Obesity remains a prominent public health concern. According to recent national estimates, 16.9% of youth and 34.9% of adults are obese (61). Obesity is often compounded with hypertension, diabetes, and atherosclerosis, contributes greatly to cardiovascular events, and manifests a direct linear relationship with mortality (74).

Obesity has been identified to initiate and affect the progression of preexisting chronic kidney disease (CKD) (77). The relative risk of developing proteinuria secondary to obesity is 1.45, comparable to hypertension (76). Obesity is also a strong independent risk factor for end-stage renal disease (ESRD) (37). In a prospective cohort study, the odds-ratio of body mass index (BMI) for developing ESRD after adjustment for age, sex, systolic blood pressure, and proteinuria was 1.3 (41), with cumulative incidences of ESRD per 1,000 screenes rising from 2.48 to 5.81 upon increment of BMI quartiles. Another case-control study that included 926 CKD patients and 998 control subjects showed a threefold increased risk of developing renal failure among patients who were overweight at age 20 but without diabetes or hypertension (25). Interestingly, a recent study showed a U-shaped association of BMI with clinical outcomes in veteran CKD patients with estimated GFR <60 ml·min$^{-1}$·1.73m$^{-2}$, with the best outcomes observed in overweight and mildly obese patients (56). This observation may reflect a protective effect of sustained body weight in patients with ESRD, which might offset the grave outcomes associated with muscle wasting in that condition. Moreover, apparent weight gain might be complicated by fluid retention. Clearly, cautious and individualized body weight management is required for patients with severe CKD and ESRD.

The prevalence of renal vascular disease, such as renal artery stenosis (RAS), is growing world-wide, especially in the elderly population and in individuals with atherosclerotic risk factors like obesity. In addition to hypertension and progressive renal functional decline, RAS is linked to cardiovascular morbidity and mortality (19). One of the major mechanisms of renovascular pathophysiology in RAS involves activation of the renin-angiotensin-aldosterone system, which instigates inflammation, oxidative stress, and microvascular remodeling in the kidney, promoting tissue scarring (85). Such irreversible tissue remodeling is at least partly responsible for the disappointing renal outcomes after revascularization (20).

Not only does obesity contribute to atherosclerosis that initiates RAS, it also aggravates kidney damage directly, thereby worsening the structural and functional outcomes of renovascular disease. Although the pathways activated in obesity are incompletely understood, adaptations to increased body mass/excretory load, sodium retention, activation of the renin-angiotensin-aldosterone system, and adverse effects of insulin resistance (IR) are all important pathogenic factors implicated in obesity-induced kidney injury (2). Of these, the most prominent effects on the stenotic kidney seem to involve exacerbation of microvascular loss and inflammation.

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Post-Stenotic Kidney Hemodynamics in Obesity

Substantial evidence has shown that obesity directly influences renal hemodynamics. A 1-mo high-fat diet promptly increases the extracellular fluid and causes a shift in sodium balance (33). Elevated aldosterone levels due to activation of the renin-angiotensin-aldosterone system and increased sympathetic activity in obesity are likely the major culprits that promote sodium retention (4, 30) by increasing tubular reabsorption. Elevated salt reabsorption at the segment proximal to the macular densa also induces a rise in glomerular filtration rate (GFR) through tubuloglomerular feedback. In addition, when the filtration fraction is elevated (13), glomerular hyperfiltration could increase protein concentration in the postglomerular circulation and elevate oncocytic pressure in the plasma entering the peritubular capillaries compared with the systemic circulation, which promotes proximal tubular sodium reabsorption and salt retention (38, 63). However, in obese individuals with parallel increases in GFR and renal plasma flow and with a normal filtration fraction (13), this mechanism is unlikely to play a major role. However, augmented proximal tubular reabsorption and glomerular hyperfiltration may comprise a vicious cycle underlying altered renal and systemic hemodynamics.

The hemodynamic changes elicited by obesity in the poststenotic kidney may also increase renal blood flow (RBF) (77), at least at its early stages. Nevertheless, the apparent preservation of stenotic kidney GFR and RBF (48, 83) does not halt the pathological events taking place in the stenotic kidney during obesity. In fact, the stenotic kidney of obese swine shows diminished microvascular reactivity (50), greater inflammation, and fibrosis (83). This might be due to oxidative stress and inflammation initially evoked by ischemia and amplified by obesity, which subsequently offsets its ostensible protective effect on GFR and RBF. Furthermore, the deleterious effects of obesity in unilateral RAS can be detected in both kidneys. The contralateral kidney in RAS often is characterized by pronounced hyperfiltration, which is further augmented in obesity (83). Excessive kidney hypertrophy is followed by pronounced hyperfiltration, which is further augmented in obesity (83). Excessive kidney hypertrophy is followed by increased intrarenal pressures, impaired pressure natriuresis, and hypertension (34). Furthermore, proximal tubular epithelial cells can undergo hypertrophy in obese patients (73), which may account for increased sodium reabsorption and elevation of arterial pressure.

In obesity, aldosterone can be excessively produced by adrenal glomerulosa cells, which possibly receive signals from hepatocytes responding to fatty acids (31). In addition, adipocytes are rich sources of the precursor protein of ANG II and angiotensinogen (82) as well as aldosterone synthase (4). In rodents, adipose tissue contains angiotensinogen mRNA, reaching 68% of liver levels (55), and all the enzymes necessary to produce ANG II and its receptors (86). Aldosterone produced by adipocytes can also be stimulated by extrinsic source of ANG II (4), which is commonly upregulated in RAS. Obese subjects show elevated aldosterone levels in both the plasma (5) and urine (35). A 5% weight loss in obese females leads to a reduction of renin-angiotensin-aldosterone activity not only in the adipose tissue but also in the plasma (26). The fall in plasma angiotensinogen is highly correlated with the waist circumference decline (26). Furthermore, in 1,674 subjects in the general population, plasma aldosterone was independently associated with obesity (odds ratio 1.34) (5). Taken together, these findings strongly suggest activation of the renin-angiotensin-aldosterone system in obesity which may serve as an important pathophysiological pathway in individuals with coexistence of RAS and obesity. Notably, due to the presence of RAS and a decrease in perfusion pressure, the stenotic kidney may be initially protected from systemic hypertension, and the effects of magnified blood pressure likely affect mainly the nonstenotic kidney.

Post-Stenotic Kidney Microcirculation

Obesity is characterized by tissue microvascular remodeling, involving dysregulated expression of angiogenic factors and neovascularization. Both human and animals studies have shown proangiogenic effects of obesity in the liver, heart, and kidney (16, 75, 84). Neovascularization evolves as obesity progresses (39), is often associated with increased vascular endothelial growth factor (VEGF) signaling (66, 83), and triggered by adipokines (8, 39). However, microvascular proliferation might be short-lived, because these newly formed microvessels are unstable and prone to loss, especially in tissues subjected to other concurrent insults that jeopardize the vasculature. Indeed, in the poststenotic kidney, obesity may precipitate or magnify loss of renal microvessels (83), thereby aggravating tissue injury. Although additional studies are needed, in swine this bidirectional effect on microvascular viability is accompanied by increased oxidative stress and inflammation, which disrupts the growth and stability of microvessel (52, 83) (Fig. 1). Furthermore, obese patients show impaired endothelium-dependent vasodilation (23), possibly consequent to an imbalance between nitric oxide (NO) and decreased sympathetic nerve activity (10, 62), the contribution of which is underscored by the antihypertensive potency of renal denervation in obesity (54). Increased visceral and retroperitoneal fat may also boost hypertension by compressing the kidneys. The intra-abdominal pressure in obese patient can be double that (70) of normal subjects (17), and excessive fat accumulation in and around the kidneys is associated with increased intrarenal pressures, impaired pressure natriuresis, and hypertension (34). Furthermore, proximal tubular epithelial cells may undergo hypertrophy in obese patients (73), which may account for increased sodium reabsorption and elevation of arterial pressure.
endothelin (ET)-1 production in the microvascular endothelium (9, 42), or enhanced thromboxane receptor activity (80). Hence, microvascular dysfunction might magnify microvascular injury in obesity. Collectively, obesity can adversely affect the microvasculature of the ischemic kidney by impairing angiogenesis and vasoactivity, which might in turn dysregulate renal hemodynamics. Other than the intrarenal microvessels, to date no studies have shown whether obesity affects the severity of the renal arterial lesion.

Inflammation

Obesity involves a chronic inflammatory and oxidative milieu. The adipose tissue, especially the visceral depot, is a major source of cytokine secretion, so that inflammatory cells, especially bone marrow-derived macrophages, invade it early in obesity (78). Subsequently cytokines can be elaborated by adipocytes (e.g., leptin), infiltrating macrophages (e.g., tumor necrosis factor-α), or both (e.g., interleukin-6) (79), and together establish the inflammatory state that characterizes obesity. Leptin, a satiety hormone produced by the adipose tissue, potentiates secretion of tumor necrosis factor-α and interleukin-2 and -6 (53) and enhances expression of monocyte chemoattractant protein (MCP)-1 (81), thereby amplifying inflammation. Leptin may also increase formation of reactive oxygen species in a process coupled with increased fatty acid oxidation and activation of protein kinase A (81), and upregulate NAD(P)H oxidase expression and activity (24) to promote oxidative stress. Conversely, adiponectin is inversely associated with MCP-1, elevates antioxidant defenses, and lower lipid peroxidation. Also, its levels are reduced in obese subjects (32), further potentiating the proinflammatory and oxidative effects of the adipose tissue.

In addition, ectopic lipid deposition in the kidney as a result of systemic hyperlipidemia also causes structural and functional changes in mesangial cells, podocytes, and proximal tubular cells (46). Such “fatty kidneys” in humans have been shown to double the risk for developing parenchymal damage (27). Whether perirenal fat is capable of causing

Fig. 1. Representative microcomputed tomography images showing the intrarenal microvasculature in lean, obese, renal artery stenosis (RAS), and obese+RAS pigs. Microvascular density is markedly decreased in Obese+RAS kidneys compared with RAS alone, suggesting aggravated microvascular loss.
local inflammation in the adjacent kidney remains to be established.

**IR**

Over the past decade, a large number of endocrine, inflammatory, neural, and cell-intrinsic pathways have been shown to be dysregulated in obesity, and their dynamic interplay underlies the pathophysiology of IR (64). IR that often develops in obesity has been implicated in the progression of kidney disease (22). This might be expected, given that the kidney is highly responsive to insulin, which binds to all the cells of the glomerulus and the entire length of the renal tubules (6, 59).

Podocytes, a major component of the glomerular filtration barrier, seem to have the highest levels of insulin receptors compared with endothelial and mesangial cells (58). In fact, insulin may control podocyte contractility that contributes to glomerular permeability (43, 44). Insulin may also regulate GFR through local renal vasodilatation, which can be blocked by indomethacin (18) and augmented by activation of endothelial NO synthase (36), implicating prostaglandins and NO, respectively, in the effect of insulin.

In the context of obesity, IR has been shown linked to alterations in renal structure or function. Podocytes isolated from the db/db mouse model of obesity and type 2 diabetes demonstrate reduced response to insulin and develop albuminuria, early glomerular disease, and decreased cell viability (71). A fall in adiponectin level, which is linked to insulin sensitivity, leads to exacerbation of podocyte injury and greater tissue damage in mice (65, 68). On the other hand, IR developing in the absence of overt obesity or diabetes might also contribute to renal injury, and vice versa. For example, uremia can cause IR by inducing a post-receptor defect in the insulin pathway (29) involving toxic components in the uremic serum (57). The effect of insulin in increasing of GFR in normal individuals might be lost in nonobese subjects with IR (72). Moreover, in slightly overweight patients (mean BMI = 26.3 kg/m²) without diabetes, the prevalence of CKD significantly and progressively rises with increasing levels of serum insulin and IR (15). These observations underscore a potential interaction between IR and kidney disease. Indeed, insulin-sensitizing compounds, such as thiazolidinediones, have been shown to exert renoprotective effects by abrogating interstitial fibrosis in Zucker obese rats fed a high-protein diet (60). Nonetheless, a causal link between IR and renal injury distal to RAS is yet to be identified, and whether thiazolidinediones can slow renal injury in obesity warrants further studies.

**Interventions in Renovascular Disease Complicated by Obesity**

Since large clinical trials have consistently shown that renal revascularization is successful in a minority of individuals with RAS, novel strategies that directly alleviate parenchymal renal injury might be important in managing RAS patients, especially those with concurrent obesity and diffuse atherosclerosis. Clearly, as obesity is often linked to unfavorable outcomes, lifestyle modifications including controlling body weight are essential as a first-line therapy. Studies have shown that in obese patients with renal hyperfiltration, a decrease of BMI elicited a fall in GFR, plasma flow, and albumin excretion rate (14). An increase in unsaturated free fatty acids protects the podocytes from both apoptotic and necrotic cell death (69) and improves endothelial function in renovascular hypertensive-obese rats (47). Along with dietary modifications, medications or bariatric surgery may be considered in selected patients.

If dietary intervention and weight loss are unsuccessful, alternative interventions may target specific mechanisms underlying target organ injury in obesity. Renin-angiotensin-aldosterone blockade has proved to be a successful in alleviating proteinuria, especially in patients with diabetes, and may decrease obesity-related target organ injury (67). Angiotensin...
RAS are urgently needed to alleviate tissue injury and remodelling, preserve renal function, and slow the progression of kidney disease.

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**DISCLOSURES**

No conflicts of interest, financial or otherwise, are declared by the authors.

**AUTHOR CONTRIBUTIONS**

Author contributions: X.Z. and L.O.L. contributed conception and design of research; X.Z. prepared figures; X.Z. drafted manuscript; X.Z. and L.O.L. edited and revised manuscript; L.O.L. approved final version of manuscript.

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