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Review Article

Incidental Chronic Kidney Disease in Metabolic Syndrome

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Abstract

The prevalence of metabolic syndrome (MetS) and chronic kidney disease (CKD) are increasing worldwide. Patients with these conditions are strongly prone to the development of and death from cardiovascular disease. Emerging data suggest that the process of development of incident CKD in patients with MetS is independent of that for diabetes and hypertension. However, the mechanism for the emergence of CKD remains elusive. Renal histopathologic changes have been recognized in MetS, including tubular atrophy, interstitial fibrosis, and arterial sclerosis, suggesting microvascular disease. Moreover, glomerular lesions in patients with MetS often have greater global and segmental glomerulosclerosis. Studies have shown several pathways linking insulin resistance and/or hyperinsulinemia with incidental CKD. First, insulin resistance with compensatory hyperinsulinemia promotes inappropriate activation of the renin–angiotensin system which induces aldosterone excess and glomerular hypertension. Second, insulin resistance increases oxidative stress which has also been implicated in the renal progression of glycoxidation and lipid peroxidation Third, insulin resistance enhances mesangial cell proliferation and extracellular matrix protein expansion via the stimulation of endothelin-1 and growth factors including transforming growth factor-β1 and insulin-like growth factor-1. Finally, insulin resistance downregulates the renal action of peroxisome proliferator activated receptors which elicit foam cell formation, renal lipotoxicity and endothelial dysfunction. Identification of MetS may help clinicians to be aware of its components so that therapeutic intervention on components of MetS can be initiated to avoid incident CKD and further cardiovascular disease. [*Tzu Chi Med J* 2010;22(1):11–17]

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1. Introduction

The epidemic prevalence of metabolic syndrome (MetS) and subsequent medical disorders increased in the late 20th century and have become significant issues worldwide. Furthermore, MetS has been associated with the added risks of obesity, diabetes, cardiovascular disease (CVD), and other clinical conditions, including peripheral and brain vascular disease, sleep apnea, polycystic ovarian syndrome, nonalcoholic steatohepatitis, gallstones, and hyperuricemia [1]. In Taiwan, the prevalence of MetS in one study was 12.9% (15.5% in men, 10.5% in women); women had a significantly higher tendency toward development of all components of MetS with age [2].

Another worldwide health issue is chronic kidney disease (CKD). In addition to MetS, CKD has been reported to be a predictor of CVD death [3]. Emerging data indicate that nondiabetic adults with MetS are prone to incident CKD, although the pathophysiology between these two conditions remains obscure [4]. Furthermore, prevention of MetS and CKD to avoid CVD deaths is challenging. Therefore, we will discuss and review the clinical evidence, renal histopathology, and pathogenesis of MetS in subjects who subsequently develop incident CKD.

2. What is metabolic syndrome?

Syndrome X, introduced by Reaven in 1988, was characterized by a cluster of metabolic disturbances [5], including central obesity, hyperglycemia, dyslipidemia, and high blood pressure. Therefore, syndrome X is recognized to be analogous to MetS. In fact, the development of MetS is derived from the consequences of insulin resistance and compensatory hyperinsulinemia, which have numerous causes (Table 1) [6–14]. The expression of insulin resistance with compensatory hyperinsulinemia has been found to be the result of complex interactions among unhealthy diets or lifestyle, obesity, male sex, and genetic and environmental factors. Among them, central obesity may play a major role in triggering insulin resistance via the active adipocytokine and complex pathways [12]. Furthermore, associated studies have suggested a genetic predisposition to MetS, such as the genetic expression of adipocytokines and perilipin [14].

The mechanisms of insulin resistance with the consequent development of endocardiovascular disease and atherosclerosis are illustrated in Fig. 1. First, activation of the renin–angiotensin system (RAS) with subsequently elevated angiotensin II and aldosterone contributes to alter insulin/insulin-like growth factor-1 signaling pathways and reactive oxygen species formation to destroy endothelial function, with eventual development of CVD [15]. Second, the blunted actions of peroxisome proliferator activated receptors (PPARs) have been found to be important in metabolic disorders and even atherosclerosis through modification of the innate immune system, lipotoxicity, and endothelial dysfunction [16]. Third, several adipocytokines have a central role in the regulation of insulin resistance, down-regulation of PPARs by decreasing adiponectin, and activation of aldosterone and inflammatory cytokines such as tumor necrosis factor and interleukin-6, as well as many aspects of endovascular atherosclerosis [17]. Fourth, sympathetic nerve overactivity stimulates RAS activity, promotes sodium reabsorption, and increases heart rate, stroke volume and peripheral vascular resistance, thus inducing hypertension and increasing cardiovascular risk [18,19]. Finally, the development of insulin resistance has an adverse impact not only on endovascular disease but also on atherosclerosis.

Table 1 — Potential causes of insulin resistance

Quality of diet
High fructose, sucrose or glucose-enriched diets [6,7]
High fat diets [8]
Excessive salt diets [9]
Ethanol diets [10]
Smoking [11]
Physical stress
Unhealthy and sedentary lifestyle
Obesity [12]
Male sex [13]
Genetic [14]

The diagnostic criteria of MetS were redefined by the World Health Organization (WHO) [20], National Cholesterol Education Program Adult Treatment Panel (NCEP-ATP III) [21] and International Diabetes Federation (IDF) [22] beginning in 1998 (Table 2) [20–23]. The plasma fasting glucose threshold was lowered to 100 mg/dL in the modified NCEP-ATP III criteria. According to the IDF definition of MetS, the threshold for waist circumference is lower in Asians than in Europeans and varies with race. In addition, central obesity is an essential criterion of the IDF. In one study, the IDF criteria prediction of CVD was modest and similar to other criteria, and the waist-to-hip ratio was strongly associated with CVD risk [24]. In Taiwan, the diagnostic criteria for MetS were further revised by the Department of Health and adopted in public health screening and education for related diseases [23].

3. Emerging evidence of incident chronic kidney disease in metabolic syndrome

A cross-sectional study, the Third National Health and Nutrition Examination Survey in the US, first described CKD as an incident development in patients

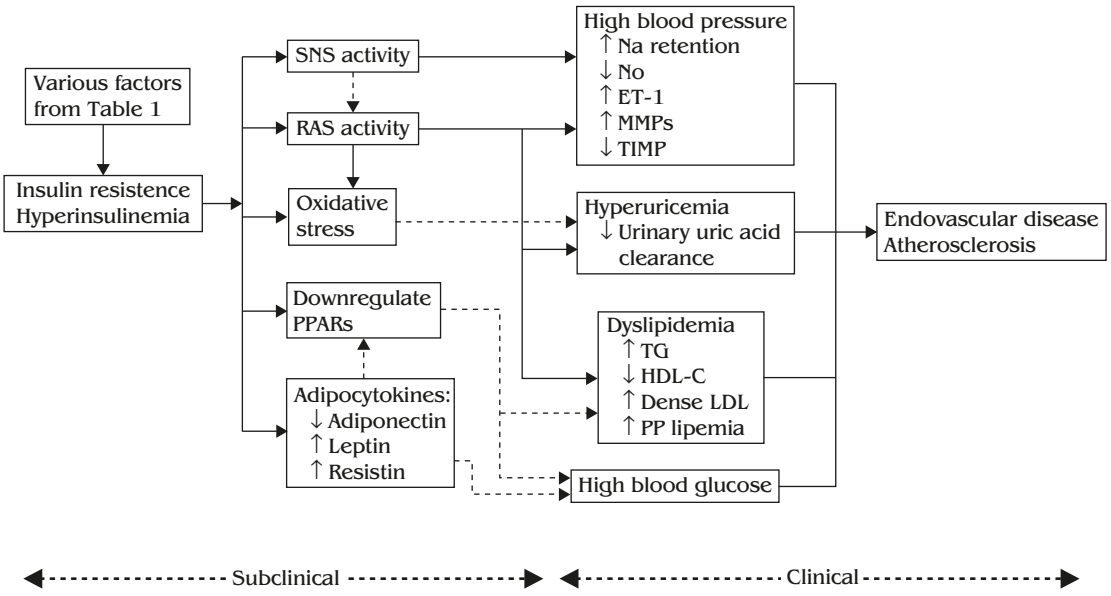

Fig. 1 — A schematic of the mechanisms of insulin resistance with the consequent development of endovascular disease and atherosclerosis. SNS=sympathetic nervous system; RAS=renin–angiotensin system; PPARs=peroxisome proliferator activated receptors; NO=nitric oxide; ET-1=endothelin-1; MMPs=matrix metalloproteinases; TIMP=tissue inhibitors of metalloproteinase; TG=triglycerides; HDL-C=high-density lipoprotein cholesterol; LDL=low-density lipoprotein; PP=postprandial.

with MetS (25). This research showed that the odds ratio (OR) of CKD, defined as a glomerular filtration rate <60 mL/min/1.73 m^2, was 2.60 (95% confidence interval (CI), 1.68–4.03) in patients with MetS compared with 1.89 (95% CI, 1.34–2.67) in patients without MetS. The OR of CKD in patients with MetS increased with an increasing number of components of MetS, with a value of 5.85 in patients with five components of MetS (95% CI, 3.11–11.0). In addition, high blood pressure was the most powerful predictor of CKD in patients with MetS, and the OR was 2.66 (95% CI, 1.62–4.35). Another prospective survey also demonstrated that MetS patients have a risk of CKD (OR, 1.88; 95% CI, 1.26–2.8), but there was no risk after exclusion of subjects with hypertension (OR, 0.925; 95% CI, 0.446–1.917; $p=0.844$). This further emphasizes the contribution of hypertension towards incident CKD (26). These investigations suggest that MetS is a cluster of multiple risk factors, especially hypertension, and not a unique biologic phenomenon.

A 9-year follow-up survey of 10,096 nondiabetic subjects in the Atherosclerosis Risk in Communities study reported an OR of 1.43 for the development of CKD among participants with MetS (95% CI, 1.18–1.73). The OR was 1.24 (95% CI, 1.01–1.51) after adjusting for the subsequent development of diabetes and hypertension during the course of the study (4). The results of several prospective population-based studies are shown in Fig. 2 (4,25–35). It is clear that MetS promotes the course of CKD even after adjustment for diabetes and hypertension.

Obesity, another component of MetS, has been reported to predict not only CKD but also end-stage renal disease (ESRD). For example, obesity is solely related to an enhanced risk of CKD in nondiabetic and nonhypertensive adults (36). A high body mass index was associated with an increased risk of development of ESRD in men in the general population of Okinawa, Japan (37). In addition, waist circumference, as an index of visceral obesity, is a more sensitive predictor of CKD than body mass index. For example, not only overweight and obese subjects, but also lean subjects with central fat distribution are at risk of CKD (38). Similarly, weight loss in overweight patients with chronic proteinuric nephropathies could induce a significant decrease in proteinuria after bariatric surgery (39).

4. Potential histopathology and mechanisms of incident chronic kidney disease in metabolic syndrome

MetS is an important risk factor for proteinuria and chronic renal disease independent of diabetes and hypertension (40–43). However, the underlying mechanisms have not been elucidated. Early, increasing urinary albumin is an indicator of hyperinsulinemic MetS. Nephrin, one of the glomerular podocyte proteins, is critical for the action of insulin on human glomerular podocytes (40). In addition, some studies have reported that hyperuricemia and gout precede

Table 2 — Various definitions of metabolic syndrome

	Essential criteria	No. of criteria	Diagnosis
World Health Organization, 1998 [20]	Type 2 diabetes, glucose intolerance or insulin resistance	Waist/hip ratio >0.90 (men) >0.85 (women) or BMI≥30 kg/m^2 HDL <35 mg/dL (men) <39 mg/dL (women) TG ≥150 mg/dL BP ≥140/90 mmHg Microalbuminuria	Essential criteria +≥2 No. of criteria
Modified NCEP-ATP III, 2005 [21]	Nil	Waist ≥102 (men) ≥88 (women) Glucose or on drug therapy ≥100 mg/dL HDL or on drug therapy <40 mg/dL (men) <50 mg/dL (women) TG or on drug therapy ≥150 mg/dL BP or on drug therapy ≥130/85 mmHg	≥3 No. of criteria
IDF, 2005 [22]	Waist In men ≥94 cm (European) ≥90 cm (Chinese) ≥90 cm (South Asian) ≥85 cm (Japanese) In women ≥80 cm (European) ≥80 cm (Chinese) ≥80 cm (South Asian) ≥90 cm (Japanese)	Glucose ≥100 mg/dL HDL <40 mg/dL (men) <50 mg/dL (women) TG ≥150 mg/dL BP ≥130/85 mmHg	Essential criteria +≥2 No. of criteria
Department of Health, Taiwan, 2006 [23]	Nil	Waist ≥90 (men) ≥80 (women) Glucose or on drug therapy ≥100 mg/dL HDL or on drug therapy <40 mg/dL (men) <50 mg/dL (women) TG or on drug therapy ≥150 mg/dL BP or on drug therapy ≥130/85 mmHg	≥3 No. of criteria

NCEP-ATP III=National Cholesterol Education Program Adult Treatment Panel III; IDF=International Diabetes Federation; BMI=body mass index; HDL=high-density lipoprotein; TG=triglycerides; BP=blood pressure.

MetS with or without impaired renal function [41–43]. Therefore, microalbuminuria and hyperuricemia can be used to predict the development of MetS and even CKD.

Several animal studies have revealed that a high-fat or high-fructose diet is associated with chronic renal disease in MetS [44–46]. A high-fat diet could lead to altered lipogenesis and lipolysis in the kidney, subsequent renal accumulation of foam cells and type IV collagen, an increase in urinary 8-hydroxy-2′-deoxyguanosine and albumin excretion, and impaired sodium handling, as well as renal sclerosis [44–46]. Furthermore, a high-fructose diet can stimulate redox- and urate-dependent inflammatory mediators in the proximal tubular cells through xanthine oxidoreductase, and production of monocyte chemotactic protein 1 and reactive oxygen species. These processes can lead to glomerulosclerosis and interstitial fibrosis [47].

Obesity is associated with glomerulomegaly, hyperfiltration, proteinuria and, in extreme cases, focal segmental glomerulosclerosis even in the absence of diabetes and hypertension [48,49]. In addition, a study

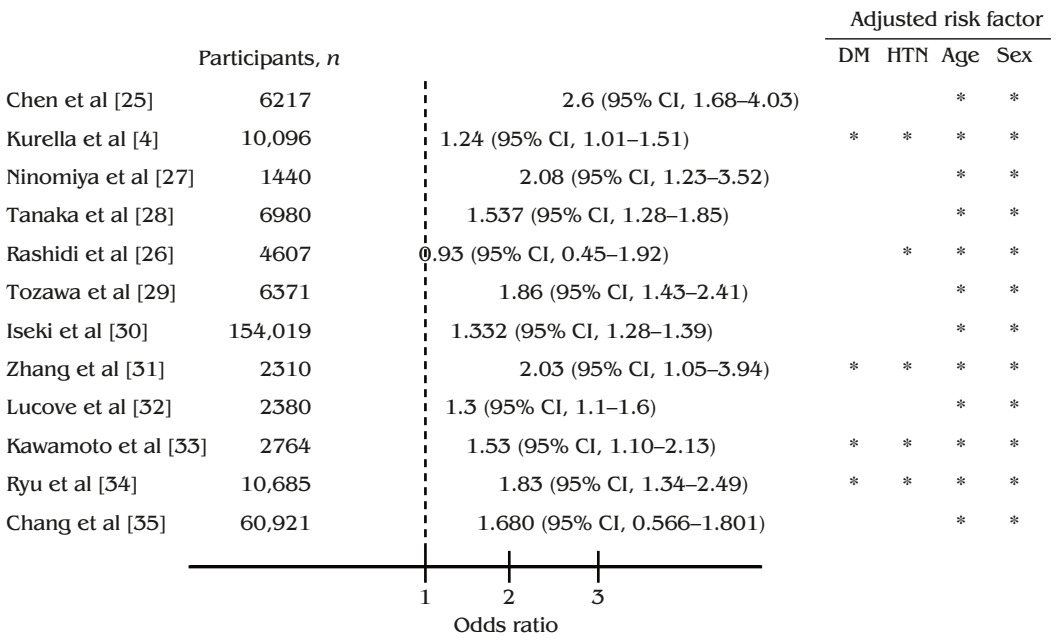

Fig. 2 — Odds ratio of incident chronic kidney disease in metabolic syndrome. DM=diabetes mellitus; HTN=hypertension; CI=confidence interval.

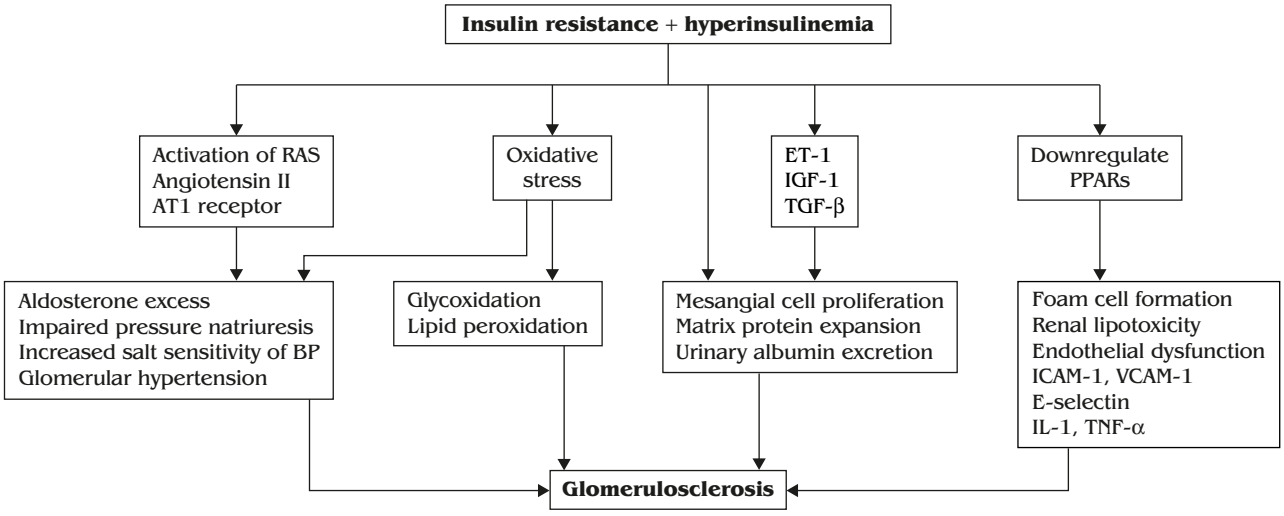

Fig. 3 — Pathomechanisms of insulin resistance and incident chronic kidney disease. RAS=renin–angiotensin system; AT1=angiotensin II type I receptor; BP=blood pressure; ET-1=endothelin-1; IGF-1=insulin-like growth factor-1; TGF-β=transforming growth factor-β; PPARs=peroxisome proliferator activated receptors; ICAM-1=intercellular adhesion molecule-1; VCAM-1=vascular cell adhesion molecule-1; IL-1=interleukin-1; TNF-α=tumor necrosis factor-α.

in rats showed that consumption of a high-fructose diet could promote glomerular sclerosis, tubular atrophy, tubular dilatation, and cellular infiltration in the kidneys via increased renal monocyte chemoattractant protein-1 (50). Nodular glomerulosclerosis was reported in a patient with MetS without diabetes (51). A cross-sectional study showed that patients with MetS have a greater prevalence of tubular atrophy, interstitial fibrosis, and arterial sclerosis, suggesting microvascular disease. Moreover, glomerular lesions in patients with MetS often have greater global and segmental glomerulosclerosis (52).

Fig. 3 shows several pathways linking insulin resistance and/or hyperinsulinemia with glomerulosclerosis (16,53–55). First, insulin resistance enhances the deleterious effects of angiotensin II in the kidney such as impaired pressure natriuresis, salt-sensitive high blood pressure, and glomerular hypertension (53).

Second, insulin resistance increases oxidative stress, which has also been implicated in the renal progression of glycoxidation and lipid peroxidation (53). Third, insulin resistance promotes the proliferation of mesangial cells and extracellular matrix expansion via stimulation from insulin itself and some growth factors including endothelin-1, insulin-like growth factor-1 and transforming growth factor-β (54). Finally, insulin resistance downregulates the renal action of PPARs which elicit foam cell formation, renal lipotoxicity and endothelial dysfunction from the co-effects of intercellular adhesion molecule-1, vascular cell adhesion molecule-1, E-selectin and some cytokines such as interleukin-1 and tumor necrosis factor-α (16,55).

5. Conclusion

MetS leads to the development of CKD independent of diabetes and hypertension. Renal histopathologic changes have been recognized in MetS patients, including tubular atrophy, interstitial fibrosis, and arterial sclerosis, suggesting microvascular disease. The pathogenesis of insulin resistance and/or hyperinsulinemia in the development of incidental CKD involves insulin resistance with compensatory hyperinsulinemia, which can activate the RAS, increase oxidative stress, stimulate endothelin-1 and growth factors (transforming growth factor-β1 and insulin-like growth factor-1), and downregulate the renal action of PPARs. Identification of MetS may help clinicians to be aware of its components so that therapeutic intervention on MetS components can be initiated to avoid incident CKD and further CVD.

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