REVIEW ARTICLE

The metabolic syndrome and chronic kidney disease

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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 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. Inflammation and IR 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. (Translational Research 2016;■:1–11)

Abbreviations: ■■■ = ■■■

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; (4) hypertension; and (5) elevated fasting glucose.[1] The International Diabetes 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 94 cm for Europid males is considered central obesity, whereas 90 cm 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

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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 5800 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 the development of CKD, defined as fall of 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 with 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 intrarenal interlobar 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 16-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 (IL-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 (Fig 1, Top) was associated with the upregulated expression of vascular endothelial growth factor,[22] possibly secondary to oxidative stress[24] commonly seen in MetS, and hyperinsulinemia that directly increases vascular endothelial growth factor 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 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 the later stage of MetS intrarenal 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