Role of the Renal Microcirculation in Progression of Chronic Kidney Injury in Obesity

Alejandro R. Chade^{a–c} John E. Hall^{a, d}

^aDepartment of Physiology and Biophysics, Center for Excellence in Cardiovascular-Renal Research, ^bDepartment of Medicine, ^cDepartment of Radiology, and ^dMississippi Center for Obesity Research, University of Mississippi Medical Center, Jackson, Miss., USA

Key Words

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Abstract

Background: Obesity is largely responsible for the growing incidence and prevalence of diabetes, cardiovascular and renal diseases. Current strategies to prevent and treat obesity and its consequences have been insufficient to reverse the ongoing trends. Lifestyle modification or pharmacological therapies often produce modest weight loss which is not sustained and recurrence of obesity is frequently observed, leading to progression of target organ damage in many obese subjects. Therefore, research efforts have focused not only on the factors that regulate energy balance, but also on understanding mechanisms of target organ injury in obesity.

Summary and Key Message: Microvascular (MV) disease plays a pivotal role in progressive kidney injury from different etiologies such as hypertension, diabetes, and atherosclerosis, which are all important consequences of chronic obesity. The MV networks are anatomical units that are closely adapted to specific functions of nutrition and removal of waste in every organ. Damage of the small vessels in several tissues and organs has been reported in obesity and may increase cardio-renal risk. However, the mechanisms by

which obesity and its attendant cardiovascular and metabolic consequences interact to cause renal MV injury and chronic kidney disease are still unclear, although substantial progress has been made in recent years. This review addresses potential mechanisms and consequences of obesity-induced renal MV injury as well as current treatments that may provide protection of the renal microcirculation and slow progressive kidney injury in obesity.

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Introduction

The worldwide population is not only growing in numbers but also in size. Overweight and obesity are the major epidemics of the 20th and 21st centuries. Although recent epidemiologic assessments may suggest a slowdown, they also show that growth in obesity is in the upslope of its trajectory and prevalence is steady or increasing in developed and developing countries, among men and women, children, adolescents and adults [1, 2]. Obesity should be one of the most preventable diseases but it is evident that recent and current educational efforts have failed to counteract current trends. Therefore, we are now facing the impact and consequences of obesity as a major risk factor and cause for cardiovascular,

renal, gastrointestinal, metabolic and rheumatic diseases, with a tremendous impact on quality of life and health-care costs.

Recent statistics from the Centers for Disease Control [3], the National Institutes of Health [4] and the World Health Organization [5] show that obesity has more than doubled since 1980 and almost 2 billion adults worldwide are overweight or obese. Currently, 68.8% of adults in the US are overweight or obese [4] at higher risk of developing life-threatening consequences; at least 35% of adults are obese and 6–8% have extreme obesity (body mass index (BMI) over 40). The prevalence of obesity is slightly higher in women than men (40.4 vs. 35%) [2]. Another frightening statistic is that over 33% of children and adolescents in the US are overweight and over 18% are obese [3, 4]. Since approximately 80% of obese children become obese adults, it is likely that the prevalence of obesity and associated cardiovascular, metabolic and kidney diseases will continue to increase unless these trends can be reversed. Therefore, we can assume that over two-thirds of the population is at higher risk of developing life-threatening consequences of overweight and obesity.

Obesity as a Major Risk Factor for Chronic Kidney Disease

The global increase in chronic kidney disease (CKD) parallels the obesity epidemic. Obesity is widely recognized to increase the risk for development of CKD through diabetes and hypertension which together account for more than 70% of end-stage renal disease (ESRD) [6]. Obesity also increases the risk of CKD in the absence of known cardiovascular risk factors or underlying nephropathy [7] and is therefore considered an independent risk factor for development of renal dysfunction and injury that can progress toward CKD and ESRD [8, 9]. Obesity may be one of the most preventable etiologies of CKD as the prevalence of CKD doubles in the obese compared to lean subjects [10]. Obesity can also exacerbate the development and progression of renal injury in other forms of renal disease such as IgA nephropathy [11] or amyloidosis [12].

In a retrospective analysis of 320,252 adults followed for 15–35 years, the rate of ESRD rose progressively as BMI increased and this relationship remained after adjustment for blood pressure, diabetes, smoking, age and several other variables [13]. Abdominal obesity is even more closely associated with CKD than overall adiposity

or increased BMI [14]. Moreover, individuals with ‘fatty kidneys’ (high renal sinus fat levels) had a higher risk for CKD even after adjustment for BMI and visceral adiposity [15]. Thus, increased adiposity, especially when it is localized in and around the kidneys, may contribute to CKD and ESRD, although the mechanisms involved are not fully understood.

While there is considerable evidence for a major role of obesity as a risk factor for CKD/ESRD, the direct pathophysiological links between obesity and CKD are still unclear due to the potential confounding effects of cardiovascular risk factors like diabetes and hypertension, which are frequently associated with obesity [7]. The effects of hypertension and diabetes in promoting renal injury in the context of obesity has been discussed in other publications [16, 17]; therefore, we will mainly discuss obesity-driven mechanisms of renal injury that may be independent of diabetes, hypertension or primary kidney disease from other etiologies.

Mechanisms of Obesity-Induced Kidney Injury

The potential mechanisms of progressive renal injury in obesity are multifold. From physical compression of the kidneys to upregulation of several injurious pathways, the kidneys are vulnerable to progressive dysfunction and evolving parenchymal damage. Pathways, in addition to hypertension and diabetes, by which obesity may cause renal dysfunction and injury include glomerular hyperfiltration, increased glomerular capillary wall tension, metabolic abnormalities (dyslipidemia and altered glucose metabolism without overt diabetes), glomerular and tubular lipid accumulation (lipotoxicity), all of which may lead to structural and functional changes of mesangial cells, proximal tubular cells and podocytes and a gradual reduction in nephron number [18–20]. In addition, increased systemic and renal oxidative stress, increased generation of inflammatory cytokines from adipose tissues, renal inflammation and progressive renal microvascular (MV) dysfunction are prominent pathological processes for progression of renal injury in obesity [21–23].

Obesity and Renal Microcirculation

MV networks are highly regulated, providing nutrition and removing waste products to meet the specific metabolic needs of each tissue. In the kidneys, the glo-

merular and peritubular capillaries carry additional indispensable burdens of glomerular filtration, tubular reabsorption and systemic recirculation of vital body fluids, nutrients, hormones and other substances. Endothelial dysfunction, vascular remodeling and loss of the renal microvessels play a prominent role in inducing renal injury associated with major cardiovascular risk factors such as hypertension, dyslipidemia, diabetes and atherosclerosis [24–27].

Increased glomerular hydrostatic pressure and renal MV endothelial dysfunction contribute to increased glomerular capillary wall permeability and development of albuminuria, which promote glomerular capillary loss and further increases in intraglomerular pressure in a positive feedback fashion [28]. Furthermore, the damage and loss of the small vessels in glomeruli and peritubular capillaries have been suggested as important mediators for the progression of renal injury [29]. Although focal segmental glomerulosclerosis and nephron loss may develop slowly, these changes are often progressive and can lead to severe CKD and eventually ESRD in many obese patients [30].

In the next sections we focus on the role of renal MV dysfunction and damage in development of obesity-induced renal injury and the mechanisms underlying such changes. We also briefly discuss potential strategies that may protect the kidney MV architecture and function.

Potential Mechanisms of Obesity-Induced MV Abnormalities

Microcirculatory dysfunction occurs throughout the body in obesity. For example, dysfunction of the small vessels at the level of both the resistance vessels and the nutritive capillaries beds in skeletal muscle or skin begins at an early age and primary stages of obesity and develops progressively as adiposity increases, resulting in endothelial dysfunction and progressive vascular remodeling [31–33]. Therefore, it is likely that some of the mechanisms leading to MV abnormalities are also activated in the kidney, which is exposed to obesity.

Obesity may augment the risk for CKD initially by increasing renal tubular reabsorption and metabolic rate which lead to compensatory renal vasodilation, glomerular hyperfiltration, higher glomerular capillary pressures and glomerular hypertrophy [34]. Although the renal hemodynamic changes and increased glomerular filtration rate (GFR) initially offset the increased tubular reabsorption and permit balance between intake and output of salt

and water, which have to be maintained, in the long term, the mechanical strain on the glomerular capillaries likely cause slow development of injury and rarefaction [35].

Through adipose tissue build up in and around the kidneys and intrarenal accumulation of extracellular matrix (ECM), the kidney is also exposed to constant compressive forces that may stimulate the renin-angiotensin aldosterone system and increase tubular reabsorption, leading to increased blood pressure [35, 36]. Physical compression of the kidneys appears to occur in obese humans, dogs and rabbits [16] but may not equally develop in rodent models of obesity. Indeed, the kidneys appear to be ‘floating’ in the excessive adipose tissue, rather than being compressed, in genetically modified and diet-induced rodent models of obesity [35].

In addition to compressing the kidneys, the fat surrounding the kidneys may be a source of stem cells and inflammatory, pro-fibrotic and angiogenic cytokines. Other ‘lipotoxic’ effects of perinephric fat and infiltration of lipids in the renal parenchyma may play contributory roles in the development of renal injury.

Extra- and Intrarenal Adipose Tissue: Not Just a Fat Storage

Development of obesity and accumulation of abdominal and visceral fat are highly related with adverse renal outcomes. Adipose tissues are not only sites of energy storage, but also a rich source of products that have effects on surrounding and distal tissues. Adipose tissues are endocrine and immunologically active organs with numerous effects on regulation of systemic energy homeostasis, inflammatory responses and are rich in immune cells that may be involved in obesity-mediated metabolic complications, including insulin resistance. The immune functions of adipose tissue are beyond the scope of this section and readers are suggested to consult elegant up-to-date published articles [37–41].

Recent studies showed that adipose tissue is also an accessible source of mesenchymal stem cells that their pluripotency can be manipulated and applied for therapeutic purposes in the heart [42, 43], kidney [44, 45] and other organs [46–49]. Adipose-derived stem cells are as effective as bone marrow-derived stem cells but with the relative advantage of being easier to access. The healing effects of adipose-derived stem cell therapy include neovascularization and vascular repair leading to amelioration of tissue injury. Importantly, evidence also supports the possibility that adipose-derived progenitor cells may modulate oxidative stress, secrete various cytokines and growth factors with immunomodulatory, angiogenic, anti-inflammatory

and anti-apoptotic effects, attenuating inflammation and tissue loss [50], although some of these effects may be tissue or milieu-specific [51]. However, despite a potential increase in the source of adipose-derived stem cells, renal injury still develops and progresses in obese patients, suggesting additional mechanisms that may interfere with these beneficial effects of adipose tissue.

Adipose tissue also serves as a source for angiogenic cytokines, which may have effects that are not limited to vascular proliferation. For example, vascular endothelial growth factor (VEGF), a major angiogenic factor, stimulates the conversion of white fat to brown fat and reduces insulin resistance, suggesting multiple autocrine and paracrine effects that go beyond angiogenesis and participate in metabolic pathways [52–55]. On the other hand, inhibitory isoforms of VEGF such as VEGF-165b are also upregulated in obesity, counteracting the pro-angiogenic effects and promoting vascular rarefaction in adipose tissue [56]. Thus, it is possible that the obesity milieu determines whether VEGF acts as a compensatory or pathological factor on the vasculature of adipose tissue and the kidneys. These findings highlight the complexity of the VEGF pathway and the challenge of determining whether VEGF may be a therapeutic target in obesity.

There are major functional differences of adipocytes related to their anatomical location in visceral or subcutaneous fat. Visceral adipose tissue and its adipose-tissue resident macrophages produce less adiponectin and more pro-inflammatory cytokines like tumor necrosis factor- α (TNF- α) and interleukin-6 (IL-6), which can induce insulin resistance and promote endothelial dysfunction [57]. Fat can infiltrate the kidneys and it is possible that the enhanced pathologic profile of visceral fat has a greater potential to increase cardiometabolic risk, propensity to hypertension and the risk for CKD more than subcutaneous fat [15, 58, 59].

Thus, although stem pluripotent cells are developed and stored in adipose tissue, type and distribution of adiposity may influence the development of MV abnormalities in various organs, including the kidneys, during obesity. It is unknown whether 'resident' adipose-derived stem cells may endogenously mobilize to the kidney in obesity but if they do, the inability to regenerate following injury suggests that these healing mechanisms may be overwhelmed. Alternatively, it is possible that based on their different biochemical profile, adipose tissues outside the kidney and fat infiltration into the renal parenchyma represent competing forces. Adipose tissue may not only serve as a source of numerous cytokines, but can also modulate their effects on mobilization and actions of

renal resident mesenchymal cells toward physiological cell turnover [60, 61], pathological angiogenesis [62], reparative angiogenesis [63] or vascular rarefaction and tissue damage [64].

Obesity-Induced Inflammation as a Promoter of Vascular Proliferation

Obesity is a chronic low-grade inflammatory condition in which adipose tissue (mainly visceral) serves as the source of inflammatory cytokines, as stated earlier. Experimental and clinical studies demonstrated that obesity-induced inflammation develops in the heart [65, 66], liver [67], large and small vessels [68, 69], brain [70] and kidneys [21, 71]. It is unclear whether development of inflammation accelerates or increases in parallel with obesity, but there is evidence that inflammation develops early and rapidly after excessive weight gain is sustained and may contribute to obesity-induced organ injury [72].

Significant renal MV dysfunction parallels chronic inflammation in obese subjects. Our study [21] using adult obese Zucker rats (OZR) as a model of obesity showed that systemic and renal inflammation progressively develops, which is paralleled by progressive renal dysfunction, fibrosis and significant increases in cortical and medullary MV density (fig. 1). To dissect the role of aging from obesity in these pathological changes, we performed these studies in young (12 weeks) and adult (32 weeks) OZR and their lean counterparts. We observed that pro-inflammatory cytokines such IL-6 and TNF- α as well as renal inflammatory infiltrates progressively increased with obesity. Lean Zucker rats of the same age did not show such changes indicating that obesity, rather than aging, was the major driving force behind inflammation and progressive renal injury [21].

Inflammation-driven neovascularization [73] might reflect a compensatory mechanism to sustain the perfusion of injured or ischemic tissues. Despite increased renal MV density, OZR displayed reduced renal blood flow and GFR and increased proteinuria [21]. This finding suggests that renal neovascularization/angiogenesis in the OZR could be a compensatory but insufficient and eventually dysfunctional response subsequent to factors that cause kidney dysfunction and/or kidney injury. Evidence supporting direct and intermediate actions of TNF- α and IL-6 as powerful instigators of angiogenesis has been shown in several pathological conditions [74–78]. Furthermore, inflammation in obesity may also be driven by augmented activity of other angiogenic pro-inflammatory cytokines such as IL-8, monocyte chemoattractant protein-1 or nuclear factor kappa B, to name a few [79–84].

Fig. 1. Top: representative renal cross sections from adult LZR and OZR, respectively showing inflammatory infiltrates, and quantification (percent of ED-1 + macrophages). Middle: representative 3D micro-CT reconstruction of the renal microvasculature, and quantification of the renal fibrosis in adult LZR and OZR. Bottom: representative bar graphs showing proteinuria and GFR from

adult LZR and OZR. Increased renal MV density in OZR was accompanied by increased inflammation, renal dysfunction and injury, suggesting pathological neovascularization. Grey bars: LZR, black bars: OZR. * $p < 0.05$ vs. LZR. Reproduced and modified from Iliescu and Chade [21]. LZR = Lean Zucker rats.

We also observed renal neovascularization in a swine model of chronic dyslipidemia, which promotes increased TNF- α and an inflammatory milieu in the kidneys. Using this model, we showed that inhibiting TNF- α led to decreased vascular proliferation and a decrease in basal renal hemodynamics [85]. These findings support the notion that inflammation-induced neovascularization might be a compensatory mechanism initially aimed at preserving renal perfusion in dyslipidemia. However, as in obesity, inflammation-driven neovascularization may result in dysfunctional or immature vessels with blind ends or loose endothelial junctions that increase vascular permeability and prevent adequate responses to changes in vascular tone, leading to abnormal removal of toxins and facilitating extravasation of injurious cytokines [85–87]. These de-

fects in newly generated vessels may further contribute to progression of renal injury as chronic inflammation is perpetuated in obesity. Therefore, it is possible that renal neovascularization in obesity (or dyslipidemia) is largely driven by inflammation and may act as a double-edged sword, that is, it may initially help to preserve renal hemodynamics but later contribute to functional and structural parenchymal damage due to significant MV abnormalities.

Renal Fibrosis as Promoter of MV Remodeling

Fibrosis results from replacement of normal, functioning renal parenchyma with scar tissue. Renal fibrosis is the common final stage of CKD/ESRD, regardless of eti-

Fig. 2. Schematic illustration of the potential mechanisms of obesity-induced renal injury. Multiple injurious pathways for the kidney are activated by direct effects of obesity and visceral fat, leading to a progressive deterioration of renal function, MV rarefaction in the glomerular and peritubular compartments, and consequent development of progressive renal dysfunction and injury. SNS = Sympathetic nervous system; RAAS = renin-angiotensin aldosterone system; NFκB = nuclear factor kappa B; MCP-1 = monocyte-chemoattractant protein-1; TGF-β = transforming growth factor-β; CTGF = connective tissue growth factor; FGF = fibroblast growth factor; TIMPs = tissue inhibitors of metalloproteinases.

ology, and is an important feature of kidney injury in obesity. As discussed previously, the kidneys of obese subjects are chronically exposed to an injurious milieu due to adipose tissue-derived inflammatory and fibrotic-promoting cytokines, hypertension and various metabolic abnormalities [88]. Chronic inflammation can lead and accelerate nephron injury and renal fibrosis initiated by multiple co-existent insults, including hemodynamic and metabolic abnormalities associated with obesity.

The dysfunction, damage, remodeling and eventual loss of the renal microvessels has been described in advanced stages of hypertension, diabetes, and atherosclerotic renovascular disease, all of them being conditions promoted by obesity. Dysfunction and damage of the small renal vessels negatively impacts perfusion, leading to tissue ischemia and activation of hypoxia-derived and redox-sensitive factors in the kidney such as transforming growth factor-β [89], connective tissue growth factor [90, 91] and fibroblast growth factor [92, 93], to name a few. In turn, some of these pro-fibrotic cytokines exert powerful effects on vascular proliferation and remodeling in addition to promoting epithelial and/or endothelial-to-mesenchymal differentiation and fibrosis [94].

An ischemic and oxidative renal environment may also chronically interfere with normal ECM turnover by

blunting activity of matrix metalloproteinases (MMPs) [95] or by increasing the resistance of ECM to degradation [96, 97] and by increasing specific tissue inhibitors of MMPs [98, 99]. Therefore, a pro-fibrotic activity paired with reduced ECM turnover could lead to build-up of fibrotic tissue and interfere with normal development, expansion and repair of the renal microvasculature. Furthermore, ECM accumulation may also affect renal microvessels by remodeling of the cortical and medullary vascular tree. Moreover, the ECM is an active source of inflammatory, pro- and anti-angiogenic cytokines [100, 101], which may further contribute to progression of renal MV abnormalities and parenchymal damage.

These potential mechanisms may also occur in kidneys exposed to obesity-associated diabetes and hypertension and contribute to progressive fibrosis. When hypertension and diabetes coexist, as occurs in many obese patients, it is likely that there are synergistic interactions that more rapidly promote kidney injury. The added physical compression of the kidneys by visceral and perinephric fat (discussed earlier) may exacerbate fibrosis and MV damage, contributing to a 'perfect storm' for progressive MV damage in the kidney exposed to obesity (fig. 2).

MV Dysfunction as Potential Instigator of Renal Injury in Obesity

It is widely recognized that obesity induces changes in the function and structure of capillaries, conductance and resistance vessels in virtually every tissue or organ and that these changes may promote organ injury. Small vessel disease as an initial instigator of renal injury in obesity and as a risk factor for CKD is recognized, and can exacerbate injurious pathways that further advance tissue injury. However, it is challenging to isolate pathological contributions to renal MV dysfunction and damage to injury from other cardiovascular risk factors since MV abnormalities may develop in association with hypertension and diabetes, both independent of and in the context of obesity, and may promote or exacerbate renal injury via similar pathological pathways.

Renal MV Dysfunction and Loss and Development of Renal Injury

The role of MV rarefaction in initiating renal injury has been shown in different settings. For example, significant renal injury may develop after anti-angiogenic therapies in cancer. Inhibition of VEGF, a pivotal angiogenic cytokine that plays crucial roles in the generation of new vessels, repair and maintenance of the MV networks throughout the body, is a powerful anti-cancer intervention against the development and expansion of tumors. However, anti-VEGF therapies are also associated with significant renal MV injury, glomerulopathy and hypertension, all of which cause severe collateral damage of anti-angiogenic strategies that have been shown to develop with a clear cause–effect relationship [102, 103].

Disruption of the renal microcirculation may participate in development and progression of obesity-induced renal damage through several avenues. Glomerular hyperfiltration is a common finding in obese persons, driven by a combination of high sympathetic activity, activation of the renin-angiotensin system and hyperinsulinemia [104, 105]. Paralleled by enhanced proximal or loop of Henle sodium reabsorption and a reduced delivery of sodium to the macula densa, a significant vasodilatation of the afferent arteriole develops and consequently, stimulation of renin synthesis [35]. The increase in angiotensin II induces constriction of the efferent arteriole, and the combination of afferent vasodilatation–efferent vasoconstriction leads to the hyperfiltration frequently observed in obese patients. This prolonged state of an abnormally transmitted arterial pressure to the glomerular capillaries may result in podocyte damage, glomerular

enlargement, later capillary rarefaction and focal glomerulosclerosis and subsequent loss of glomeruli [105–107]. In turn, glomerular efferent vasoconstriction contributes to increased intraglomerular pressure and, in combination with other metabolic and inflammatory insults, ultimately to glomerular capillary injury and nephron loss. With loss of glomerular capillary function, there is reduced downstream peritubular capillary blood flow leading to ischemia and injury of the renal tubules and parenchyma [20, 108, 109] (fig. 2).

Provocative evidence indicates that MV abnormalities may also contribute to the development of hypertension and metabolic derangements observed in obesity. MV rarefaction (functional and/or structural) may condition not only tissue vascular density, but also the maturity of the network structure and resistance to flow [110, 111]. In the kidney, such mechanisms may result in loss of glomerular and peritubular capillaries, ultimately leading to renal tubular and generalized parenchymal injury associated with reductions in renal blood flow and GFR. These hemodynamic changes may contribute to further development of hypertension, further rarefaction and a gradual loss in kidney function.

Although renal mechanisms such as pressure natriuresis may compensate for increases in blood pressure associated with increased peripheral vascular resistance in other tissues, ongoing MV disease in the obese kidney with a reduction in the number of nephrons [18–20, 112] may impair kidney function further, initiating a vicious circle that exacerbates the high blood pressure and vessel rarefaction in obesity [113, 114] (fig. 2).

Does MV Dysfunction Promote Metabolic Disorders That Contribute to Renal Injury?

Another potential consequence of MV disease in tissues such as skeletal muscle is its potential contribution to development of the obesity-induced metabolic derangements. Indeed, some investigators have suggested a potential role for abnormalities in the microcirculation to the development of metabolic defects often observed in obesity [115, 116] although others have provided evidence that does not support this hypothesis [117]. A major pathological feature in obese patients is insulin resistance, which may evolve into type 2 diabetes in patients who also have pancreatic β -cell dysfunction. Insulin resistance in skeletal muscle and liver seems to be partly driven by increased visceral adiposity that leads to a pro-inflammatory and pro-oxidative milieu and has been suggested to be closely related to MV dysfunction and remodeling [118].

Some studies suggest that MV dysfunction precedes metabolic insulin resistance, underscoring early deleterious events in the microcirculation that seem to be driven by inflammation [119, 120]. Insulin is a vasodilator, due in part to its metabolic effects, and may redirect blood flow to increase perfusion through capillary networks, consequently stimulating insulin-mediated glucose uptake. This is partly an endothelium-dependent process that is impaired in states of MV dysfunction such as obesity [121] and may also have implications for the renal MV network [118]. Although transport across the cell membrane, rather than the capillaries, is generally the rate limiting step for glucose uptake in skeletal muscle [117, 122], severe MV dysfunction may impair glucose and insulin delivery, and exacerbate impaired glucose uptake and utilization by peripheral tissues [123].

Increases in vascular permeability associated with the inflammatory milieu of obesity [85] may facilitate mobilization of injurious substances to the extravascular tissues in type 2 diabetes, commonly associated with obesity. Abundance of inflammatory cytokines and glucose may further increase vascular permeability [124], increase oxidative stress, promote vasoconstriction [125], stimulate pro-fibrotic activity and deteriorate glucose trafficking leading to endothelial cell death by interfering with mitochondrial function [126], which in turn may further increase vascular and perivascular damage in the kidney.

Potential Therapeutic Strategies: Protection of Renal Microvessels

Targeting the renal microcirculation as a potential therapeutic strategy for obesity-induced kidney injury has not been widely explored. Although the first therapeutic steps should focus on weight management and control of obesity-driven cardiovascular and metabolic derangements, protection of the microcirculation may be an additional strategy for renoprotection.

Weight Loss

Weight loss via caloric restriction and increased physical activity are core therapies for obese individuals that can improve most of the metabolic, cardiovascular and renal derangements associated with obesity such as hypertension, glucose control, proteinuria and renal function. The inclusion of bariatric surgery as a strategy for weight loss has provided additional benefits. Indeed, bariatric surgery seems to be more effective for weight loss

and has a long-term benefit on improving weight control, metabolic derangements, recovery of renal function and halting the cascade of events that cause progression of renal damage [127–129].

Weight loss by lifestyle modifications (diet, exercise) or bariatric interventions in obese patients may attenuate endothelial dysfunction, reduce cardiovascular risk and improve prognosis in the obese population [130]. Part of the improvement in endothelial function and overall MV protection by weight loss may be driven by improvements in leptin signaling (with subsequent vascular recovery [131]), restoration of circulating endothelial progenitor cells (reduced in obese patients), enhanced endogenous mechanisms of vascular and tissue repair, and decreased MV remodeling and perivascular fibrosis [132]. Weight loss also reduces production and release of cytokines responsible for the chronic pro-inflammatory and pro-fibrotic state observed in visceral obesity. Other major effects of weight loss include reductions in blood pressure, regression and diabetes and improvements in dyslipidemia, as have been recently reviewed [16, 133, 134].

Anti-Diabetic Drugs

Obesity, hypertension and poor glycemic control can lead to cardiovascular complications associated with endothelial dysfunction, vascular hypertrophy and remodeling of large blood vessels, resistance arteries and the microcirculation [135, 136]. Metformin and insulin administration are mainstream therapies in diabetes and have been shown to improve MV endothelial function directly and via improved glycemic control. Mechanisms of vascular protection by metformin include reducing endothelial cell senescence and apoptosis, attenuating hyperglycemia-induced oxidative stress [137] and promoting angiogenesis via AMP-k/eNOS pathways [138]. Similarly, insulin has a vasodilatory effect that is counteracted by chronic hyperglycemia [139] and resistance to insulin associates with MV endothelial damage driven by increased susceptibility to ischemia and loss of pro-survival effects. Weight loss and improved glucose control by some anti-diabetic drugs such as GLP-1 agonists and SGLT-2 inhibitors may at least partially correct the impaired vasodilation response to various stimuli, such as exercise, and endothelial damage which increases susceptibility to ischemia. Although most of the beneficial effects of anti-diabetic drugs and enhanced glycemic control have been described for skeletal muscle, retina or isolated endothelial cells, these drugs might also ameliorate renal MV rarefaction and slow the progression of renal injury [140, 141].

Anti-Hypertensive and Lipid-Lowering Drugs

Obesity carries a high risk for development of hypertension and lipid abnormalities. Consequently, a large number of obese patients receive treatment with anti-hypertensive and lipid-lowering drugs that may also have beneficial pleiotropic effects on the vasculature. Angiotensin converting enzyme (ACE) inhibitors and angiotensin receptor blockers (ARBs) are among the first line of anti-hypertensive medications. Considerable evidence indicates that the blood pressure lowering effect is the major driving force behind most of their protective effects on the cardiovascular subsystems and the kidneys [142]. However, some evidence that comes mainly from studies in experimental obesity show additional benefits of ACE/ARBs by reducing renal damage and, possibly via PPAR- γ mediated effects, improving insulin sensitivity, restoring vascular function and perhaps even contributing to fat redistribution away from visceral depots in some cases [143–145].

Obesity-induced dyslipidemia is counteracted by dietary interventions and lipid-lowering drugs such as HMG-CoA reductase inhibitors (statins). Beyond lipid lowering, the pleiotropic effects of statins have been described elsewhere [146, 147] and have also been suggested to have beneficial effects in the microcirculation of various tissues, including the kidneys. Indeed, based on their powerful anti-oxidant and NO-mediated vasoactive effects, statins may exert direct protective effects on vascular endothelial function. We showed that hypercholesterolemia and atherosclerotic renovascular disease cause blunted cardiac and renal hemodynamics and function that are associated with significant MV endothelial dysfunction and rarefaction, which are restored after chronic simvastatin therapy, independent of any lipid-lowering effect [94, 148–150]. Thus, protection of MV function and structure could be considered as an additional mechanism of renoprotection by anti-hypertensive and lipid-lowering strategies in obesity.

Potential Novel Therapies

In addition to VEGF, other factors that are produced by adipose-derived stem cells may induce or attenuate angiogenesis. For example, a novel factor that may serve as a powerful instigator of aberrant angiogenesis is the glial-derived neurotrophic factor (GDNF). A recent study shows that GDNF promotes pathological neovascularization by stimulating endothelial cell network formation in a VEGF-independent fashion, implying GDNF may be a target for obesity-induced organ damage [62].

Another important pro-angiogenic factor that is produced by and acts on adipose tissue and adipose-derived stem cells is the hepatocyte growth factor [151]. This factor may promote neovascularization both directly and via synergism with VEGF and has also been shown to induce protective actions on the vasculature, possibly via attenuation of pro-fibrotic and remodeling pathways [152, 153] and promoting cell mobilization and tissue repair [154].

Since the growth of adipose tissue is paralleled by vascular proliferation, as it occurs in other organs, modulation of angiogenesis may be an adjuvant intervention to reduce target organ injury. Inhibition of angiogenesis as an intervention to prevent accumulation of adipose tissue or its consequences (directly or as co-adjuvant strategy) has been attempted in experimental settings [155]. However, anti-angiogenic strategies may elicit important collateral effects such as renal injury and hypertension, which clearly limit their potential for therapeutic applications.

Conclusions and Perspectives

The epidemic growth of obesity has been the impetus for numerous experimental and clinical studies to determine the pathological consequences and mechanisms of widespread organ injury associated with higher all-cause mortality in obese patients [156, 157]. Current efforts on early dietary education, weight control, active lifestyle and interventions are abundant but have been largely ineffective in slowing the increasing prevalence of obesity. Until more effective therapies for obesity are available, research should also focus on ameliorating target organ injury.

Obese patients are at higher risk of developing CKD. Current therapies and interventions may improve, but do not halt, the progression of renal MV dysfunction and associated cardiovascular risk. Thus, major efforts are needed to understand the pathophysiological mechanisms leading to progressive renal dysfunction and damage. In the kidney, functional and structural injury to the microvasculature is increasingly recognized as a prominent instigator of renal parenchymal injury. However, kidney-targeted stimulation of MV function, neovascularization and inhibition of vascular remodeling are still experimental as therapeutic strategies and warrant additional studies. Pro-angiogenic therapies that stimulate regrowth of glomerular and peritubular capillaries appear promising in experimental studies but there are still chal-

lenges that prevent this approach from being practical in a clinical setting, such as short half-life and rapid degradation of administered pro-angiogenic peptides. Also, specific targeting of the kidney microvasculature will be needed to avoid potential deleterious effects in other organs that could occur with widespread increases in angiogenesis.

Additional research is also needed to define the potential contribution of systemic MV dysfunction to the development of metabolic derangements in obesity, whether these mechanisms are mirrored in the kidney and if they are important therapeutic targets. Elucidation of such mechanisms of renal MV damage in obesity may not only help to understand these complex processes, but

may also lead to new strategies in treating the adverse metabolic, cardiovascular and renal consequences of obesity.

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The authors have no conflicts of interest to declare.

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