

Obesity and Kidney Disease

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Abstract

The rise in the prevalence of chronic kidney disease (CKD) and an increase in the prevalence of obesity in parallel in the recent years is a great concern. CKD increases the rate of cardiovascular disease (CVD) and development of end-stage renal disease, and leads to premature death. Although no direct causality link between obesity and CKD can yet be established, this appears highly probable. CKD should be regarded as a major complication of overweight and obesity, regardless of whether the association was independent or through the influence of diabetes, hypertension, CVD and metabolic syndrome. We review the literature on the complex but positive association between obesity and CKD, the pathological effect of excess adiposity in kidney injury and the potential role of weight reduction therapy in reducing the CKD.

Keywords: Obesity, Chronic kidney disease, Proteinuria, Nephrolithiasis, Glomerulosclerosis, Overweight.

Introduction

Chronic kidney disease (CKD) affects nineteen million adults in the United States (1).

CKD is a risk factor for cardiovascular disease (2,3) and has a major impact on patients, health services and society (4).

In recent years, there has been an alarming rise in the prevalence of CKD and also parallel increase in the prevalence of obesity especially in the western world. In the last decade, the prevalence of obesity in Great Britain has almost doubled with the national survey showing the proportion of obese individuals to increase from 13.2% in men in 1993 to 23.7% in 2006 and from 16.4% in women in 1993 to 24.2% in 2006. The World Health

Organization (WHO) defines normal body weight using the body mass index (BMI) as a BMI of 18.5-24.9 kg/m², overweight as BMI ranging from 25 to 29.9 kg/m² and obesity as BMI of ≥ 30 kg/m² (4).

Obesity precedes the development of many cardiovascular disease (CVD) risk factors including diabetes (5,6), hypertension (7,8), dyslipidemia (9,10), and metabolic syndrome (11-14). Therefore, obesity may be associated with CKD through these risk factors (15).

In addition, biological pathways have been identified as potential mechanisms leading from obesity to kidney damage, such as hormonal factors, inflammation, oxidative stress, and endothelial dysfunction (16,17).

In a systematic review and meta-analysis, it was showed that respectively 24.2% and 33.9% of kidney disease cases among US men and women and 13.8% in men and 24.9% in women in industrialized countries could be related to overweight and obesity. Also, obesity increases the risk for kidney disease in the general population and this association is stronger in women (18).

Obesity and CKD

In the Framingham Heart Study of 2585 individuals with nearly 19 years of follow-up, traditional cardiovascular risk factors of age, hypertension, diabetes, obesity and tobacco use have been shown to be predictors of new-onset kidney disease (19). On multivariate analysis in this study (controlling for age, sex, glomerular filtration rate (GFR), smoking and diabetes status), increased baseline BMI was significantly associated with development of CKD, with an odds ratio of 1.23 (95%CI: 1.08-1.41) for each standard deviation in BMI. In Hypertension Detection and Follow up program, the risks of developing CKD at 5 years after adjustment for age, sex and diabetes for overweight and obese patients were 20% (95%CI: 1.04-1.39) and 40% (95%CI:1.21-1.65), respectively, in comparison with normal weight patients (20). In the large prospective cohort study of healthy male physicians, the risk of developing CKD after 14 years of follow up was approximately 30% in those who were overweight (1.32,95% CI 1.09-1.61) and obese (1.26,95%CI:1.03-1.54) after adjusting for age, smoking, exercise, alcohol consumption, diabetes, hypertension, hypercholesterolemia and coronary artery disease (21).

While high BMI is a risk factor for CKD, independent of diabetes and hypertension, some studies showing conflicting results. In a Swedish case-control study, men and women with $BMI \geq 25 \text{ kg/m}^2$ at ages 20,40 and 60 years had a threefold increased risk of CKD compared with those with $BMI < 25 \text{ kg/m}^2$, and this risk was particularly strong in diabetic patients (22).

A Taiwanese community-based cross-sectional study of 4611 adults documented a greater than twofold increased risk of CKD in obese individuals especially in participants who had hypertension and diabetes. The odds were 2.9 (95%CI: 2.11-3.97) and 2.4 (95%CI: 1.68-3.57) respectively (23).

Obesity and Proteinuria

Microalbuminuria has been described as the earliest manifestation of obesity associated kidney damage. This is associated with insulin resistance, independent of diabetes (4).

A subanalysis of the PREVENT (prevention of renal and vascular End stage Disease) study determined that in men the prevalence of microalbuminuria increased from 9.5% in those with a normal body weight to 18.3% in those who were overweight and to 29.3% in those with frank obesity. In women, these values were 6.6, 9.2 and 16%, respectively. Multivariate analysis showed that BMI was independently associated with urinary albumin excretion, and there was a relation between gender and BMI. Men had a steeper rise in urinary albumin excretion as BMI increased compared with women (16). Obese individuals commonly have increased plasma renin activity, angiotensinogen, angiotensin-converting enzyme activity, and circulating angiotensin II (renin-angiotensin-aldosterone) correlated to elevated level of leptin (24). Hyperinsulinemia, insulin resistance and increased angiotensin II are potent activators for transforming growth factor- $\beta 1$ (TGF- $\beta 1$) a fibrogenic cytokine which contributes to glomerular injury and proteinuria (25).

In addition, epoxyketoctadecenoic acid (EKODE) secreted by visceral fat stimulates the secretion of aldosterone by the adrenal gland independent of classical secretagogues (26). Aldosterone impairs podocyte function and contributes to proteinuria (27).

Focal segmental glomerulosclerosis (FSGS) or the better term "obesity related glomerulopathy" (ORG) is the most significant and frequent histologic abnormality in proteinuric morbidly obese patients, and has a rise in the past two decades which seems to be

congruent with the sharp increase in the prevalence of obesity. A large comparative study in United States of 6818 renal biopsies over 15 years (from 1986 to 2000) found a tenfold increase in the incidence of ORG. Presentation was typically by one of nephritic-range proteinuria (48%) or sub-nephrotic proteinuria (52%), accompanied by renal insufficiency (44%). None of the patients with ORG had histologic evidence of diabetic nephropathy (4).

Increase in GFR, elevated intraglomerular hypertension and decreased serum levels of adiponectin have been associated with proteinuria in obese patients, and may play a pathogenic role in the development of glomerulosclerosis (28).

Obesity and Hypertension

Both angiotensin II and angiotensinogen are formed by adipose tissue and may contribute to higher plasma angiotensinogen levels as well as enhanced vascular tone. Secretion of leptin from adipocyte enhances sympathetic nervous system activity, which may enhance vascular tone, but increases cardiac output. Vasoconstriction increases peripheral resistance, which together with increased cardiac output leads to high blood pressure.

Expression of natriuretic peptide clearance receptor (NPR-C) in adipose tissue may contribute to low plasma levels of the atrial natriuretic peptide (ANP). This in turn promotes sodium retention and volume expansion which is a strong risk factor for hypertension (24).

Obesity and Nephrolithiasis

Increased intake of protein and sodium, and surgical treatment for obesity are associated with calcium oxalate stones. Also, obesity is accompanied with uric acid stones because of low urinary pH in obese patients (28).

Obesity and Renal Cell Carcinoma (RCC)

In a systematic review and meta-analysis about association between obesity and kidney disease, 24% (16.5% in men and 26.3% in women) of kidney cancer cases (including

RCC) were attributable to overweight and obesity. Obesity increases the risk of RCC; the pooled RR is 1.87 (95%CI: 1.69-2.07) for obese women vs 1.53 (95%CI: 1.38-1.69) for obese men (18).

The Mechanism of Obesity-Induced Renal Damage

The positive association between obesity and kidney disease is both complex and not yet fully understood. High serum leptin levels are found in type 2 diabetic and non-diabetic obese individuals. Leptin is the first adipocyte-derived cytokine (adipokine) to be implicated in the pathogenesis of kidney disease in obesity. Leptin can stimulate cellular proliferation and expression of pro-sclerotic TGF- β 1 cytokine (4). It stimulates cellular proliferation, TGF- β 1 synthesis, and type IV collagen production in glomerular endothelial cells (16).

Hyperlipidemia itself can contribute to kidney injury. The obese Zucker rat, which has hyperinsulinemia and hyperlipidemia, develops progressive renal failure associated with an accentuated podocyte injury and glomerulosclerosis.

Adiponectin, another adipokine whose levels are reduced in obesity and insulin resistance, was strongly implicated in the pathogenesis of kidney injury in obesity (4). Adiponectin-deficient mice exhibited effacement and fusion of podocyte foot processes as well as increased albuminuria (4).

Finally, the role of inflammatory processes triggered by obesity should be mentioned as a mechanism for the obesity-related renal changes. It is known that adipocytes produce cytokines and that C-reactive protein (CRP) levels are elevated in obesity, suggesting a state of low-grade systemic inflammation. Several studies with long term follow-up have shown that increased levels of this inflammatory marker are associated with increased risk of coronary heart disease, stroke, peripheral vascular disease, as well as higher relative risk of impaired glomerular filtration (16).

Obesity and Glomerular Hyperfiltration

Severe obesity is associated with increased GFR and high renal plasma flow and these changes improve substantially after weight loss. This suggests a state of renal vasodilatation involving mainly or solely, the afferent arteriole in obesity, similar to diabetes (29).

Conclusion

Obesity may lead to glomerular hyperfiltration, increased urinary albumin loss and a progressive loss of renal function,

associated with a focal segmental glomerulosclerosis. These renal changes may be related to insulin resistance and/or hyperleptinaemia, but may also be mediated by a state of low-grade inflammation induced by obesity. Microalbuminuria may be an easy to measure marker to detect risk of progressive renal failure in obesity. In addition, obesity is related to increased prevalence of nephrolithiasis and hypertension that both are risk factors for CKD. Accordingly, weight reduction can rescue the kidney via multiple mechanisms.

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