, those with an increasing level of obesity (from moderate to extreme) had a "dose-dependent" increase in relative risk for developing kidney failure (also known as end-stage kidney disease [ESKD]).[2] High body mass index (BMI), a common metric used to define obesity, was an independent predictor of ESKD, even after adjusting for many clinical characteristics, including baseline blood pressure and diabetes status.

In a small fraction of obese subjects, a clinical—pathological syndrome known as obesity-related glomerulopathy (ORG) develops. This syndrome is clinically characterized by proteinuria, often in the nephrotic range, usually unaccompanied by edema or hypoalbuminemia, and by a very indolent progression, in the absence of any other known cause for a glomerulopathy.[3] The histologic hallmark of ORG is glomerulomegaly, which is likely consequent to increased metabolic demand, and functionally is evident as an increase in total glomerular filtration rate (GFR).[4] The glomerulomegaly is commonly associated with lesions of focal and segmental glomerulosclerosis (FSGS; of the not-otherwise-specified or peri-hilar histologic variants of the FSGS lesion) when moderate to severe proteinuria is present.[3] The underlying mechanism for increased GFR (hyperfiltration) is increased glomerular capillary filtration surface area accompanied by increased glomerular plasma flow and intracapillary hydrostatic pressure. An isolated increase in glomerular capillary surface alone is likely insufficient to cause hyperfiltration, as filtration pressure equilibrium by the end of the glomerular capillary network is presumed to be present. It has been postulated that the higher GFR (hyperfiltration) in very obese individuals is the result of an increased transcapillary hydraulic pressure difference in glomeruli. In a follow-up study, the same group subsequently showed that weight loss helped in reducing glomerular hyperfiltration.[5]

In this issue of *KI Reports*, Okabayashi and colleagues made an important next step in studying glomerular hyperfiltration in ORG,[6] by estimating single-nephron estimated GFR (SNEGFR) in 48 obese Japanese patients (BMI >25 kg/m^2) using the approach developed in healthy living kidney donors at Mayo Clinic.[7] There are 2 major methodological differences between these 2 studies. First, in the Mayo Clinic study, the authors used measured GFR (calculated by urinary iothalamate clearance), whereas the current study used a serum creatinine—based estimated GFR, modified for a Japanese population, de-indexed for body surface area (BSA). Second, the Mayo Clinic study used contrast enhanced pre-donation computed tomography (CT) scans that allowed quantification of kidney cortex volume separately from medulla, whereas the current study estimated the cortex volume from the kidney volumes obtained from the unenhanced CT scans. The mean SNEGFR was 59 ± 21 nl/min and 64 ± 21 nl/min in the nonobese and obese controls, respectively, and 97 ± 43 nl/min in the ORG subjects with grade 1 and grade 2 CKD. This should be compared to the value for single-nephron GFR (SNGFR) of 80 ± 40 nl/min (assessed by measured, not estimated, total GFR) found in

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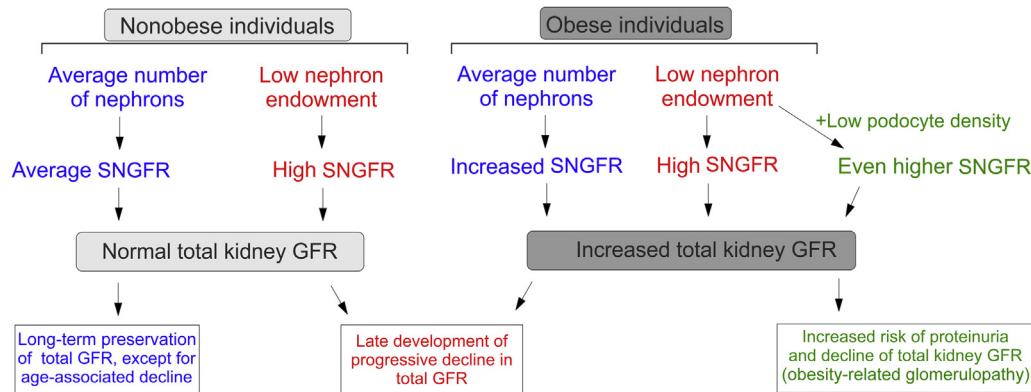
Figure 1. Conceptual diagram of how nephron endowment and podocyte density may influence increased single-nephron glomerular filtration rate (SNGFR) and proteinuria in obesity-related glomerulopathy (ORG) patients. In nonobese individuals, only low nephron endowment has been associated with high SNGFR to allow normal total glomerular filtration rate (GFR), and long-term risk of progressive GFR decline. In obese individuals, SNGFR is increased, more so in individuals with low nephron number versus those with average nephron number. All studies thus far suggest that in obese individuals, low nephron endowment with low podocyte density ultimately leads to proteinuria, increased glomerulosclerosis, and very high SNGFR, which eventually lead to decline in total GFR and development of clinically evident chronic kidney disease.

normal healthy kidney donors in the Mayo Clinic study.[7] Moreover, the authors also calculated single-nephron urine protein excretion (SNUPE), by dividing 24-hour urine protein levels by the number of functional (nonsclerotic) glomeruli.

Compared to control subjects (obese and nonobese kidney donors), the 25 ORG patients with preserved kidney function (CKD grades 1 and 2) had larger glomeruli (volume in cubic millimeters [mm³]), lower glomerular density (number of glomeruli per cubic millimeter in renal biopsy specimen), more glomerulosclerosis, and similar total number of nephrons. Interestingly, ORG patients had higher estimated total GFR than nonobese or obese controls. The net effect of this finding was higher SNEGFR in ORG patients than in nonobese or obese controls. Obese donors had a slightly higher GFR and SNEGFR compared to nonobese donors. This latter finding is in agreement with the Mayo Clinic data showing higher GFR and SNGFR in obese kidney donors.[7] Another important finding is significantly higher 24-hour urine protein excretion in ORG patients. Overt proteinuria combined with significantly larger glomeruli is

in agreement with recently proposed podometric hypothesis of secondary FSGS by Hodgin and colleagues.[8] With increasing obesity, glomeruli become enlarged, and podocytes hypertrophy (as they cannot undergo division and de-differentiation, to cover the expanded glomerular capillary loops. However, after a certain point, the "stressed" podocytes can no longer hypertrophy, and a catastrophic chain of event begins, with foot process effacement, podocyte detachment, and enhanced glomerular permeability. A lesion of FSGS ensues, and, after massive podocyte detachment occurs, the glomerular tuft collapses, with a global (solidified) glomerulosclerosis and a loss of function as a final stage.

When the authors further compared 5 ORG subgroups (based on chronic kidney disease [CKD] stage), it was found that loss of function (decline in estimated glomerular filtration rate [eGFR]) closely followed the decline in total number of nephrons. As a net effect, SNEGFR appeared to be stable in the stages G1, G2, and G3a, and with a declining trend in stages G3b and G4/5. Interestingly, the decline in SNEGFR in the last 2 CKD stages is followed by the most

significant protein leak, as evident by higher levels of both 24-hour protein and SNUPE. Another interesting finding was that glomerular size was similar across all 5 CKD subgroups. From the functional standpoint, this implies that as the response to obesity, glomeruli can hypertrophy only to a certain size, which maximizes early in the evolution of ORG. After a prolonged stress on podocytes, in the last 2 stages of CKD, there is progressive loss of nephrons, decline in total GFR and SNEGFR, and protein leak. All of these findings remain unchanged when limited to 30 ORG patients who received antihypertensive drugs at the time of biopsy.

From the clinical perspective, a key question is why only some obese individuals develop ORG changes and progress to advanced CKD stages. The authors considered that lower nephron endowment (from birth) or acquired nephron loss may be the predisposing factor that eventually leads to ORG phenotype. However, finding of a similar number of nephrons in ORG patients with preserved renal function and obese and nonobese kidney donors did not support this hypothesis. It is

important to point out a limitation that pertains to adequacy of kidney biopsy samples in kidney donors. Biopsy samples from ORG patients (average area 9.5 mm^2) were 3 times larger than donor biopsy samples (average areas 2.7 mm^2 in nonobese donors and 3.3 mm^2 in obese donors). A follow-up study is needed to clarify this issue using similar biopsy sample size across all studied groups of patients. Previous reports have also shown that low glomerular density is seen in renal biopsy samples of subjects with ORG,[S1] but this does not seem to predict the number of glomeruli when quantitated by combined renal biopsy and CT—based methods, such as those used by the Mayo Clinic group. Low glomerular density could be explained by combined glomerular and tubular hypertrophy, decreasing the number of glomeruli seen in the 2-dimensional renal biopsy assessment (larger tubules are pushing glomeruli away from each other, thereby reducing their observed density). Thus, low glomerular density is the consequence and not the cause of ORG. It also must be recognized that estimation of GFR using serum creatinine—based equations were developed in non-obese individuals and are not validated in obese individuals. A study from 2014 found low accuracy of eGFR in patients with BMI >40 kg/m^2 and when eGFR was >60 ml/min.[S2] The authors of this study proposed that in these individuals, GFR should be indexed per BSA using ideal body weight, not actual body weight. Importantly, the Okabayashi et al. study used a creatinine-based estimate for eGFR not indexed to BSA or ideal weight—based BSA.

A second hypothesis that could explain why only some obese subjects develop ORG, and that progression is very slow and

variable in ORG, is based on reports showing that there is variability in number of podocytes per glomerulus in both children and adults.[9,S3] Another important caveat is that, besides this variability in podocyte numbers (where the large glomeruli have more podocytes than the small glomeruli), the large glomeruli were found to have lower podocyte density. Virtually every organ in the human body has a way to adequately increase its function in the case of increased metabolic demand. For example, exercise leads to the compensatory increase in heart rate, respiration, and sweating. However, obesity is not a temporary stressor1 thus, in the right setting in the obese person with low podocyte density, and potentially also lower nephron endowment, increased metabolic demand may cause permanent stress on enlarged glomeruli, ultimately leading to podocyte loss, glomerulosclerosis, and loss of kidney function (Figure 1).

A third hypothesis is that the nephron loss, FSGS, and proteinuria seen in ORG is a "second hit" phenomenon. Factors such as inherited podocyte gene mutation, particularly the R224Q mutation of NPHS2,[S4] hyperaldosteronism with activation of the Wnt/β-catenin signaling pathway,[S5] loss of adiponectin support for podocytes or leptin induced injury,[S6] and lipid toxicity,[S7] among others, have been postulated to be operative in ORG.

Whatever the true mechanism is for ORG, the finding of increased SNEGFR in patients with the disease is an important and novel addition to our knowledge concerning this relatively uncommon but slowly progressive disease. Further work is needed to unravel the complex series of events that link obesity with a podocytopathy in ORG. Animal models of ORG

may be very useful in the pursuit of this goal.[S6]

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