Pathogenesis of Hypertension and Renal Disease in Obesity

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Key Words: Blood pressure, insulin, sympathetic nervous system, renin–angiotensin–aldosterone system, insulin resistance, obesity-related, glomerulopathy, proteinuria

Introduction

Obesity, hypertension, and renal injury are linked by complex inter-relationships. Obesity-associated metabolic abnormalities promote both systemic hypertension and renal injury; hypertension in turn results from, and contributes to, progressive renal damage, regardless of primary cause. It is now well established that obesity dramatically increases the risks of type-II diabetes and diabetic nephropathy; yet even in the absence of diabetes, obesity predisposes to chronic kidney disease and accelerates its progression. In this chapter we discuss the pathogenesis of hypertension and renal disease in obese adults and children and reflect on their implications for therapy.

Hypertension

Epidemiology

Elevated systemic blood pressure (BP) is a leading contributor to the global disease burden, promoting the development and progression of heart disease, stroke, and kidney damage. The life-threatening complications of chronic hypertension rarely manifest during childhood, but elevated BP among children and adolescents predicts the development of hypertension in adulthood (1), and several intermediate endpoints of hypertensive end-organ damage, including left ventricular hypertrophy, carotid artery intima-media thickness, endothelial dysfunction, proteinuria, and renal scarring are now seen.
with increasing frequency in obese children (2). Recent projections indicate that childhood hypertension will contribute significantly to the overall future burden of cardiovascular and renal diseases in adulthood and hasten development of these complications in the pediatric population.

Childhood obesity is now recognized as one of the strongest predictors of hypertension in young adulthood (2–4). Compared with the 25% prevalence of hypertension in adults, only about 3–5% of children are affected. However, establishing pediatric norms and defining hypertension have been complicated by difficulties in obtaining pressure readings in children, a lack of standardization of the measurements, and changes in pressure levels that occur during normal maturational development. The most recent normative BP tables used data acquired from the 1999–2000 National Health and Nutrition Examination Survey (NHANES). BP recordings in 8–17-year-olds, collected between 1963 and 1988, documented a decreasing trend for hypertension (3). By contrast, data collected after 1988 revealed a reversal in the downward trend, with both hypertension and pre-hypertension levels increasing in the childhood population. This reversal in the hypertension trend is widely believed to reflect the increasing prevalence of childhood adiposity.

The association between adiposity and hypertension is well established in adults. The prevalence of hypertension is 3 times higher and the incidence 5 times higher in obese adults than in normal weight individuals. It is estimated that at least 50% of the rise in the prevalence of hypertension is attributable to escalating BMI. The obesity–hypertension relationship has now also been convincingly demonstrated in children and adolescents (2–5). Obese children are at threefold higher risk for developing hypertension than non-obese children. As in adults, the risk occurs across the range of BMIs. Thus, some 20–30% of 5–11-year olds with weight >120th percentile of ideal have elevated systolic or diastolic pressure. Overweight adolescents (BMI >75th percentile) have an eightfold increased risk of developing hypertension as adults. The strong association between childhood obesity and hypertension has been confirmed in many parts of the world. As in adults, the prevalence of overweight and elevated blood pressure is higher in Native Americans, African-Americans, Hispanics, and Asians than in white children (2,3,5–7). Citing potential differences and inadequacy in blood pressure measurement techniques and differences in definition of hypertension, some reservations had been raised as to whether obesity-related hypertension in children has affected the overall prevalence of hypertension in the pediatric population. However, using the newest blood pressure criteria for hypertension and pre-hypertension in children, Din-Dzietham et al. demonstrated that development of hypertension lagged behind the uptrend in obesity by 10 years (6). The report concluded that obesity is indeed the most important driving force in childhood hypertension, especially in African-American and Hispanic children. Figure 1 illustrates the recent trends in the impact of obesity on childhood hypertension.

![Fig. 1. Impact of obesity rise on hypertension in children. High blood pressure prevalence and 95% confidence interval obtained in 8–17 year olds in the National Health and Nutritional Examination Survey 1963–1988 (NHANES III) (open columns) and 1988–1999 (NHANESIV) (black columns). Adapted from Din-Dzietham et al. (6).](image-url)
**Blood Pressure Homeostasis**

Blood pressure is the force exerted by the blood against a unit area of vessel wall and is defined as

\[ \text{BP} = \text{CO} \times \text{TPR} = (\text{HR} \times \text{SV}) \times \text{TPR} \]

where BP is blood pressure, CO is cardiac output, HR is heart rate, SV is stroke volume, and TPR is the total peripheral resistance. CO and TPR are intimately dependent on the extracellular fluid volume, which is determined primarily by the renal excretion of sodium and water.

Adiposity affects all of these parameters (8). Obese and overweight individuals have increased resting CO by virtue of increased heart rate, which reflects heightened sympathetic tone and reduced vagal tone. Perturbed autonomic regulation has been implicated in obesity-related blunting in heart rate variability that is linked to cardiovascular disease, including hypertension. Obesity also increases stroke volume; this results from expansion in the circulatory volume necessary to perfuse the increased adipose tissue mass and fat-free mass that accompany weight gain. The increased stroke volume also reflects increased ventricular filling pressure and blood volume that follows an increase in tubular sodium reabsorption. As in all hypertensive states, obesity-associated hypertension is associated with impaired pressure natriuresis, a mechanism that normally allows the kidney to regulate systemic BP. Thus, obese individuals have an inappropriately limited natriuretic response to a saline load; this necessitates that obese individuals require a higher blood pressure than those of normal weight to excrete a given sodium load. The mechanisms for impaired renal pressure natriuresis in this setting include augmented sympathetic nervous system activity, activation of the renin–angiotensin–aldosterone system, and increased intrarenal pressure.

The homeostatic mechanisms that maintain the balance between cardiac output and peripheral vascular resistance are disrupted in obesity. Compared with normal weight or obese individuals who are normotensive, peripheral vascular resistance is increased in hypertensive obese individuals despite the increase in CO. This abnormal vascular response is especially apparent in obese/overweight individuals whose fat is centrally distributed. Indeed, even in the absence of overt obesity, there is an independent association between central adiposity and increased CO and/or increased (or insufficiently reduced) vascular resistance. This suggests that the metabolically active visceral fat contributes directly or indirectly to body requirements for blood flow supply.

The underlying mechanisms include enhanced vasoconstriction, endothelial dysfunction with impaired vasodilation, and vascular wall remodeling associated with deposition of lipids, advanced glycation end-products, and extracellular matrix components that impair normal adjustments in vasomotor tone. Early stages of overweight and obesity are characterized by an exaggerated vasoconstrictive response. However, as obesity becomes severe, there ensues a progressive impairment in the vascular response. Such findings suggest that the initially heightened vasomotor response is followed by vascular remodeling that limits the hemodynamic response. Markers of endothelial dysfunction and vessel remodeling, including impaired brachial artery flow-mediated dilation and increased carotid artery intima-media thickness, previously established in adults, have now been well documented in obese children.

**Pathophysiologic Mechanisms**

**Sympathetic Nervous System Activity**

Direct and indirect evidence supports an important pathophysiological role for an overactive sympathetic nervous system in obesity-associated hypertension (9). Experimental studies show that a high-calorie diet that leads to obesity also causes hypertension. This effect is not observed in obese
animals with pharmacologic blockade of α- and β-receptors or animals with bilateral renal denervation that achieve similar weight gain (10). Obese humans have elevated plasma and urinary catecholamine levels as well as heightened sympathetic neural activity (11). A cross-sectional study found that BMI and plasma norepinephrine levels independently predict vasconstriction and blood pressure elevation in obese hypertensive individuals. This association is especially apparent in children and adults with central obesity (12).

Obesity-related changes in sympathetic tone not only promote vasoconstriction but also impair vasodilation, as assessed by the response to cold stress, mental stress, or handgrip. All vascular beds (e.g., skeletal, mesenteric, renal) may be impacted though their responses to adrenergic stimulation are heterogeneous, modulated by local as well as systemic factors. The physiological mechanisms by which activated sympathetic tone can increase BP include direct vasoconstriction, increases in heart rate and stroke volume that increase cardiac output, and expansion of the extracellular volume by increases in renal tubule sodium reabsorption. These effects are mediated by reductions in insulin sensitivity and concomitant changes in plasma leptin, insulin, adiponectin and free fatty acids, which in combination with activation of the renin–angiotensin system (9) heighten sympathetic tone (Fig. 2).

Fig. 2. Mechanisms contributing to obesity-associated hypertension.
Pharmacologic blockade of sympathetic activity with a combined α- and β-adrenergic receptor blocker causes greater reduction in BP in obese than in lean individuals. It is interesting that Pima Indians, who have increased propensity for obesity, do not have heightened sympathetic tone and do not develop hypertension to the same degree as other racial groups. These observations suggest that BP is modulated by ethnic/genetic factors that may counteract the effects of adiposity on sympathetic drive. These factors may promote the differential reactivity of vascular beds. Thus, normotensive obese individuals have elevated sympathetic nerve activity in skeletal muscle but a normal vasodilatative response to α-adrenergic receptor blockade (13). Similar counterbalancing effects may be provided by other vasodilators including nitric oxide and natriuretic peptides or local regulators of sympathetic nerve activity, such as insulin or leptin. Thus, while obesity is regularly accompanied by enhanced sympathetic outflow, the heightened sympathetic tone may be modulated by compensatory mechanisms and/or local factors to achieve the final/sustained vascular tone.

**RENIN–ANGIOTENSIN–ALDOSTERONE SYSTEM (RAAS)**

The renin–angiotensin–aldosterone system (RAAS) has a causal role in obesity-related hypertension (Fig. 2). Even in the setting of the volume-expanded state that characterizes obesity, all the components of the RAAS are inappropriately normal or elevated (14). Conversely, weight reduction is followed by decrease in RAAS activity. For example, dietary restriction that produced a 5% reduction in weight led to a 7-mmHg reduction in ambulatory systolic blood pressure that was accompanied by a 27% decline in angiotensinogen, 43% decline in renin, 12% reduction in adipose tissue ACE activity, and 20% reduction in the angiotensinogen expression in adipose tissue (15). Mice deficient in components of the RAAS are leaner and gain less weight when fed a high-fat diet than mice with an intact RAAS. White adipose tissue itself (particularly visceral as opposed to subcutaneous adipose) has all the molecular machinery for local angiotensin II (Ang II) generation and Ang II-stimulated signal transduction. Indeed, adipose tissue overexpression of angiotensinogen increases blood pressure in mice (16). Furthermore, an autocrine positive feedback loop for the RAAS appears to amplify generation of its components. Activated RAAS may potentiate obesity by stimulating appetite and by acting as a trophic factor for adipocytes; this increases adipocyte mass and preadipocyte differentiation and fuels a vicious cycle.

Ang II is a powerful stimulus for aldosterone synthesis; yet elevated plasma levels of aldosterone in obesity cannot be explained solely by renin or by elevated potassium levels (17). Moreover, other aldosterone-activating factors originating from adipocytes, including leptin, adiponectin, interleukin-6 (IL-6), or tumor necrosis factor-α (TNF-α), are not involved. Instead, fat cell activation of Wnt-signaling molecules stimulates frizzled receptors in the adrenals to increase secretion of aldosterone as well as cortisol (18). These observations suggest a direct link between adiposity, aldosterone, and hypertension.

**HYPERINSULINEMIA/INSULIN RESISTANCE**

Hypertension is regularly associated with increased plasma levels of insulin, and experimental and clinical studies find that increased adiposity promotes hyperinsulinemia. Such observations led to the idea that insulin is a key factor underlying obesity-related hypertension. It is true that insulin increases sodium reabsorption and expands extracellular fluid volume but this is not sufficient to produce sustained hypertension. Rather, obesity-associated insulin resistance contributes to hypertension (Fig. 2). The effects of insulin resistance are exerted in combination with other metabolic, hormonal,
and hemodynamic disturbances of obesity, such as activated sympathetic tone and increased activity of the RAAS, and increased levels of fatty acids, leptin, resistin, and glucocorticoids.

**Obstructive Sleep Apnea (OSA)**

In adults, OSA is an independent risk factor for the presence as well as future development of hypertension. As many as 30% of hypertensive adults have obesity-linked OSA, the severity of which parallels the elevation in blood pressure (19). Even in the absence of obesity, OSA predicts hypertension; conversely, its treatment can in some cases reduce blood pressure. Experimentally, cyclical intermittent upper airway obstruction in non-obese rats and dogs led to hypertension during the waking periods.

OSA in childhood has long been linked to neurocognitive and behavioral problems, but recent studies reveal an association with metabolic and hemodynamic abnormalities, especially in the setting of obesity. Children with OSA have elevated diurnal and nocturnal systolic and diastolic pressure (20). Interestingly, even individuals with primary snoring, which is considered a mild form of OSA, have increased daytime blood pressure with reduced arterial distensibility. It is therefore possible that the link between OSA and hypertension demonstrated in adults begins early in childhood, especially in obese children.

The pathogenesis of increased blood pressure and hypertension with OSA includes recurrent episodes of apnea and intermittent hypoxia/carbon dioxide retention and negative intrathoracic pressures, which depress myocardial contractility, elevate heart rate, and activate the sympathetic nervous system and RAAS. In addition, OSA has been linked to enhanced inflammation and oxidative stress, which likely disrupt nitric oxide bioactivity and lead to endothelial dysfunction and elevated blood pressure.

**Adipose Tissue-Related Metabolic Factors**

*Adiposity.* Although increased weight is regularly accompanied by increased blood pressure, there is considerable inter-individual variability and not all obese individuals become hypertensive. As noted above, the divergence between obesity and hypertension has been taken to reflect ethnic and genetic factors as well as the differential impact of varying components of adiposity. There is now strong evidence that fat distribution, specifically visceral adiposity, is a key determinant of hypertension (21). Even normal weight individuals who demonstrate insulin resistance and hypertension have increased intra-abdominal fat mass. Waist circumference and waist-to-height ratios are also good predictors of hypertension in children, especially obese children, suggesting a pathophysiologic role of visceral fat per se (22). Fat mass assessed by bioimpedence correlated not only with established hypertension but also with blood pressure within the entire normal range in healthy children (23).

Visceral fat, as opposed to subcutaneous or intramuscular fat, has strong associations with many pathophysiologic features. Accumulation of large poorly differentiated preadipocytes in visceral fat augments production of bioactive molecules including angiotensinogen, plasminogen activator inhibitor (PAI-1), endothelin, and reactive oxygen species that can vasoconstrict and remodel blood vessels. Moreover, visceral fat is often infiltrated by macrophages that constitute an important source of pro-inflammatory mediators including TNF-α, IL-6, monocyte chemoattractant protein 1 (MCP-1), and inducible nitric oxide synthase (iNOS). Fatty acids released by adipocytes stimulate TNF-α released by macrophages which, in turn, can enhance production of IL-6 by fat cells, further amplifying the inflammatory response. Notably, mice deficient in IL-6 have a blunted hypertensive response to stress (24). Many of the bioactive substances produced by macrophages also inhibit preadipocyte differentiation, further expanding a population of large, dysfunctional, insulin-resistant adipocytes that may fuel the vicious cycle between obesity and hypertension.
**Free fatty acids.** Non-esterified free fatty acids (NEFA) derived from lipolysis of triglycerides are major secretory products of adipose tissue. Acute elevation in plasma NEFA increases blood pressure in experimental animals and humans (25,26). Chronic elevation of NEFA observed in those with central obesity correlates with elevated blood pressure. Baseline elevation of NEFA is a highly significant independent risk factor for developing hypertension in non-diabetic, non-hypertensive men. The pathophysiological mechanisms involve stimulation of α-adrenergic tone which causes vasoconstriction, reduces baroreflex sensitivity, and enhances tubular sodium reabsorption. NEFA also stimulate expression of angiotensinogen in preadipoocytes and aldosterone in adrenal cells that can increase blood pressure through vasoconstriction, vascular remodeling, and sodium reabsorption. NEFA reduce endothelial nitric oxide synthase and thus nitric oxide(NO)-mediated vasodilatation as well as insulin-induced vasodilatation, which is NO-dependent. Finally, NEFA increase oxidative stress in vivo and in vitro, another mechanism postulated for development of hypertension.

**Leptin.** Leptin is an adipocyte gene product that regulates food intake, energy expenditure, and intracellular lipid homeostasis. Circulating levels of leptin parallel fat stores, increasing with overfeeding and decreasing with fasting or caloric deprivation. Absence of leptin or a mutation in the leptin receptor causes massive hyperphagia in animals and humans. Yet these mutations are not accompanied by hypertension; this underscores the complexity of leptin modulation of blood pressure.

Increased leptin levels in obesity are associated with increased blood pressure. However, the relationship is modulated by the duration of hyperleptinemia and its site(s) of action (centrally or systemic) (27). Leptin’s pressure effect also depends upon the relative contributions of sympathetic tone, endothelin-1, reactive oxygen species, activation of endothelial nitric oxide synthase, and renal regulation of sodium-volume balance. For example, while both intracerebral and systemic infusion of leptin increased sympathetic nerve activity to a similar degree, the lack of pressure elevation following systemic administration indicates a counter-regulatory systemic vasodilation that likely reflects NO production (28–30).

Leptin also modulates renal handling of sodium and water (29). The normal leptin-induced increase in urinary sodium and water excretion is blunted in obesity. The perturbation appears independent of systemic or even renal hemodynamics and may reflect a direct tubular effect. The increase in sodium and water reabsorption appears to reflect enhanced renal sympathetic tone and decreased local NO.

**Adiponectin.** In contrast to other adipocytokines which are elevated in obesity, adiponectin levels are depressed. Plasma levels are inversely related to obesity and suggest that adiponectin may have protective or adaptive functions. Indeed, adiponectin has insulin-sensitizing, anti-diabetic, anti-inflammatory, and anti-atherogenic effects. Hypoadiponectinemia was shown to be an independent risk factor for hypertension in cross-sectional and prospective studies in lean and obese hypertensive adults and adolescents, even after adjustments for BMI, age, glucose, and cholesterol levels (31,32). It is notable that antihypertensive treatment (ACE inhibition with ramipril or angiotensin receptor antagonism with valsartan) elevates circulating adiponectin level and insulin sensitivity in parallel with their effects on blood pressure. It is of further interest that a subset of obese individuals with adiponectin concentrations similar to those of normal weight subjects did not have metabolic abnormalities including hypertension (33). Experimentally, adiponectin replenishment ameliorated obesity-related hypertension in the KKAy mouse model, while hypertension in salt-fed adiponectin-deficient mice was reversed by adiponectin treatment (34). Hypoadiponectinemia likely contributes to hypertension by way of endothelial dysfunction that is independent of insulin resistance, BMI, or lipid status; adiponectin upregulates endothelial NO synthase expression and reduces ROS production, resulting in heightened NO production and bioavailability in endothelial cells. Experimental and clinical hypoadiponectinemias are associated with endothelial cell dysfunction and impaired endothelium-dependent vasodilation as well as disinhibition of leukocyte-endothelium adhesion and activation of the RAAS.
RENAL DISEASE

*Clinical Spectrum of Obesity-Related Glomerulopathy (ORG)*

High-grade proteinuria in obese adults that remitted with weight loss and returned with weight gain was first described in 1974 (35). The renal histology was comparable to idiopathic focal segmental glomerulosclerosis (FSGS). The term obesity-related glomerulopathy (ORG) is now used to describe this secondary form of FSGS. From the 1980s to the 1990s, a 10-fold increase in biopsy-proven ORG was noted in adults (36). Underscoring the gravity of ORG in obese adults, the progression to end-stage renal disease occurs in 3% of patients at 2-years follow-up and in 33% at 10 years (36,37).

ORG is increasingly recognized in the pediatric population. One report documented ORG in an 8-year-old child with BMI 58.1 kg/m², but in most series ORG is detected in the second decade of life (36,38–40). The clinical characteristics of ORG in pediatric patients are similar to those in adults. The condition is milder than idiopathic FSGS; daily protein excretion is lower (1.8–4.5 g/day), serum albumin is normal or only minimally depressed, and edema is absent or mild. About half of pediatric patients with ORG are hypertensive or hyperlipidemic. Some also have obstructive sleep apnea. Many have been shown to respond to inhibition of the renin–angiotensin system with marked reduction in proteinuria, though as in adults, this may not prevent progressive glomerulosclerosis (37–39). While this chapter focuses primarily on ORG, there is accumulating evidence that obesity potentiates progression of other renal diseases including IgA nephropathy, transplant nephropathy, and renal damage associated with congenitally reduced endowment of nephron number (41,42).

In clinical practice, proteinuria is a well-accepted indicator of renal injury and comprises a spectrum from microalbuminuria (30–300 mg/g creatinine; not detectable by routine urinalysis) to overt proteinuria (>300 mg/g creatinine, detectable by dipstick). As in other glomerulopathies, obesity-associated microalbuminuria appears to be an early indicator of renal damage (43). The prevalence of microalbuminuria in obesity is increased and parallels the BMI. Further, even among normoglycemic first-degree relatives of type-II diabetics, central obesity has been found to be an independent risk factor for microalbuminuria (44). Likewise, in 10,000 young adults, BMI>35 showed significant increases in albuminuria compared to lower BMI groups (45). Albuminuria correlates with substantial renal structural alteration even with normal renal function (see below) (43). As with any renal injury, the presence of hypertension accelerates glomerular injury.

Thus, it is reasonable to assess urine albumin excretion in obese pediatric patients. Children and adolescents with BMI>95th percentile should be assessed for microalbuminuria and glomerular filtration rate by serum creatinine. Thereafter, urine microalbumin should be followed yearly. Currently there are limited data to guide therapeutic interventions, although reports of efficacy by inhibition of the renin–angiotensin system in advanced obesity-related glomerulopathy suggest a potential benefit. Control of hypertension is essential to limit progression of renal disease.

*Renal Hemodynamics*

There are significant changes in renal hemodynamics even at the early stages of obesity. One study showed that adults with mean BMI 43.8 kg/m² had glomerular filtration rate (GFR) 51% higher than that of normal weight controls. The renal plasma flow (RPF) is also elevated, though not to the same degree (46). As a result, the filtration fraction (defined as GFR/RPF) is increased, a hemodynamic adjustment that parallels the degree of BMI and adipose mass (47,48).

Glomerular filtration is determined by the pre- and post-glomerular arteriolar tone, both of which are altered by obesity. Molecular sieving experiments in obese individuals suggest that afferent arteriolar vasodilatation together with efferent arteriolar vasoconstriction contribute to the increase in filtration fraction (46). Experimentally, obese rats have been found to have heightened renal vascular resistance in response to infusions of Ang II. As the Ang II type-I receptor density is highest
in the efferent arteriole, these data suggest that obesity promotes renal efferent arteriolar vasoconstriction (49). Furthermore, inhibition of Ang II action in obese subjects increases renal plasma flow, again pointing to efferent arteriolar vasoconstriction as a prominent renal response to obesity (50). Increased filtration fraction has been linked to glomerular injury and scarring through mechanisms that include elevated glomerular pressure and stimulation of local growth factors. In this connection, obesity-induced GFR increase is not fixed. Several studies report that hyperfiltration may normalize following gastroplasty (51,52).

**Tubuloglomerular Feedback**

Tubuloglomerular feedback (TGF) describes the coupling of each nephron’s distal tubule flow to glomerular filtration. Nephron anatomy dictates that the distal tubule signals to its originating glomerulus and contributes to the formation of the macula densa, which encompasses specialized tubular cells abutting the afferent and efferent arterioles. The stimulus to adjust GFR includes the rate of distal tubular flow and the composition of tubular fluid. The signal is perceived in the macula densa and transmitted to the vascular structures of the nephron, particularly the afferent arteriole, which adjusts the rate of filtration. An inverse relationship between tubular flow and filtration is thus established, such that an increase in tubular flow decreases glomerular filtration and vice versa. In simplest terms, increased luminal NaCl leads to a decrease in glomerular filtration through afferent arteriolar vasoconstriction (53).

In obesity, volume expansion is due, at least in part, to increased salt reabsorption in the proximal tubule; this is mediated by increased sympathetic tone, Ang II, adipokines, and increased oncotic pressure of the tubular blood supply caused by glomerular hyperfiltration. By lowering tubular NaCl relative to GFR, these obesity-dependent change mechanisms disrupt the TGF response, preventing suppression of GFR (54). Given the high rate of hypertension in obese individuals, the inadequacy of TGF feedback and failure to constrict the afferent arteriole may allow transmission of systemic BP to the glomerulus, contributing not only to increased GFR but eventually to renal damage (55).

**Proteinuria**

A hallmark of renal manifestations of obesity/ORG is proteinuria, the magnitude of which is relatively modest and not usually associated with nephrotic syndrome. Thus, presentation with hypoalbuminemia and edema is rare (36–38). The lack of edema may delay detection of proteinuria and increase the chance for progressive glomerulosclerosis and loss of renal function. Indeed, in one study of ORG, those who progressed to end-stage renal failure (ESRD) had elevated serum creatinine at presentation (37). In a Chinese cohort of patients with ORG, protein excretion rose with increasing BMI (56). Yet, the severity of glomerulosclerosis on biopsy was similar across the range of BMI, suggesting that additional intrarenal hemodynamic derangements contributed to excess proteinuria with increasing adiposity.

It should be emphasized, however, that a third of the cohort with biopsy-proven ORG had only mild proteinuria (400 mg/24 h). These findings suggest that the renal pathophysiologic processes that culminate in ORG are already present at a time when proteinuria is only modestly elevated or even before overt proteinuria is detected.

Proteinuria in ORG can in some cases be dramatically lessened with weight loss (35,57). Bariatric surgery has in some studies normalized protein excretion in adult and pediatric patients with ORG (39,58). However, enthusiasm for surgery is tempered by its association with oxalate nephropathy and renal failure post-op (59). As noted previously, pharmacologic agents that reduce blood pressure may (in some but not all cases) reverse microalbuminuria and limit the progression of renal disease in obese subjects.
Renal Morphology

The primary light microscopic feature of ORG that differentiates it from primary FSGS is glomerulomegaly (36,37,60) (Fig. 3). Increased glomerular filtration due to increased transcapillary hydraulic pressure likely contributes to glomerulomegaly (60). Glomerulomegaly has been linked to the pathogenesis of glomerulosclerosis, with a correlation between glomerular size and degree of sclerosis in a given glomerulus during the early stages of injury (61). Increased glomerular size may not directly cause sclerosis, but may be an early manifestation of processes that promote cell growth and extracellular matrix synthesis. Additionally, the link of glomerulomegaly and sclerosis may reflect the limited capacity of mature podocytes to divide. Thus, with increasing glomerular size, the resulting reduction in relative podocyte density may become a stimulus for further injury. In this regard, a study of patients with ORG found that glomerulomegaly was accompanied by a 45% reduction in podocyte density (60). Experimentally, loss of podocytes (through immune targeting) has been shown to induce glomerulosclerosis (62).

![Image of glomerulopathy](image)

**Fig. 3.** Morphologic changes of obesity-related glomerulopathy. (a) Glomerulomegaly and focal small segmental adhesion with early sclerosis (Jones silver stain, ×100). (b) Glomerulomegaly and hilar segmental sclerosis at the vascular pole (periodic acid–Schiff, ×400). (c) Transmission electron microscopy showing subtotal foot process effacement (×4,000) (39).

It is important to underscore that progressive glomerular destruction, regardless of cause, will culminate in tubulointerstitial fibrosis. It is therefore of interest that compared with idiopathic FSGS, obesity-associated FSGS has less interstitial alpha smooth muscle actin and TGF beta and lower interstitial volume, suggesting relative preservation of the tubulointerstitium (63). Such observations may explain the lower rates of progression to ESRD of ORG compared to idiopathic FSGS.

It is interesting that glomerular pathology is also observed in obese patients without clinically apparent renal disease. Thus, autopsies of two boys with Prader–Willi syndrome without renal dysfunction or proteinuria revealed marked glomerulomegaly (64). Similarly, examination of renal morphology in extremely obese adults (mean BMI 52 kg/m²) revealed that 5% of patients had segmental glomerulosclerosis in 6% of glomeruli. Mean glomerular planar area was 50% higher compared to normal weight controls (43). As noted in other studies, only 4% of these individuals had significant proteinuria (none >500 mg/day). Even obese individuals, considered well enough to serve as renal transplant donors, had 15% larger glomeruli compared to non-obese donors. No data exists as to persistence of glomerulomegaly in these donor kidneys in non-obese recipients, though the possibility of correction in a non-obese milieu seems plausible (65).
Pathophysiologic Mechanisms

RENNIN–ANGIOTENSIN–ALDOSTERONE SYSTEM (RAAS)

The RAAS is a major regulator of systemic and renal vasomotor tone that affects renal blood flow and glomerular filtration and promotes the growth of renal cells. As noted previously, the adipocytes and infiltrating macrophages of adipose tissue constitute important sources of RAAS components. For example, per weight of tissue, visceral fat expression of angiotensinogen (Aog) is comparable to that of the liver. Circulating levels of Aog correlate with increasing BMI both at normal and elevated weight. Conversely, fasting dramatically reduces adipocyte expression of Aog in experimental animals. Weight loss also reduces the serum levels of angiotensin-converting enzyme (ACE), the predominant enzyme necessary for production of the effector ligand angiotensin II (66). The Ang II type-1 receptor (AT1), primarily responsible for post-glomerular (effenter) arteriolar vasoconstriction, is dramatically elevated in the renal cortex of obese Zucker rats compared to lean Zucker controls (67). Renal AT1 is also upregulated in transgenic mice overexpressing angiotensinogen exclusively in adipocytes (68). These studies suggest that an adipose-derived increase in circulating RAAS ligands and an adipose-driven increase in renal AT1 receptor provide a powerful combination for increasing effenter arteriolar vasoconstriction, glomerular pressure, and cellular proliferation that promote structural damage.

As with other chronic proteinuric glomerulopathies, inhibition of the renin–angiotensin system has been employed successfully to treat obesity-related glomerulopathy. Likewise, aldosterone blockade lessens renal injury in the vascular, glomerular, and tubulointerstitial compartments. These benefits are independent of its antihypertensive effects; presumably, the drugs block the effects of aldosterone on plasminogen activator inhibitor-1 and TGF-β, reactive oxygen intermediates, inflammatory mediators, and podocyte function (69). Aldosterone antagonism attenuates obesity-induced glomerular hyperfiltration in high fat-fed dogs (70). While the role of aldosterone in renal damage in obese humans has not yet been explicitly demonstrated, the compelling nature of animal data has prompted suggestions to use aldosterone antagonism for obesity-related kidney injury (71). The antiproteinuric benefits of angiotensin-converting enzyme inhibition or aldosterone blockade may be reversed by progression of obesity or weight re-gain (37–39).

METABOLIC/ADIPOCYTE FACTORS

Receptors for leptin have been demonstrated in the renal inner medulla and in vascular structures of the renal corticomedullary region. Rapid diuresis follows a single intraperitoneal injection of leptin; this may serve to counterbalance its effect on adrenergic activity. Leptin also affects renal cellular growth. Cultured glomerular endothelial cells proliferate when stimulated by leptin and increase TGF-β production (72). In mesangial cells, leptin increases collagen type I production, cellular hypertrophy (but not proliferation), and the expression of TGF-β receptors, thereby sensitizing them to the increased TGF-β produced by adjacent glomerular endothelial cells (73). Chronic leptin infusion resulted in increased glomerular type-IV collagen as well as an increase in proteinuria in rats. Conversely, in a mouse model of renal tubulointerstitial injury, leptin deficiency was protective. Thus, after unilateral ureteral obstruction, the leptin-deficient mice had less cellular infiltrate, less TGF-β expression, less alpha smooth muscle actin and fibronectin staining, and less interstitial fibrosis than wild-type controls (74).

As noted previously, hypoadiponectinemia is associated with insulin resistance, inflammation, atherosclerosis, and hypertension (32,75). In the kidney, adiponectin supports normal function of the podocyte (76). Thus, adiponectin-null mutant mice have podocyte foot process effacement and albuminuria, both of which normalize with adiponectin treatment. Even wild-type podocytes in culture
become more impermeable to albumin when treated with adiponectin. Not surprisingly, adiponectin-null mutant mice have poorer outcomes following renal injury, including increased inflammatory mediators, increased TGF-β, increased glomerular collagen deposition, glomerulomegaly, and albuminuria (77). Taken together, these findings suggest that hypo-adiponectinemia may contribute to obesity-related renal injury. Indeed, among obese African-Americans, there is a strong negative correlation between plasma adiponectin levels and albuminuria, pointing to potential podocyte injury (76). Adiponectin deficiency leads to an increase in NADPH oxidase; renal injury augments this deleterious response with increases in urinary reactive oxygen species (76,77). Conversely, adiponectin stimulates phosphorylation of glomerular AMP-activated protein kinase, which inhibits oxidative stress and maintains normal podocyte architecture (76,78) (Fig. 4). Pharmacologic maneuvers to raise adiponectin levels (such as PPAR-γ agonists) have been proposed as a potential treatment for ORG (76).

![Diagram](image)

**Fig. 4.** Adiponectin is essential to normal podocyte function. Low adiponectin in obesity triggers glomerular podocyte effacement and albuminuria. Potential mechanisms include increased oxidative stress through NADPH oxidase 4 (Nox4) enhancement and reduction of 5AMP-activated protein kinase (AMPK) activation. Adapted from Zoccali et al. (78).

Other adipocytokines have relevance for renal damage. For example, TNF-α levels rise with increasing adiposity (79) and reduce adiponectin levels. Glomeruli from ORG patients have increased expression of TNF-α and a doubling of TNF receptor 1 (80). These observations suggest that TNF-α may directly contribute to obesity-induced renal damage, possibly through stimulation of TGF-β, macrophage infiltration, and apoptosis.

Circulating levels of interleukin-6 (IL-6) increase with obesity, with as much as 30% derived from adipose tissue (81). IL-6 is the most important regulator of the hepatic acute phase response, which includes C-reactive protein (CRP). Strong epidemiologic data connect CRP with poor cardiovascular outcomes, and CRP may participate directly in vascular wall pathology (82). Visceral adipose volumes were highly correlated with circulating IL-6 and CRP levels in Framingham subjects, and even obese children show dramatic elevation of CRP compared to normal weight controls (83,84). Evidence for IL-6 involvement in vascular and renal disease beyond CRP is found in IL-6 induction of ATI receptor...
in vitro and in vivo and subsequent increase in angiotensin-mediated oxidative stress (79). Glomeruli from patients with ORG show a twofold increase in expression of IL-6 signal transducer, pointing to the possibility of direct IL-6 pathogenicity in glomeruli (80). However, whether increased IL-6 plays a pathogenic role in ORG or is only an epiphenomenon is currently not known.

Obesity causes other metabolic disturbances that may contribute to renal damage. Excess intracellular free fatty acids are thought to be shunted toward the production of reactive intermediates such as fatty acyl CoA, diacylglycerol, and ceramide which are cytotoxic. LDL has numerous glomerular effects, promoting mesangial cell proliferation and mesangial cell production of extracellular matrix, plasminogen activator inhibitor (PAI-1), and TGF-β. Sterol regulatory element binding transcription factor-1 (SREBP-1) is upregulated in high-fat-fed, obese C57BL/6 J mice that develop glomerulosclerosis and proteinuria (85). Transgenic overexpression of SREBP-1a resulted in increased lipid accumulation in glomeruli and tubular cells as well as glomerulosclerosis. Conversely, mutant mice with inactivated SREBP-1c were protected from glomerulosclerosis when fed a high-fat diet. Glomerular expression of these lipid-related transporters was upregulated in glomeruli from patients with ORG; fatty acid-binding protein was upregulated fourfold, LDL-receptor twofold, and SREBP-1 twofold (80). Thus, lipid disturbances often associated with obesity provide additional mechanisms for glomerular injury.

**SUMMARY**

While hypertension and renal damage have long been recognized to be interrelated, obesity dramatically amplifies each of these abnormalities. The obesity epidemic, now well entrenched in the pediatric population, is expected to increase these complications. Current therapies aimed at lessening elevated blood pressure and slowing progressive renal damage will likely be supplemented by interventions aimed at obesity-specific targets.

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**Editor’s Questions and Authors’ Response**

- **What are the indications for renal biopsy in an obese child with microalbuminuria?**

  Renal biopsy is commonly performed in children with urine albumin excretion exceeding 1 g/day. However, significant renal damage may occur in obese subjects with lower levels of proteinuria and normal renal function; the mean level of proteinuria in a recent series of adults with biopsy-proven ORG was only 400 mg/day. It seems reasonable therefore to consider renal biopsy in obese children and teens with urine albumin excretion >400 mg/g creatinine.

- **Do we have long-term data on the benefits of pharmacologic treatment of microalbuminuria in children?**

  While data on the long-term benefits of treatment with inhibitors/antagonists of the renin-angiotensin system do not exist, biopsy findings of significant structural changes in obese patients with only microalbuminuria suggest a benefit for such intervention. Thus, even in the absence of hypertension or increased creatinine, persistent or increasing microalbuminuria (albumin to creatinine ratio of >30 μg/mg creatinine in a first morning void documented at least 3 times in a 6-month period) warrants treatment with an angiotensin-converting enzyme inhibitor or receptor antagonist. There is currently little data on the use of aldosterone inhibitors in this setting.
REFERENCES


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