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# The Metabolic Syndrome and Chronic Kidney Disease

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## Abstract

The metabolic syndrome (MetS) is a cluster of cardiovascular risk factors including insulin resistance (IR), dyslipidemia and hypertension, which may also foster development of chronic kidney disease. The mechanisms of MetS-induced kidney disease are not fully understood. The purpose of this review is to summarize recent discoveries regarding the impact of MetS on the kidney, particularly on the renal microvasculature and cellular mitochondria. Fundamental manifestations of MetS include insulin resistance (IR) and adipose tissue expansion, the latter promoting chronic inflammation and oxidative stress that exacerbate IR. Those in turn can elicit various kidney injurious events through endothelial dysfunction, activation of the renin-angiotensin-aldosterone system, and adipokine imbalance. IR and inflammation are also major contributors to microvascular remodeling and podocyte injury. Hence, these events may result in hypertension, albuminuria, and parenchymal damage. In addition, dyslipidemia and excessive nutrient availability may impair mitochondrial function and thereby promote progression of kidney cell damage. Elucidation of the link between MetS and kidney injury may help develop preventative measures and possibly novel therapeutic targets to alleviate and avert development of renal manifestations.

### Keywords

metabolic syndrome; insulin resistance; kidney; microcirculation

## Epidemiology

According to the American Heart Association, individuals with the metabolic syndrome (MetS) show 3 or more of the following conditions: 1) Central or abdominal obesity (by waist circumference); 2) Elevated triglyceride levels; 3) Low high-density lipoproteins (HDL); 4) Hypertension; 5) Elevated fasting glucose.[1] The International Diabetes

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Federation criteria are similar, but more specific regarding the definition of central obesity categorized by country or ethnic group.[2] A waist circumference greater than 94cm for Europids males is considered central obesity, whereas 90cm are indicative in Asian males.

Although greater awareness of MetS may have contributed to improvements in treatment of risk factors like hypertension and diabetes, nearly 35% of all adults and 50% of those 60 years or older were still estimated to have MetS.[3] MetS is an important contributor to cardiovascular morbidity and mortality. Among 12,561 subjects from the United States Third National Health and Nutrition Examination Survey, 13.3% of the excess cardiovascular mortality in the United States could be attributed to higher prevalence of MetS and MetS with baseline cardiovascular disease.[4] Moreover, Mets often progresses to frank type-2 diabetes, particularly in subjects with hyperglycemia. In a recent study of 28,209 patients, yearly conversion rates to diabetes were only 0.6% in MetS individuals with normoglycemia or mild hyperglycemia, but 2.5% in those with intermediate hyperglycemia (6.1–7.0 mmol/L)[5], leading to particularly elevated risk for cardiovascular complications.

Studies have suggested that individuals with MetS are also at increased risk for developing chronic kidney disease (CKD), reflected by microalbuminuria[6, 7] and renal dysfunction.[8] Patients with 1–2 traits of MetS are twice more likely to have microalbuminuria than those without the syndrome, and the likelihood rises to 130% in those with more than 3 traits.[6] In a study including 5,800 patients with type-2 diabetes, MetS independently predicted the new-onset of CKD.[4] After adjustments for diabetes and hypertension, MetS remained an independent risk factor contributing to development of CKD, defined as a fall the kidney function over a 9-year follow-up.[8] Patients with MetS undergoing nephrectomy also showed a higher prevalence of features characterizing CKD, including global and segmental glomerulosclerosis and loss of renal function, compared to those without MetS.[9] Recent studies also suggest that the presence of MetS before renal transplantation predicts subsequent development of new-onset diabetes after transplantation, and the presence of MetS after transplantation adversely influenced allograft survival.[10, 11] Over an 18-month follow-up post-transplantation, the hazard ratio for creatinine elevation was 2.6, and patient survival was significantly diminished.[10] These observations establish MetS as a trigger for renal injury in CKD, which magnifies the adverse impact of other insults. Given the central role of the kidney in maintenance of bone homeostasis,[12] MetS may also contribute to bone mineral disorders in these subjects.[13]

The pathways activated by MetS to induce kidney disease are not fully understood. Over the past few years, studies have identified several new injurious pathways that MetS activates in the kidney.[14] Central tenets of MetS include insulin resistance (IR) and chronic inflammation, a major contributor to microvascular remodeling. In addition, dyslipidemia and excessive nutrient availability may induce mitochondrial dysfunction; adipokines, the renin-angiotensin system, and oxidative stress may permit development of hypertension. Better understanding of the mechanisms by which MetS injures the kidney may direct future studies and possibly novel therapeutic targets to alleviate and prevent the development of renal manifestations of MetS.

## Microvascular Remodeling

We and others have observed that in humans and animals MetS induced renal parenchymal damages, such as tubular atrophy and interstitial fibrosis.[9, 15] Microvascular remodeling manifesting as arterial and arteriolar sclerosis within kidney lesions in patients with MetS have also been observed,[9] and ultrasound revealed elevated resistive indices in intra-renal inter-lobar arteries,[16, 17] indicating vasoconstriction and microvascular remodeling. Direct evidence for the effects of MetS on microvessels has been obtained from studies in animal models. In rats, a 6-week MetS diet (60% fructose) induced wall thickening in outer cortical and juxtamedullary afferent arterioles,[18] mimicking arteriolar sclerosis observed in humans. In MetS Ossabaw pigs, dysregulated angiogenesis was observed after a sixteen-week diet, accompanied by increased tissue fibrosis,[15] partly due to elevation of Angiotensin II (AngII), consistent with activation of the renin-angiotensin-aldosterone system observed in MetS.[19] Accumulation of visceral adipose and fat infiltration of the kidney may also induce inflammation-driven neovascularization through multiple cytokines that are enriched in adipose tissue, such as tumor necrosis factor (TNF)-α and interleukin-6. [20, 21]

Using a 3-dimensional micro-CT, we found that at its early stage MetS in fact stimulated microvascular proliferation in the kidney.[22, 23] The increase in microvascular density (Figure 1, Top) was associated with upregulated expression of vascular endothelial growth factor (VEGF),[22] possibly secondary to oxidative stress[24] commonly seen in MetS, and hyperinsulinemia that directly increases VEGF production.[25] The small microvessels (20–40 μm) that proliferated [22, 23] may contribute to maintain renal perfusion, and may initially account for elevated renal blood flow (RBF) and glomerular filtration rate (GFR) that characterize the early stage of MetS. However, those newly generated vessels often have disorganized architecture, because following a 16-week MetS diet they become more torturous,[23] suggesting that at later stage of MetS intra-renal vessels may be dysfunctional and unstable. In addition, sustained mechanical strain on glomerular capillaries due to hyperfiltration likely increases propensity for microvascular loss.[26]

Furthermore, under physiological condition insulin may regulate GFR through local renal vasodilation, which can be blocked by indomethacin[27] and augmented by activation of endothelial nitric oxide (NO) synthase.[28] However, this effect of insulin might be lost over time in MetS subjects with IR,[29] who manifest endothelial dysfunction due to downregulated expression of eNOS and increased endothelin-1 levels.[30] Uric acid, which is often elevated in MetS, also inhibits NO production, thus contributing to endothelial dysfunction.[18] Renal microvascular endothelial dysfunction increases glomerular capillary wall permeability and albuminuria, which may also promote glomerular capillary loss[21] in prolonged MetS and progression of renal injury. Indeed, MetS patients show a steeper decrease in kidney function over time compared to non-MetS patients, suggesting limited renal reserve, which might be the consequence of kidney vascular remodeling and parenchymal damage in MetS.[9] Moreover, MetS may impose vascular remodeling and accelerate development of atherosclerotic lesions. Renal artery stenosis, detected in 16% patients with cardiovascular events,[31] further decreases blood supply to the kidney and exacerbates renal damage. Indeed, in post-stenotic swine kidneys, MetS precipitates or

magnifies loss of microvessels,[15] thereby aggravating tissue injury. This synergistic interaction between MetS and renal ischemia is associated with increased oxidative stress and inflammation, which disrupt microvascular stability.[15, 23] As renal artery stenosis is increasingly observed in the aging modern society, the link between MetS and the severity of intra-renal microvascular remodeling in stenotic kidneys needs to be considered during management of these patients.

## Inflammation and insulin resistance

Low-grade chronic inflammation is a hallmark of MetS[32], and its the severity seems to depend on the prevalent number of components of MetS.[33] In fact, the pivotal role of metabolically-induced inflammation is underscored by the proposed term “metaflammation”.[34]

Animal studies have highlighted the kidney as a target organ often involved in the inflammatory response.[15, 35] A 16-week MetS diet in pigs elevated the levels of circulating oxidized low-density lipoprotein (LDL) and soluble (s)E-selectin that recruits inflammatory cells,[15] and increased infiltration of pro-inflammatory macrophages in the kidney (Figure 1, Bottom), accompanied by development of glomerulosclerosis.[15] Similary, Zucker fatty diabetic rats show macrophage infiltration in the tubular-interstitium space and neutrophils in peritubular capillaries, associated with wide-spread fibrosis.[35] Hence, inflammation may mediate development of renal fibrosis and glomerulosclerosis in MetS.

One of the plausible hypotheses is that MetS-induced disruption in many physiological regulatory systems due to excessive energy intake, provoking stressor stimuli that subsequently trigger inflammatory and oxidative pathways.[34] This response might aim to block major anabolic signaling pathways, such as the insulin/insulin growth factor (IGF) pathway, thereby diverting energy sources from synthetic pathways.[34] *In vitro* studies demonstrated that the inflammatory mediator interleukin (IL)-6 exerts inhibitory effects on IGF-1 signaling pathways (extracellular-regulated protein kinase (ERK)1/2 and Akt) by blocking its receptor substrate (IRS)-1[36], or by increasing its clearance.[37]

Adipose tissue expansion, a central tenet of MetS, represents a major source of inflammatory cytokines. In human subjects adipocyte size correlates with levels of TNF-α, IL-6, and high-sensitivity C-reactive protein (CRP).[38] Experimental studies in MetS animals have shown substantial infiltration of inflammatory macrophages and TNF-α in the abdominal and peri-renal fat tissue[15, 39], which could serve as a channel for inflammatory cytokines to access the kidney. In addition, renal arterial endothelial function was blunted when incubated in vitro with perirenal fat harvested from MetS pigs, and restored by TNF-α inhibitor, substantiating its injurious effect on the renal vasculature.[39] Weight loss improves both inflammatory (CRP, TNF-α, IL-6 and leptin) and anti-inflammatory (adiponectin) markers in human subjects[40, 41], and MetS rats treated with anti-inflammatory mycophenolate mofetil showed reduced systemic and renal inflammation and limited renal fibrosis.[35] Therefore, measures to control inflammation in MetS may be beneficial for the kidney.

Even in the absence of other co-existing MetS components, inflammatory mediators alone can trigger IR. For example, in humans uremia can cause IR by disrupting insulin signaling.[42] *In vitro*, stimulated macrophages produce IL-1β and IL-18, contributing to pancreatic β-cell death with chronic hyperglycemia and progression of diabetes.[43] These observations suggest that inflammation can be upstream to metabolic derangement. Clinical studies have found that Salsalate, a prodrug of salicylate which suppresses inflammation, attenuates IKKβ/NF-κB activity, improves glycemic control in patients with type-2 diabetes,[44] and alleviates IR.[45] TNF-α blockade improved fasting glucose and improved the levels of anti-inflammatory adiponectin in obese subjects with abnormal glucose homeostasis.[46] Clearly, the cause and effect relationship between inflammation and MetS remains to be discerned, and the ability of management of inflammation to alleviate kidney injury in MetS warrants further studies.

Evidence indicated that IR is not infrequently associated with CKD.[47, 48] In a 9-year study, the severity of IR was directly related to the risk of developing CKD.[48] In slightly overweight non-diabetic patients, the prevalence of CKD significantly and progressively rises with increasing levels of serum insulin and IR.[49] As mentioned earlier, hyperinsulinemia may induce glomerular hyperfiltration, endothelial dysfunction, and increased vascular permeability,[50] leading to albuminuria. In nondiabetic subjects, even a short-term insulin infusion increases urinary albumin excretion.[51] In turn, albumin in the tubular lumen may lead to tubulo-interstitial injury and fibrosis.[52] The link between IR and kidney disease might be attributable to the dependence of the kidney on insulin, which binds to all nephron cells, including the glomerulus and the entire length of the renal tubules.[53, 54] Particularly, the glomerular podocytes, major components of the glomerular filtration barrier, have higher expression of insulin receptors compared with endothelial and mesangial cells,[55] and insulin may control podocyte contractility associated with glomerular permeability.[56, 57] Conceivably, changes in the abundance or sensitivity of insulin receptors in MetS may regulate renal physiology and/or pathology. Furthermore, elevated insulin levels have been found to stimulate IGF-1 production, which increases connective tissue growth factor, causing renal fibrosis.[58] Indeed, insulin-sensitizing compounds, such as thiazolidinediones (TZD), abrogate interstitial fibrosis in Zucker obese rats fed a high-protein diet.[59] These findings suggest that the interaction of insulin with its receptor bears direct ramification for renal structural and functional impairment in MetS. As hyperglycemia becomes more evident, advanced glycation end products (AGEs) also participate in kidney damage via their receptors on podocytes and endothelial cells. Deposition and activation of AGEs promote cellular hypertrophy and apoptosis, as well as inflammation.[60] Whether systemic levels of AGEs correlate with severity or progression of kidney damage in MetS needs to be examined.

More recently, adipocytokines linked to IR, low grade inflammation, endothelial dysfunction, and vascular damage have been proposed to modulate kidney function.[61] Adiponectin, which is linked to insulin sensitivity, regulates function of podocytes, major sites of adiponectin receptor in the kidney.[62] Mice with reduced or abolished expression of adiponectin exhibit exacerbation of podocyte injury, albuminuria, and renal fibrosis compared with wild-type animals.[63–65] The regulatory role of adiponectin on podocyte function is likely mediated through the 5’ AMP-activated protein kinase (AMPK) pathway,

and adiponectin-knockout mice exhibit increased albuminuria and fusion of podocyte foot processes. In cultured podocytes, adiponectin administration was associated with increased activity of AMPK, and both adiponectin and AMPK activation reduced podocyte permeability to albumin and podocyte dysfunction.[64]

Conversely, serum levels of leptin, which regulates hunger and satiety, are 5–10-fold higher in obese than in healthy individuals. In vitro, leptin induces glomerular mesangial cell hypertrophy,[66] which subsequently increases the amount of filtered protein and albumin. Leptin has been shown to activate several cell signaling pathways in a cell-specific manner. In vitro, leptin can alter rat glomerular cell size via activation of the mitogen-activated protein kinase pathway through ERK 1/2,[67] and hypertrophy in glomerular mesangial cells via activation of phosphoinositide 3-kinase and ERK1/2.[66] Leptin enhanced tissue growth factor (TGF)-β/smad signaling in rat kidney fibroblasts, and leptin deficient ob/ob mice had significant reduction in TGF-β mRNA levels, Smad-2/3 activation, and fibrotic tissue.[68]

Resistin, an adipose sensor that contributes to obesity,[69] is also independently associated with albumin excretion.[70] Although the mechanisms of resistin-related kidney injury is less clear, studies have shown that it upregulates expression of Intercellular Adhesion Molecule-1 and vascular cell adhesion molecule-1.[71] In addition, both leptin and resistin enhance renal sympathetic nerve activity,[72] the latter possibly via phosphatidylinositol 3-kinase.[73]

Therefore, IR and dysregulated adipokines in concert target different renal cell types via various pathways to elicit kidney disease in MetS. Nonetheless, while IR is speculated as an important mediator of MetS-related CKD,[19] its complex role in regulating renal function, solute transfer, and blood pressure needs to be better defined.

## Obesity

Substantial evidence has shown that obesity directly influences renal hemodynamics and structure. A 1-month high-fat diet promptly increases the extracellular fluid and causes a shift in sodium balance.[74] 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[75, 76] by increasing tubular reabsorption. Elevated salt reabsorption at the segment proximal to the macular densa also induces a rise in GFR through tubulo-glomerular feedback, contributing to hyperfiltration.

Yet, obesity-related glomerulopathy (ORG) may not be mediated solely by hemodynamic factors. As an individual gains weight, each podocyte must undergo mechanical stretch to cover a larger surface area to accommodate the increased glomerular volume,[77] resulting in decreased podocyte density and increased foot process width in adults with ORG.[78] Podocyte number increases in size in animals fed ad libitum in proportion to the extent of glomerular hypertrophy at the early stage.[79] Over time, when podocyte enlargement is no longer proportional to glomerular hypertrophy, podocytes fail and detach, causing localized denudation of the glomerular basement membrane, subsequent adhesions to the Bowman capsule and parietal cell coverage, forming a nidus for development of segmental sclerosis,

[80] and result in proteinuria.[81] In addition, an average of 12% individuals with ORG progress to focal segmental glomerulosclerosis (FSGS), which typically affects hypertrophied glomeruli.[82, 83] Although those pathological alterations can be prevented by calorie restriction,[79] development to FSGS is often irreversible and may eventually lead to end-stage renal disease.[81]

## Oxidative stress and mitochondrial dysfunction

Oxidative stress, characterized by elevated reactive oxygen species (ROS) levels, causes damage to proteins, lipids and DNA, and has been proven to play an important role in MetS.[84, 85] In humans, lipid peroxidation, represented by plasma thiobarbituric acid reactive substance and urinary 8-epi-prostaglandin-F2α, correlate with BMI and waist circumference.[86]

A major source of ROS MetS is the NADPH oxidase (NOX) family of enzymes, and accumulating evidence has shown that NOX, particularly NOX1,2, and 4 which are highly expressed in the kidney,[87] play vital roles in intrarenal oxidative stress. Upregulated by metabolic factors, NOX leads to glomerular overproduction of ROS in podocytes, endothelial cells, and mesangial cells, which is closely associated with the initiation and progression of kidney diseases. Exposure of cultured mouse podocytes to high glucose resulted in apoptosis, which involved increased NOX activity and ROS production.[88] The transgenic TG(mRen2)27 rats, which harbor the mouse renin transgene and renin-angiotensin system activation, shows increases in systolic blood pressure, albuminuria, renal NOX activity, accompanied by periarteriolar fibrosis and podocyte foot-process effacement.[89] NOX4 has also been identified as a critical mediator of high glucose- or angiotensin II-induced mesangial cell activation.[90, 91]

Even short exposure of vascular smooth muscle cells to AngII, which is often augmented in MetS, increases mRNA expression of NOX1 and NOX4 several-fold,[92] suggesting NOX activity is Ang II-dependent,[89]. Furthermore, additional mechanisms in injured kidneys may exacerbate oxidative stress, resulting in a vicious circle. TGF-β increased in the rat kidney fibroblasts the activity of both NOX2 and NOX4.[93] Hence, there is close link between oxidative stress and kidney health. Therapeutic strategies targeting oxidative stress may be useful to prevent or alleviate kidney injury in MetS.

The mitochondrion is an intracellular organelle crucial for handling ROS production, which when excessive impairs cellular function. Under normal condition, mitochondria extract energy stored in nutrients that drives work within the body,[94–96] and a series of feedback and regulatory steps enables matching the rate of mitochondrial oxidative phosphorylation with cellular ATP demands.[97, 98] As the kidney has high energy demand and is rich in mitochondria, mitochondrial dysfunction plays a critical role in the pathogenesis of kidney diseases by affecting almost all renal cell types,[99, 100] including participating epithelial-mesenchymal transition which contributes to loss of functional parenchyma.[101, 102]

In the setting of MetS, excessive nutrient availability supplies superfluous electrons to the respiratory chain, while lack of physical activity results in low ATP demand, favoring

mitochondrial dysfunction and disproportionate superoxide formation.[103] Several elements that prevail in MetS may further disrupt mitochondrial function. Oxidized-LDL increases mitochondrial membrane potential and impairs redox status,[104] leading to apoptotic events; it may also cause vascular endothelial dysfunction by translocating mitochondrial proteins.[105] Patients with diabetic nephropathy demonstrate lower gene expression of the renal mitochondrial inner membrane organic anion transporters 1 and 3, and of genes and proteins critical for mitochondrial biogenesis.[106] Similarly, their urine exosomes has decreased mitochondrial DNA.[106] NOX4-derived ROS decrease mitochondrial function in endothelial cells via disruption of the electron transport chain I, [107] and causes extracellular matrix protein accumulation in mesangial cells.[108, 109] Interestingly, these changes are associated with AMPK inactivation,[108] and its activation reduced renal fibrogenesis.[109] A key pathway by which AMPK stimulation protects cells in a calorie-deprived state is by stimulating the master regulator of mitochondrial biogenesis, PPAR-γ coactivator-1α.[110] AMPK also inhibits activity of mammalian target of rapamycin, which mediates NOX4-induced podocyte injury,[111, 112] thereby preventing kidney damage progression.[113, 114] Furthermore, AngII not only increases mitochondrial production of ROS,[115] but may also promote mitochondrial degradation through the AT1-receptor, and suppress their biogenesis through the AT2-receptor.[116, 117] Therefore, MetS may affect renal mitochondrial structure and function through several different pathways.

Mitochondrial dysfunction might also cause or worsen IR.[118] A 35% decrease of mitochondrial DNA (mtDNA) density in peripheral blood cells precedes development of type-2 diabetes in patients.[119] Genetic studies also identified human mtDNA haplogroups that can modulate susceptibility to type-2 diabetes.[120] Interestingly, Rosiglitazone, one of the TZDs that increase insulin sensitivity, also recovers mitochondrial electron transport function in mice with aldosterone-induced mitochondrial dysfunction.[121] We have recently also found cardioprotective effects of mitochondrial-targeted peptides in MetS,[122] yet their effects on the kidney remain to be explored.

Taken together, mitochondrial function is vital in sensing and modulating energy metabolism in MetS, and development of mitochondria-targeting therapeutics may potentially benefit patients with MetS and associated tissue injury.

## Hypertension

Hypertension is an important hallmark of MetS and a common cause of kidney disease. Several mechanisms link hypertension to MetS, among which obesity is a major contributor. Obesity alone is associated with an increase in the severity of hypertension and the number of required antihypertensive medications, and impedes achieving blood pressure control. [123] The direct link between hypertension and dyslipidemia-induced obesity was shown in animal studies. In rabbits, blood pressure rises by 6% after a one-week high–fat diet, and falls back after resumption of normal diet.[124] Adipocytes are rich sources of the precursor protein of AngII and angiotensinogen[125] as well as aldosterone synthase.[75] Indeed, plasma aldosterone is independently associated with obesity.[126] A 5% weight loss in obese women reduces renin-angiotensin-aldosterone activity in both adipose tissue and plasma.[127] In addition, increased visceral and retroperitoneal fat may boost hypertension

by compressing the kidneys. The intra-abdominal pressure in obese patients can be double that of normal subjects,[128, 129] and excessive fat accumulation in and around the kidneys is associated with increased intrarenal pressures, impaired pressure natriuresis, and hypertension.[130]

In addition to the effects of fat, high serum insulin level is associated with an increase in circulating levels of the potent vasoconstrictor endothelin-1 in healthy and IR individuals.[131] Endothelin-1 receptor antagonism effectively reduced blood pressure in animal models of IR and hypertension,[132] implicating endothelin-1 in their pathogenesis. Furthermore, when coexisting with hyperglycemia, insulin exhibits anti-natriuretic effect by promoting sodium retention.[133] As proximal tubular epithelial cells often undergo hypertrophy in obese subjects,[134] together they may account for increased sodium reabsorption and elevation of arterial pressure. As discussed earlier, increased leptin and reduced adiponectin in obesity may also increase sympathetic nerve activity,[135, 136] thus contribute to hypertension.

## Uric acid (UA)

Hyperuricemia is commonly observed and strongly associated with MetS. The prevalence of MetS increased from 5.9% for uric acid levels under 6mg/dL to 59.0% for levels 10mg/dL or greater,[137] and hyperuricemia correlates with elevated fasting insulin level.[138] Moreover, based on a recent systemic review including 13 studies containing 190,718 participants, elevated serum uric acid levels showed an increased risk for development of chronic renal dysfunction.[139]

Animals studies have revealed that hyperuricemia caused IR possibly due to the proinflammatory effect of uric acid on adipocytes [140, 141] and impairment of insulin-dependent glucose uptake.[142] Using a uricase inhibitor, which leads to hyperuricemia, enabled observing a direct relationship between blood pressure and uric acid. In mice, blood pressure increases by 10-mm Hg for each 0.03-mmol/L (0.5-mg/dL) incremental rise in serum uric acid.[143] Allopurinol, a uric acid lowering drug, prophylactically prevented hyperinsulinemia, systolic hypertension, and hypertriglyceridemia.[140] In rat kidneys, hyperuricemia increased juxtaglomerular renin and downregulated macula densa neuronal NO synthase.[143] *In vitro*, uric acid inhibited NO production in endothelial cells,[144] and dose-dependently inhibited endothelial vasodilatory response to acetylcholine,[140] which may in turn compromise blood and oxygen supply to the kidney. Evidently, decreasing uric acid levels may have beneficial effects in MetS.

## Conclusion

Clearly, the impact of the MetS on the kidney is multifactorial. The current nutritional habits and lifestyles of many modern human subjects favors metabolic overload, which underpins chronic metabolic diseases. The kidney is a target organ susceptible to MetS (Figure 2), yet the appropriate treatment strategy for MetS-associated kidney disease remains to be identified. As MetS and type-2 diabetes share some common pathways (e.g. hyperfiltration, oxidative stress, etc.), MetS-associated kidney damage may resemble the early stage of

diabetic nephropathy and merits further studies. In addition to screening, life-style modifications, and management of MetS risk factors and CKD, target-specific therapeutic interventions are in need and warrant investigation to prevent the development and slow the progression of CKD in MetS.

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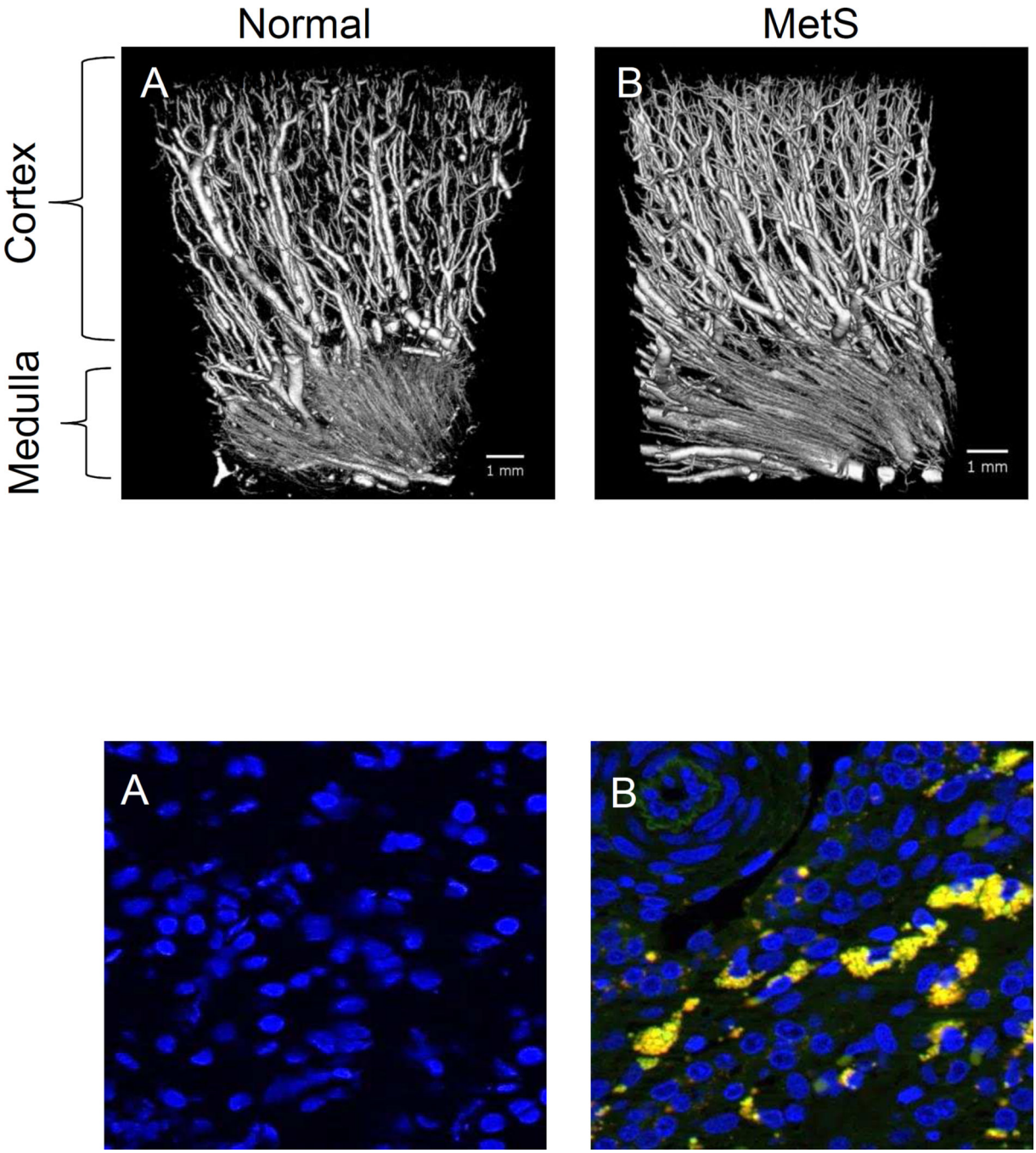


**Figure 1.**

(Top) Microvascular proliferation in MetS kidneys. Three-dimensional micro-CT reveals increased microvascular density in swine MetS (B) compared to normal (A) kidney. Reproduced with permission.19 (Bottom) Proinflammatory macrophages infiltration in MetS kidney. Amplified infiltration of proinflammatory CD68+ (green) and inducible nitric oxide synthase+ (red) double-positive (yellow, white arrow) macrophages in a stenotic kidney with concurrent MetS (B) compared to control kidney (A).

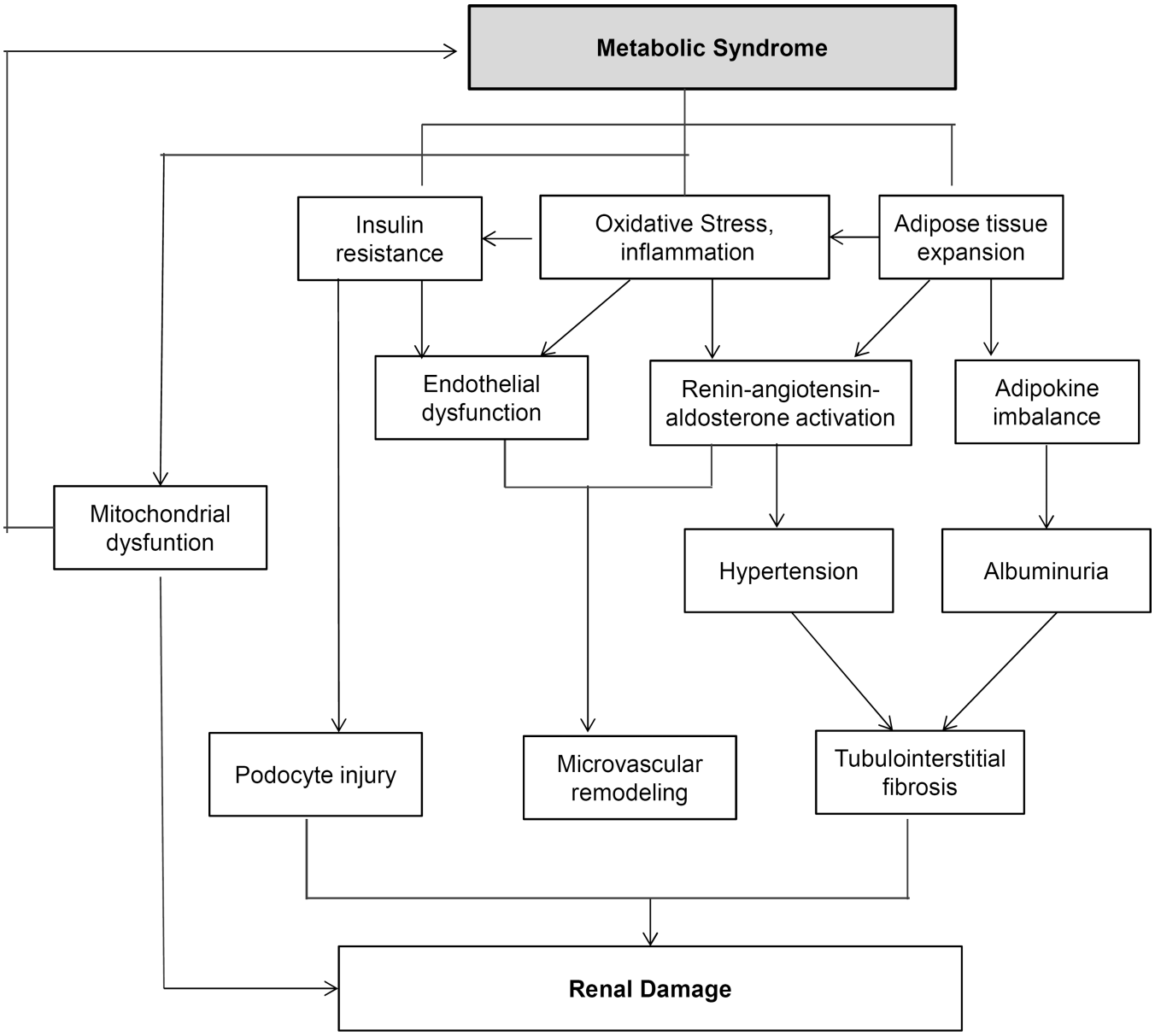


**Figure 2.**

Potential mechanisms by which MetS promotes kidney injury. Fundamental manifestations of MetS include insulin resistance and adipose tissue expansion, the latter promoting chronic inflammation and oxidative stress, which exacerbate insulin resistance. Those in turn can elicit various kidney injurious events through endothelial dysfunction, renin-angiotensin-aldosterone activation, and hypertension, as well as via adipokine imbalance. MetS is also closely linked to mitochondrial dysfunction, which can both promote progression of kidney damage and development of MetS.