

## Impact of obesity on kidney function and blood pressure in children

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in the incidence of chronic kidney disease (CKD) and hypertension. Results of several studies have demonstrated that obesity and metabolic syndrome were independent predictors of renal injury. The pathophysiology of obesity related hypertension is complex, including activation of sympathetic nervous system, renin angiotensin aldosterone system, hyperinsulinemia and inflammation. These same mechanisms likely contribute to the development of increased blood pressure in children. This review summarizes the recent epidemiologic data linking obesity with CKD and hypertension in children, as well as the potential mechanisms.

**Key words:** Obesity; Chronic kidney disease; End-stage renal failure; Hypertension; Blood pressure

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**Core tip:** Excess weight gain appears to be a major risk factor for chronic kidney disease and hypertension. The potential mechanisms involve insulin resistance, inflammation, renal renin-angiotensin-aldosterone hyperactivity, and sympathetic nervous system hyperactivity. Increased awareness is needed in children for early diagnosis and implementation of prevention and treatment measures.

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### Abstract

In recent years, obesity has become an increasingly important epidemic health problem in children and adolescents. The prevalence of the overweight status in children grew from 5% to 11% from 1960s to 1990s. The epidemic of obesity has been paralleled by an increase

### INTRODUCTION

Throughout the world, the increasing rate of childhood obesity has been steadily on the rise over the past

decades. In the first decade of this century, up to 28% of school and 12% of preschool children were determined to be overweight or obese in developed countries, and the international obesity task force addressed childhood obesity as a global "public health crisis"<sup>[1]</sup>. The impact of obesity on metabolic disease has been well demonstrated, and recently there is increasing evidence that obesity appears to be an independent risk factor for chronic kidney disease (CKD). Baseline body mass index (BMI) has been suggested as an independent predictor of CKD progression<sup>[2]</sup>. Obesity is strongly associated with the two most common causes of end-stage renal disease (ESRD), namely hypertension and diabetes. In addition, the metabolic syndrome, a major consequence of obesity, also seems to be an independent risk factor for ESRD<sup>[3]</sup>. Recent evidence also supports the hypothesis that reduced insulin sensitivity and hyperinsulinemia are among the most important factors leading to renal injury<sup>[4]</sup>. In concert with the increasing prevalence of obesity in children, hypertension has also made an epidemiological shift. Hypertension is a common feature present in a large proportion of obese and overweight individuals. It is correlated with the degree of obesity and significantly increased the risk of coronary artery, stroke and peripheral artery diseases. Moreover, the burden of hypertension attributable to obesity is very high<sup>[5]</sup>. This review focuses on the impact of obesity on the kidney and blood pressure in children as well as the mechanisms linking obesity to CKD and hypertension.

## IMPACT OF OBESITY ON THE KIDNEY FUNCTION

### *Epidemiology of obesity*

The BMI has been used to define obesity based on associated health risk factors in adult individuals. The National Institute of Health (NIH) in the United States determined an adult with a BMI of < 18.5 as underweight, 18.5-24.9 as normal, 25-29.9 as overweight and > 30 as obese. However, the criteria used to define children who are overweight or obese has varied. Most studies concerning childhood obesity or overweight in the United States are based on the Centers for Disease Control and Prevention (CDC) growth charts in 2000. The CDC defined children with > 85<sup>th</sup> percentile BMI to be overweight and BMI > 95<sup>th</sup> percentile to be obese<sup>[6]</sup>. The National Health and Nutrition Examination Survey (NHANES) data demonstrated almost doubling in prevalence of children with BMI > 85<sup>th</sup> percentile from 1999 to 2004. Recently, the NHANES showed stable prevalence of high BMI in children < 19 years old, with 10% of infants and toddlers < 2 years old with a weight-for-height  $\geq$  95<sup>th</sup> percentile, 17% of children aged 2-19 years old  $\geq$  95<sup>th</sup> percentile, and 32%  $\geq$  85<sup>th</sup> percentile

of BMI for age<sup>[7,8]</sup>.

### **Obesity and the risk factors for CKD**

Childhood obesity is fast becoming a worldwide epidemic, and the state of being overweight/obese continues to persist into adolescence. Clustering of cardiovascular risk factors has been shown in obese children with the highest degree of insulin resistance, and these children are likely to develop obesity related kidney damage. In fact, there is a rapidly increasing prevalence of overweight and obese patients with CKD<sup>[9]</sup>. Reports in a Californian cohort of 330252 persons suggested a strong dose-response relationship between the baseline BMI and the risk of CKD. According to recent studies, obesity also appears to be an independent risk factor for CKD in children. Pediatric nephrology patients had consistently markedly higher BMI z-scores than the normal population at a tertiary center in Canada over a period of two decades. In another study of children with renal transplants, kidneys obtained from obese donors (BMI > 30 kg/m<sup>2</sup>) had a lower glomerular filtration rate (GFR) and higher allograft dysfunction rate than kidneys obtained from lean individuals (BMI < 25 kg/m<sup>2</sup>)<sup>[10-13]</sup>. Furthermore, Pantoja Zuzúárregui *et al.*<sup>[14]</sup> demonstrated that obese children have larger kidneys than those of normal weight patients.

### **Role of obesity in CKD initiation**

This question still remains whether obesity and obesity-related metabolic syndrome could directly induce renal injury. Though the theory needs to be confirmed by cause-and effect studies, more and more epidemiologic studies and clinical observations suggested that the obesity metabolic syndrome played a key role in the development of CKD<sup>[15]</sup>. Recently, several researches indicated that CKD is temporarily related to obesity independently of hypertension. Bonnet *et al.*<sup>[16]</sup> demonstrated that excessive body weight was considered to be a new independent risk factor for clinical and pathological progression in IgA nephritis. Obesity was also shown to independently affect the process of CKD, for instance in patients with unilateral renal agenesis<sup>[17]</sup> or after unilateral nephrectomy<sup>[18]</sup>. In addition, kidneys that were obtained from obese individuals (BMI > 30 kg/m<sup>2</sup>) were more likely to correlate with a lower GFR and a higher rate of renal allograft dysfunction than kidneys that were obtained from lean donors<sup>[12]</sup>. These results indicated that obesity could contribute to or even initiate the development of CKD. Kincaid-Smith challenged the long-held notion that hypertension accounts for > 30% of cases of ESRD in the United States and suggested that insulin resistance may be the real culprits in the development of glomerulosclerosis<sup>[19]</sup>. This notion is supported by the fact that there are no pathologic studies or large clinical studies to provide strong evidence of a relation between

hypertension and ESRD<sup>[18]</sup>.

### **Obesity related glomerulopathy**

Obesity is associated with glomerular hyperfiltration and hypertension. Obesity related glomerulopathy (ORG) is clinically characterized by moderate proteinuria, minimal edema, lower serum cholesterol and higher serum albumin<sup>[20]</sup>. ORG has been described as a secondary form of focal segmental glomerulosclerosis (FSGS) occurring in obese patients. The first research between obesity and renal injury was reported in 1974<sup>[21]</sup>. One year later, Cohen also described the presence of significant glomerular enlargement, variable widening of mesangial regions and mild hypercellularity in obese patients, and these features also were found even in children as young as 3 years old<sup>[22]</sup>. Obese children have larger kidneys and increased renal blood flow than normal weight individuals of similar age. Recently, some reports of improvement in ORG with reduction in body weight were demonstrated. In a recent clinical report, a 17-year-old girl with ORG and nephrotic-range proteinuria, one year after bariatric surgery, her renal function was normal and had no proteinuria<sup>[23]</sup>. However, the improvement in proteinuria might not correlate with histological change. The pathology of ORG may be biased by the fact that most of the kidney samples were obtained in patients with proteinuria. It suggested that ORG could not be the histopathological feature in nonproteinuric obese individuals with renal dysfunction.

### **Metabolic syndrome, inflammation and renal injury**

The metabolic syndrome or insulin resistance syndrome represents a clustering of CKD risk factors. According to Bogalusa Heart study, metabolic syndrome was characterized as having four of the aforementioned components at or above the 75<sup>th</sup> percentile for age and gender in children<sup>[24]</sup>. The primary cause of the metabolic syndrome seems to be obesity. In the NHANES III study, the prevalence of metabolic syndrome was 28.7% in overweight adolescents, compared with 0.1% in those with normal BMI and 6.1% in adolescents at risk of being overweight<sup>[25]</sup>. Up to 90% of overweight individuals had at least one component of the syndrome, and about 56% had two components of the syndrome. There is a plausible association between metabolic syndrome and obesity. One of the important features of metabolic syndrome is insulin resistance. Insulin resistance may lead to a proinflammatory state in obese children. Plasma concentrations of some inflammatory mediators such as tumor necrosis factor (TNF- $\alpha$ ), C-reactive protein (CRP) and interleukin (IL)-6 were increased in patients with metabolic syndrome<sup>[26]</sup>. These results suggest that inflammation is a key risk factor for obesity and inflammation has been strongly associated with the metabolic syndrome. Recent evidence shows that inflammation is linked to obesity in CKD patients. Beddhu *et al.*<sup>[27]</sup> found that in the NHANES

III cohort, the metabolic syndrome was associated with greater odds for inflammation at various levels of creatinine clearance. Wu *et al.*<sup>[28]</sup> showed that lipid metabolism related genes and inflammatory cytokines were increased in glomeruli of patients with ORG compared with gender and age matched glomeruli of control kidney samples. Ramkumar *et al.*<sup>[29]</sup> also demonstrated a strong relationship between high BMI and inflammation characterized by a CRP level > 3 mg/dL in patients with CKD. These findings strengthen the notion that inflammatory risk factors and lipid byproducts play a key role in the progress of renal dysfunction in obese patients. Strong evidence shows that obesity, in particular central body fat distribution, has been implicated in kidney dysfunction. In fact, obesity and overweight are associated with many other risk factors, *i.e.*, hyperinsulinemia, hypertension, impaired glucose metabolism and hyperlipidemia, renin-angiotensin-aldosterone (RAAS) activity, oxidative stress and proinflammatory cytokines. Above all, reduced insulin sensitivity presents the most important relationship between obesity and other metabolic complications (Figure 1), which leads to CKD<sup>[30,31]</sup>.

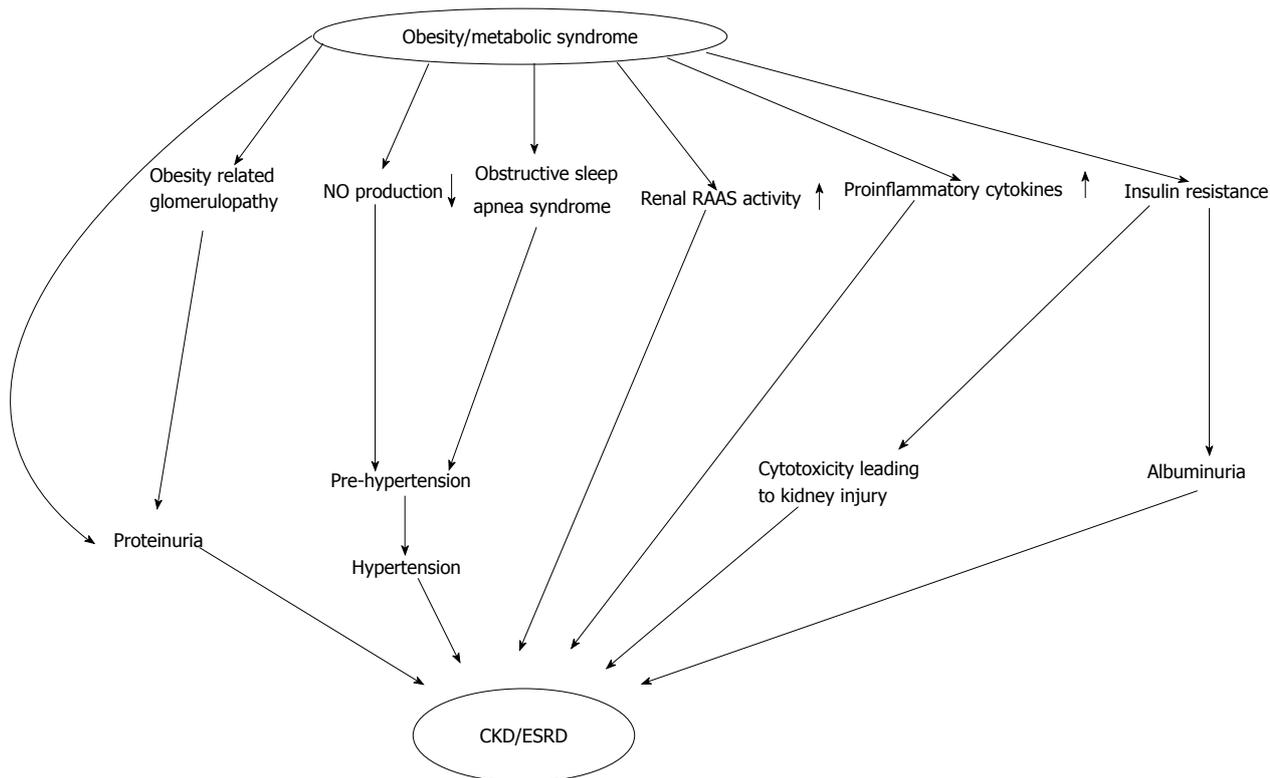
## **IMPACT OF OBESITY ON BLOOD PRESSURE**

### **Epidemiology**

Hypertension is a common feature in a large proportion of obese and overweight individuals. It is correlated with the degree of obesity and significantly exaggerated the risk of stroke, coronary and kidney disease. The association between obesity and hypertension in children has been reported in many studies. Rosner *et al.*<sup>[32]</sup> collected data from 8 US epidemiological studies including over 47000 children and the results demonstrate that blood pressures differ between white and black children in relation to their body size. They found the risk of increased blood pressure was markedly higher in the upper compared with the lower decile of BMI irrespective of race, age and gender. Freedman *et al.*<sup>[33]</sup> showed that overweight children were 4.5 and 2.4 times as likely to have increased systolic and diastolic blood pressure, respectively, than normal children. Sorof *et al.*<sup>[34]</sup> recently demonstrated that there was a 3 times prevalence of hypertension in obese compared with non-obese adolescents in a school based hypertension and obesity screening study.

### **Obesity as a major cause of hypertension**

More recent evidence shows that excess weight gain is one of the best predictors of the development of obesity. In addition, blood pressure is closely correlated with BMI and other biochemical and anthropometric indices of obesity, such as serum insulin, leptin and waist to hip ratio<sup>[5,35]</sup>. The strong relationship between obesity and hypertension cannot be attributed to



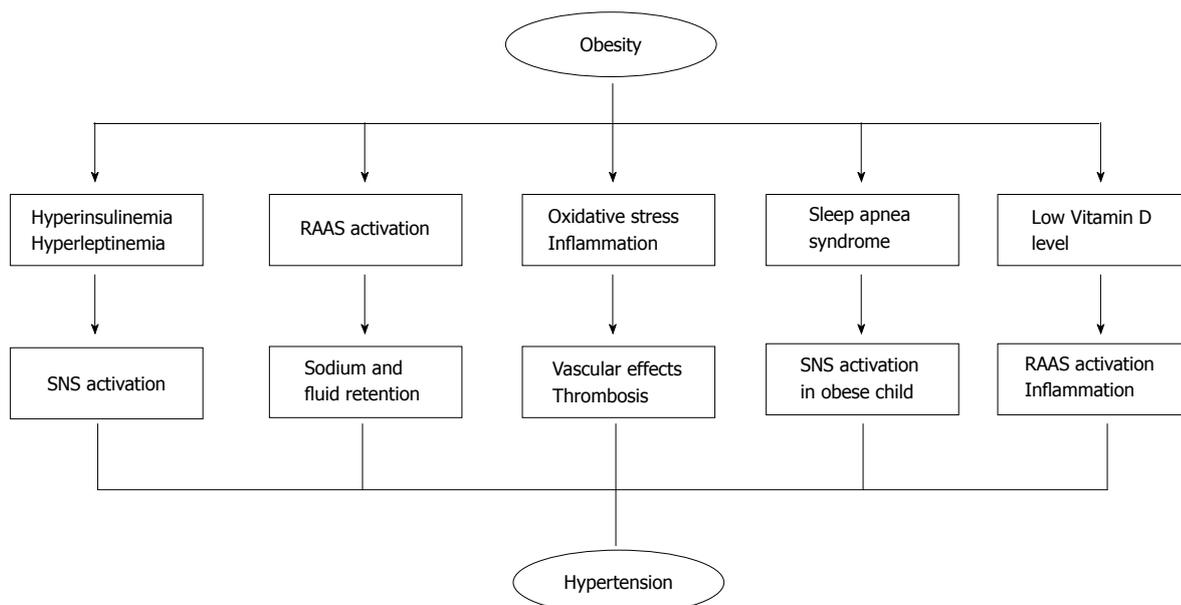
**Figure 1** Obesity leads to progression of chronic kidney disease through various pathways. NO: Nitric oxide; RAAS: Renal angiotensin aldosterone system; CKD: Chronic kidney disease; ESRD: End-stage renal disease.

genetic factors, because the association between obesity and hypertension has been observed in diverse populations throughout the world. Although the precise contribution of excess weight to hypertension has not been clearly established, Garrison *et al*<sup>[5]</sup> reported that about 78% hypertension in men and 65% in women may be directly attributed to excess body mass. Moreover, this association between obesity and hypertension can be modified by factors, such as the duration of obesity and the distribution of body fat. Clinical research has also demonstrated the therapeutic role of weight loss for reducing blood pressure. Even weight loss in “normotensive” overweight individuals can decrease the blood pressure. Experimental research of dietary-induced or genetic animal models of obesity has permitted mechanistic insights into these factors that link hypertension and obesity. Dobrian *et al*<sup>[36]</sup> showed that weight gain induced by long-term high-fat diets consistently increased blood pressure in a rat model<sup>[37]</sup>. In addition, renal and metabolic changes observed in animal models of diet-induced obesity seem to mimic very closely the findings in obese humans.

**Mechanisms of hypertension in obesity**

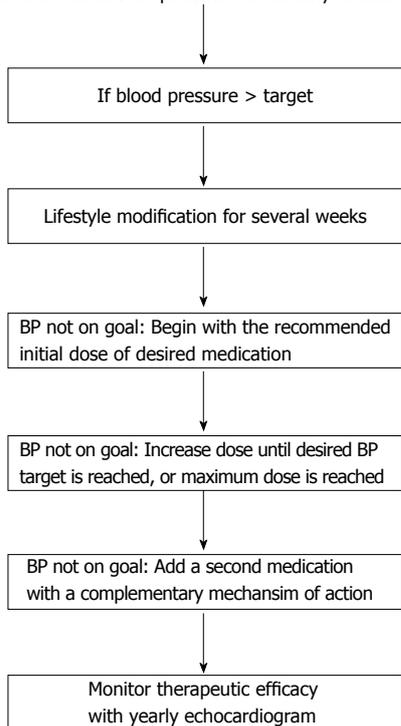
Obesity-associated hypertension is a complex multi-factorial disease, including activation of RAAS, altered vascular function and increased sympathetic nervous system (SNS)<sup>[38]</sup>. The potential relationship among these mechanisms is shown in Figure 2. Insulin resistance alone, or in combination with hyperleptinemia, activates

the SNS, which cause vasoconstriction and reduced renal blood flow, leading in turn to activation of RAAS and water and sodium retention<sup>[39]</sup>. The serum level of leptin has a strong association with increased blood pressure, and eventually activated SNS. In addition, recent reports show that other mechanisms may be involved in the pathogenesis of hypertension in obese children, such as proinflammatory cytokines and oxidative stress pathway. These signaling pathways likely contribute to increased arterial stiffness and endothelial dysfunction (Figure 2)<sup>[40]</sup>. Moreover, sleep apnea syndrome or poor sleep quality often increase the risk of the development of hypertension in obese children<sup>[41]</sup>. The potential mechanisms for sleep apnea or poor sleep quality may be triggered by intermittent hypoxia and increased inflammatory cytokines, and may eventually exacerbate the progression of hypertension in obese individuals. Pacifico *et al*<sup>[42]</sup> demonstrated that low serum 25(OH)<sub>2</sub>D<sub>3</sub> levels were associated with metabolic syndrome and hypertension in Caucasian children and adolescents. This suggests that low vitamin D level often observed in obese children, may have a strong association with hypertension and metabolic syndrome. The uric acid may be also involved in obesity-induced hypertension. A high fructose diet can lead to hyperuricaemia owing to increased uric acid production by adipose tissue in obese individuals<sup>[43]</sup>. Several researches have demonstrated a strong relationship between uric acid and hypertension in children and adolescents. The Moscow Children’s hypertension study showed hyperuricaemia (> 8.0 mg/dL) only in 9.5% of children with normal blood



**Figure 2** Mechanisms of hypertension in obesity. RAAS: Renal angiotensin aldosterone system; SNS: Sympathetic nervous system.

Treatment methods for patients with obesity related hypertension



**Figure 3** Stepped-care approach to antihypertensive therapy in obese children. BP: Blood pressure.

pressure, but as high as 49% in children with borderline hypertension, and up to 73% of children with moderate and severe hypertension<sup>[44]</sup>. These findings also need to be confirmed by large-scale epidemiological studies.

**Therapeutic approaches for obesity related hypertension**

Lifestyle interventions were recommended for all the obese children with hypertension. These include

increased physical activity, low sodium diet and other healthy dietary choices for weight loss<sup>[45]</sup>. The effects of high sodium intake may have an important role of elevated blood pressure in overweight and obese adolescents compared with the general individuals. In addition, decreasing sodium intake may have a beneficial effect on blood pressure in obese individuals<sup>[46]</sup>. Pharmacological and surgical options were limited for the treatment of obese children. Calcium channel blockers and angiotensin converting enzyme (ACE) inhibitors are the most frequently prescribed drugs for primary hypertension in children and adolescents<sup>[47]</sup>. Because of the important role of RAAS and SNS activation in obesity related hypertension, ACE inhibitors are considered a very good choice for the treatment of hypertension<sup>[48]</sup>. Moreover, ACE inhibitors and angiotensin receptor blockers may have additional reno-protective role in obese patients<sup>[45]</sup>. Beta blockers may impair lipid and glucose metabolism and they are not preferably the first choice therapy in obese hypertensive individuals<sup>[49,50]</sup>.

The current approach for obesity-related hypertension in children is summarized in Figure 3<sup>[51]</sup>. Lastly, obesity related hypertension should be considered a chronic medical condition and likely requires long-term treatment.

**CONCLUSION**

Obesity has reached epidemic proportions and continues to be a growing problem worldwide. Excess weight gain appears to be a major risk factor for CKD and hypertension. The potential mechanisms involve insulin resistance, inflammation, renal RAAS hyperactivity, SNS hyperactivity, and perhaps other unknown mechanisms. Obesity related renal injury and hypertension is already well recognized in the adult population. Increased awareness is needed in children for early diagnosis and

implementation of prevention and treatment measures.

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