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Carol Liu Shen
Washington University School of Medicine in St. Louis

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Pediatric Obesity-related Renal Disease

Carol Liu Shen

Obesity has become a worldwide epidemic. The proportion of children who are overweight or obese in the US has increased dramatically in the last four decades. Obesity is a known risk factor for hypertension, cardiovascular disease, and stroke, among many other complications. It is a major cause of morbidity and mortality in the U.S. There is great interest in elucidating the effects of obesity on kidney disease. As the prevalence of obesity among children in the US continues to increase, more attention should be directed towards understanding the consequences of obesity on kidney disease in children.

Epidemiology

The percentage of children classified as obese according to the U.S. Centers for Disease Control and Prevention has more than tripled since the 1970s.\(^1\) According to the 2015 National Center for Health Statistics, the prevalence of obesity among U.S. youth was 17\% in 2011-2014.\(^2\) The International Obesity Task Force predicts that by 2020, >45\% of children in America will be overweight or obese.\(^3\)

The prevalence of end-stage kidney disease (ESKD) has risen in the past three decades, paralleling the progression of the obesity epidemic. A number of studies have demonstrated a correlation between body mass index (BMI) with kidney disease and risk for ESKD.\(^4\) Obesity is strongly correlated with diabetes and hypertension, which are the two most common causes of ESKD.\(^3\) In addition, obesity-related metabolic syndrome, characterized by decreased insulin sensitivity and elevated blood glucose, appears to independently predict risk for chronic kidney disease (CKD) and ESKD in the absence of overt manifestations of diabetes and hypertension.\(^5\) These results suggest that obesity-related kidney dysfunction may appear long before hypertension or diabetes are manifest in patients with metabolic syndrome.
Relatively few studies have focused on the consequences of childhood obesity on the development of kidney disease, but growing evidence suggests that childhood obesity also leads to increased risk of kidney disease and its consequences. Studies show that obesity independently predicts risk of progression of CKD in IgA nephropathy. Compared to non-obese patients, obese patients with unilateral renal agenesis either congenital or due to surgical nephrectomy have a higher risk of kidney disease. Obesity prior to transplant and increased BMI after renal transplant are found to correlate with decreased long-term renal allograft survival in adult and pediatric patients.

**Pathophysiology**

Obesity-related glomerulopathy refers to glomerular dysfunction as a result of abnormal physiological changes in obesity. It is characterized pathologically by glomerular enlargement, mild hypercellularity, variable widening of mesangial regions, thickening of the glomerular basement membrane, and at times focal segmental glomerulosclerosis (FSGS). The exact pathogenesis of obesity-related glomerulopathy is unknown. D'Agati et al. summarizes the potential etiologies as follows: altered renal hemodynamics, maladaptive cell and hormone responses, lipid deposition, and abnormal lipid metabolism.

*Altered renal hemodynamics*

Obesity is associated with reduced pre-glomerular vascular resistance and increased glomerular flow, increased glomerular filtration rate, renal plasma flow, filtration fraction and tubular sodium reabsorption. These changes are in part due to the overactivity of the renin-angiotensin-aldosterone system (RAAS) and the renal sympathetic nervous system (RSNS) in obese individuals. The resultant hemodynamic changes lead to glomerular hypertension, adaptive enlargement of the glomerulus, and microvascular stretching which eventually lead to podocyte loss and development of FSGS lesions. Glomerular hyperfiltration in obesity could have a tubular etiology similar to that of diabetic nephropathy. As in diabetic nephropathy,
increased SGLT2 and SGLT1-mediated glucose and sodium reabsorption in the proximal tubule would lead to decreased sodium load delivered to the macula densa and distal tubule. Tubuloglomerular feedback would then induce afferent arteriolar vasodilation and increased glomerular filtration rate.\textsuperscript{11} Thus, the potential benefit of SGLT2 inhibitors in obesity-related glomerulopathy in the absence of diabetes could warrant further investigation.

\textit{Maladaptive cell and hormone responses}

Adipose tissue is a source of hormones and chemokines collectively called adipokines. Adipokines could exert distant effects in the kidney by means of paracrine signaling. In experimental settings, adipokines such as leptin, adiponectin, and resistin stimulate kidney cells to undergo maladaptive responses to hyperfiltration. These responses include cellular hypertrophy, extracellular matrix deposition and renal fibrosis.\textsuperscript{10}

\textit{Lipid deposition}

Obese individuals may have higher levels of nonesterified fatty acids (NEFA) in the circulation, resulting in deposition in non-adipose tissues such as liver, heart and kidney. In human nephrectomy specimens from obese individuals, lipid was found to be deposited predominantly in the proximal tubules and to a lesser degree in glomeruli. Thus, ectopic lipid in the kidney or a ‘fatty kidney’ may constitute a biomarker of obesity-related kidney disease. Ectopic lipid accumulation in the kidney promotes insulin resistance of podocytes. Insulin has been shown to affect angiogenesis and cellular growth by interacting with VEGF and mTOR signaling pathways in the kidney. Thus, insulin resistance may result in maladaptive responses to renal hyperfiltration, which could eventually lead to podocyte dysfunction and glomerulosclerosis.\textsuperscript{10}

\textit{Abnormal lipid metabolism}

Altered fatty acid and cholesterol metabolism have been implicated as key mediators of renal lipid accumulation, inflammation, oxidative stress and fibrosis.\textsuperscript{10} A recent study showed that several markers of oxidative stress and nitric oxide metabolism are increased in overweight
and obese children, and the presence of these markers are correlated with degree of kidney function and various cardiometabolic risk factors\textsuperscript{12}.

**Clinical presentation**

The most common clinical presentation is the detection of proteinuria in an obese patient with normal urinary sediment. Other common findings are hypertension (50–75\% of patients) and dyslipidaemia (70–80\% of patients).\textsuperscript{10} In most cases, proteinuria does not reach the nephrotic range (>40mg/M\textsuperscript{2}/hour or >3 grams in 24 hours). However, even in cases of nephrotic-range proteinuria (10\% to 48\% of patients), the presence of full nephrotic syndrome is rare (0–6\%).\textsuperscript{10} The typical features of edema, hypoalbuminemia and hyperlipidemia of nephrotic syndrome are characteristically absent in obesity-related glomerulopathy. The absence of overt nephrotic syndrome despite substantial proteinuria suggests that a progressive increase in proteinuria could remain undetected for years, leading to late clinical recognition of kidney dysfunction.

A study of eighteen hundred and thirty school children in Japan identified children with abnormal urinary findings detected by a screening program for kidney disease. Children with persistent proteinuria and hematuria were compared to those without urinary abnormalities in terms of BMI, blood pressure, and serum total cholesterol level. There was a significant association between BMI and systolic blood pressure and findings of proteinuria and hematuria, suggesting that obesity may contribute to a variety of kidney abnormalities, leading to varied clinical presentations of obesity-related kidney disease.\textsuperscript{13}

**Differential diagnosis and diagnostic evaluation**

The diagnosis of obesity-related renal disease is typically made by the presence of obesity, presence of features of metabolic syndrome with or without overt diabetes and hypertension, and proteinuria in the absence of clinical features of nephrotic syndrome. The
incidence of biopsy proven obesity-related glomerulopathy has increased over the last 30 years, and signs of overt kidney disease (acute kidney injury, proteinuria) are common indications for renal biopsy.\textsuperscript{10} One study in adults defined the diagnostic criteria for obesity-related glomerulopathy as BMI $\geq 30$ kg/m\textsuperscript{2} and the presence of glomerulomegaly on biopsy with or without FSGS. The mean BMI of patients with obesity-related glomerulopathy was 41.7 kg/m\textsuperscript{2} (range 30.9–62.7 kg/m\textsuperscript{2}). Only 54% patients had morbid (class 3) obesity, suggesting obesity-related glomerulopathy is not restricted to patients with morbid obesity.\textsuperscript{14}

The characteristic feature of proteinuria in the absence of nephrotic syndrome is also present in other hyperfiltration-induced kidney diseases, such as reflux nephropathy or FSGS associated with kidney mass reduction. In an obese individual who presents with proteinuria accompanied by other components of nephrotic syndrome, suspicion should be raised for minimal change disease, primary FSGS, membranous nephropathy or other glomerular diseases that cause nephrotic syndrome.

Since FSGS lesions can be found in obesity-related glomerulopathy, efforts must be made to distinguish obesity-associated FSGS from primary FSGS. For example, the proteinuria in obesity-related FSGS is typically slowly increasing; whereas in primary FSGS, the onset of proteinuria is sudden. Obesity-related FSGS typically presents with an absence of nephrotic syndrome, whereas full nephrotic syndrome is frequently observed in primary FSGS. Obesity-related FSGS is typically associated with glomerulomegaly, whereas normal glomerular volume is observed in primary FSGS.\textsuperscript{11} Finally, there is relatively mild effacement of foot processes in obesity-related FSGS compared to primary FSGS. In a comparative study, mean foot process effacement was 40% in ORG versus 75% in primary FSGS.\textsuperscript{10}

**Treatment**

The cornerstone of treatment of obesity-related glomerulopathy revolves around correcting renal hemodynamic changes and reversing the effects of metabolic syndrome. In
retrospective studies of obese patients with proteinuria or biopsy-proven obesity-related glomerulopathy, treatment with ACE inhibitors or angiotensin-receptor blockers led to a substantial decrease in proteinuria to 30–80% of baseline values.\textsuperscript{15}

Weight loss has also been found to be beneficial to reducing proteinuria. Moreover, the degree of weight loss seems to be correlated with the extent proteinuria reduction. A randomized controlled trial studying the effect of hypocaloric diet on proteinuria showed a mean weight loss of 4%, and a mean proteinuria decrease of 30% after 5 months of a hypocaloric diet. Those patients who achieved even greater weight losses of >6–10% showed reductions in proteinuria to >60–70% of baseline values.\textsuperscript{16} Two randomized controlled trials compared the effects of weight loss by hypocaloric diet or orlistat treatment to those of RAAS blockade in obese patients with proteinuria, and both studies found similar reductions in proteinuria by both interventions.\textsuperscript{17}

Finally, a case report demonstrates normalization of proteinuria in an adolescent with obesity-related FSGS after bariatric surgery.\textsuperscript{18} Laparoscopic gastric bypass surgery was performed in a 17 year-old with obesity-related FSGS refractory to diet, exercise and ACEi/ARB therapy. Within 2 weeks post-surgery, the patient had lost 5.7 kg and showed a decrease in urinary protein excretion to one tenth of pre-surgery levels. More than 1 year after surgery, the patient’s urine protein and kidney function had remained normal while off RAAS inhibition therapy.

Bariatric surgery as treatment for obesity-related glomerulopathy remains controversial. Bariatric surgery can be associated with severe kidney complications such as nephrolithiasis, oxalate nephropathy and acute kidney injury. Retrospective studies on outcomes of bariatric surgery have shown that the number of postoperative complications correlate with the presence of chronic kidney disease.\textsuperscript{10} Therefore, randomized controlled trials are necessary to conclude if the benefit of bariatric surgery in treating obesity-related glomerulopathy outweighs the risks.
References:


