

Review Article

Metabolic Syndrome and Renal Injury

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Both metabolic syndrome (MetS) and chronic kidney disease (CKD) are major global health issues. Current clinical markers used to reflect renal injury include albuminuria and estimated glomerular filtration rate (eGFR). Given the same eGFR level, urine albumin might be a better risk marker to predict progression of CKD and future development of cardiovascular diseases (CVDs). Serum Cystatin C is emerging as a new biomarker for early detection of renal injury associated with MetS and cardiovascular risk. In addition to each component, MetS per se influences the incidence and prognosis of renal injury and the odds ratios increased with the increase in the number of metabolic abnormalities. Hyperinsulinemia, activation of rennin-angiotensin-aldosterone system, increase of oxidative stress, and inflammatory cytokines are proposed to be the plausible biological link between MetS and CKD. Weight control, strict control of blood pressure, glucose, and lipids disorders may lead to lessening renal injury and even the subsequent CVD.

1. Introduction

MetS, a complicated clinicopathological entity with clustering of CVD and metabolic risk factors, includes central obesity, hypertension, dyslipidemia, and glucose intolerance. It has been pervasively recognized that individuals with MetS are associated with the increased risks of type 2 diabetes and CVD [1–3]. Abdominal fat plays an important role in MetS, because it is predictive of sensitivity to insulin [4, 5]. It has been reported that obesity adversely affects renal function and may be associated with morbidity and mortality in patients with CKD [4]. Recent evidence also indicated that presence of MetS is associated with an increased risk of developing CKD [6, 7]. As a matter of fact, both MetS and CKD are major global health issues with regard to the increasing prevalence of obesity and aging society [8–11]. What is more alarming is the fact that the prevalence of end-stage renal disease has more than doubled in the recent ten years [9]. Although the relationship between MetS and CKD was established, the detailed understanding of quantitative association between MetS and its components implicated in

kidney damage is still limited. In this paper, we will review the following issues:

- (1) epidemiological association between MetS and CKD incidence and/or progression,
- (2) reliable markers of MetS associated with renal injury,
- (3) plausible biologic links between MetS and CKD,
- (4) impact of treating the MetS on the risk of renal injury or CKD progress.

2. Epidemiological Association between MetS and CKD Incidence and/or Progression

The association between MetS and CKD in different populations varies with odds ratio (OR) ranging from 0.93 to 2.60 according to our review (Table 1). In a group of 118,924 nondiabetic Chinese patients with a mean followup for 3.7 years, Sun et al. reported that multivariable adjusted HR for CKD in subjects with MetS (ATP-III-MetS) was 1.30 (95% CI, 1.24–1.36) and 1.37 (95% CI, 1.30–1.44), evaluated

by proteinuria and eGFR, respectively [12]. In American Indians without diabetes, it is reported that adjusted hazard ratio for incident CKD (measured by using eGFR and urinary albumin-creatinine ratio) was 1.3 (95% CI, 1.1–1.6) [7]. In a survey conducted in nondiabetic native Americans (the intertribal heart project), the MetS was associated with a twofold increase on prevalence of microalbuminuria [13]. In The Third National Health and Nutrition Examination Survey (NHANES III), independent excess risks for CKD were hypertension, low HDL cholesterol, hypertriglyceridaemia, fasting hyperglycemia, and large waist circumference after adjustment for several confounding factors [14]. Notably, the ORs of CKD (eGFR < 60 mL/min per 1.73 m²) were 2.60 (95% CI, 1.68–4.03) and 1.89 (95% CI, 1.34–2.67) in patients with or without MetS, respectively. This study also found that even mildly elevated blood pressure or mild hyperglycemia may portend an increased risk of CKD and microalbuminuria. Remarkably, high blood pressure was the most powerful predictor of CKD in patients with MetS and with the OR of 2.66 (95% CI, 1.62–4.35) [14, 15]. In Atherosclerosis Risk in Communities (ARIC) study, a 9-year follow-up survey of 10,096 nondiabetic patients, the OR was 1.43 (95% CI, 1.18–1.73) for the development of CKD in subjects with MetS [16]. Furthermore, the OR was 1.24 (95% CI, 1.01–1.51) even after being adjusted for the subsequent development of diabetes and hypertension [16]. Accordingly, it is suggested that diabetes and hypertension were responsible for the renal injury progress. In addition, previous studies also suggested that dyslipidemia may also affect the prognosis of CKD [17–20]. Observations in the Modification Diet Renal Disease (MDRD) cohort indicated that low high-density lipoprotein (HDL) cholesterol predicts faster CKD progression [14, 21].

The findings of several previous studies conducted different ethnicities have that MetS per se affected CKD. A population-based study of native American adults resulted in multivariate-adjusted ORs of CKD for patients with 0 or 1 component of the MetS; patients with 2, 3, 4, and 5 components of CKD had multivariate-adjusted ORs of 2.21 (CI, 1.16 to 4.24), 3.38 (CI, 1.48 to 7.69), 4.23 (CI, 2.06 to 8.63), and 5.85 (CI, 3.11 to 11.0), respectively. The corresponding multivariate-adjusted ORs of microalbuminuria for patients with 3, 4, and 5 components were 1.62 (CI, 1.10 to 2.38), 2.45 (CI, 1.55 to 3.85), and 3.19 (CI, 1.96 to 5.19), respectively [14]. Another study in the US showed that the OR for microalbuminuria was 1.8 for one MetS component, 1.8 (95% CI, 1.0 to 3.2) for two components, and 2.3 (95% CI, 1.1 to 4.9) for three or more components (versus no traits) after controlling age, sex, smoking, body mass index, education, and family histories of diabetes and kidney disease [13]. A cross-sectional survey of Chinese adults resulted that the multivariate-adjusted ORs (95% CI) of CKD in participants with and without the MetS were 1.64 (1.16–2.32) and 1.36 (1.07–1.73). Compared to participants without any component of the MetS, the multivariate-adjusted ORs (95% CI) of CKD were 1.51 (1.02, 2.23), 1.50 (0.97, 2.32), 2.13 (1.30, 3.50), and 2.72 (1.50, 4.93) for those with 1, 2, 3, and 4 or 5 components, respectively. The corresponding multivariate-adjusted ORs (95% CI) of

elevated serum creatinine were 1.11 (0.88, 1.40), 1.39 (1.07, 2.04), 1.47 (1.06, 2.04), and 2.00 (1.32, 3.03), respectively [26].

In summary, high blood pressure and hyperglycemia seem to be the most powerful predictors of CKD in subjects with MetS. Several population-based studies supported the effect of MetS on CKD even after adjusting for the influences of diabetes and hypertension. Although the ORs of renal injury in different ethnicities were varied widely (Table 1), all these results suggested that OR was higher in patients with MetS than those without even adjusting for age and gender. Furthermore, previous studies also suggested that the ORs of renal injury increased with the increase in the number of metabolic abnormalities, and the findings seem to be independent of ethnicity. These findings suggest that MetS per se is an important causative factor for CKD.

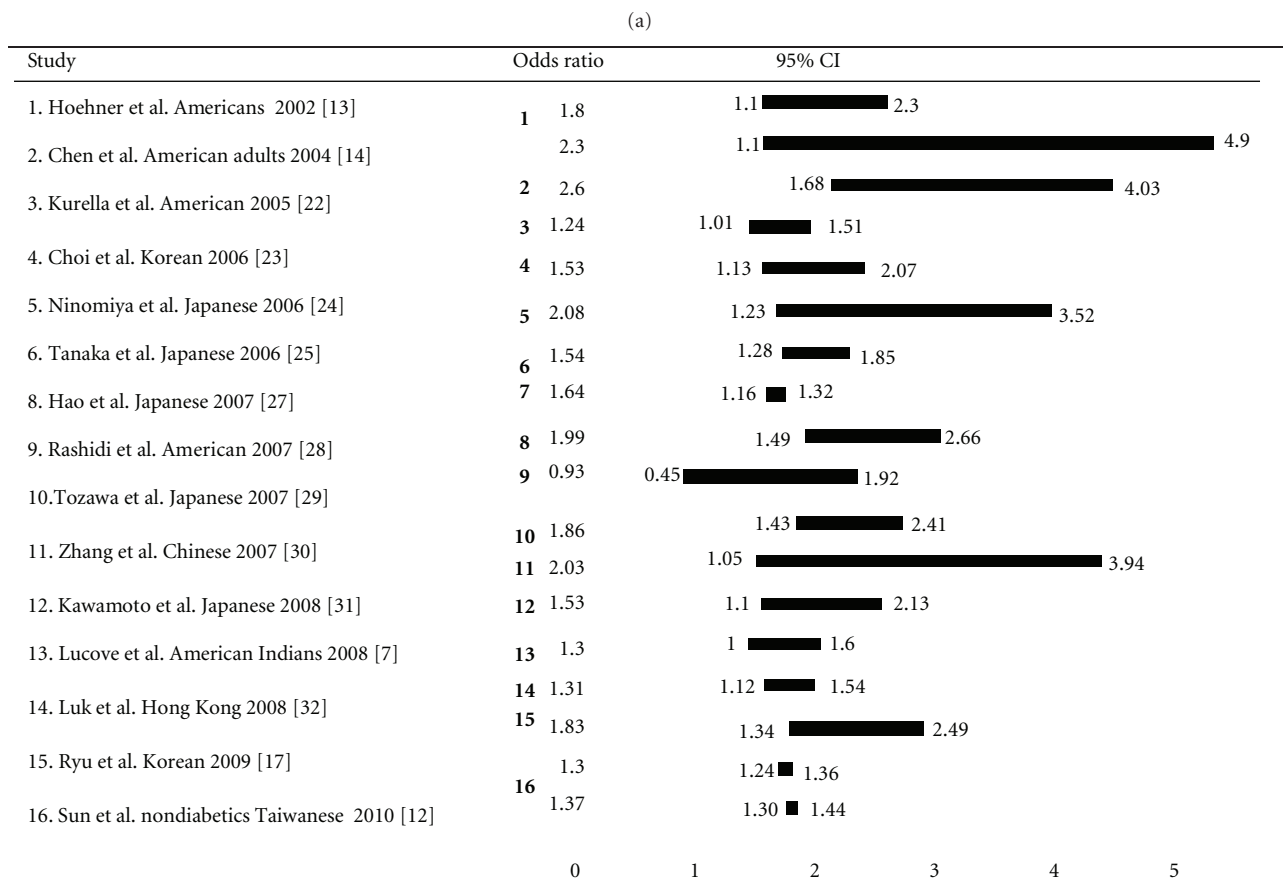
3. Reliable Markers of the Renal Injury

3.1. The Definitions of Metabolic Syndrome. In 1988, “Syndrome X” was introduced by Reaven, who proposed that insulin resistance plays a crucial role in glucose intolerance, hyperinsulinemia, hypertension, increased plasma triglyceride (TG), and decreased HDL cholesterol, all of which are associated with atherosclerosis and increased risk of coronary artery disease [1, 33]. The potential causes of insulin resistance include the unhealthy life style, obesity, and male, genetic, and environmental factors [34–37]. World Health Organization (WHO) designated the clustering of the cardiovascular and metabolic risk factors as “MetS” [38]. Other diagnostic criteria of MetS include National Cholesterol Education Program Adult Treatment Panel (NCEP-ATP III) [2, 39] and International Diabetes Federation (IDF) [40]. Each diagnostic criterion has its essential criteria, for example, central obesity is a prerequisite for the MetS according to the IDF criteria, but microalbuminuria is considered a criterion only by the WHO. Recently, a cross-sectional epidemiological study of Taiwan population had reported that the adjusted ORs of microalbuminuria based on five different definitions of MetS are varied (Table 2) [41]. Insulin resistance is considered to be the key mechanism of MetS [1, 42–44], but it is difficult to be quantified. In order to increase predictive power, some experts suggest that more related biomarkers may be needed, such as high-sensitivity C-reactive protein, uric acid, and other inflammation marker [36, 45–48].

3.2. The Reliable Markers of the Renal Injury. In general, biomarkers are used for diagnosis, severity classification, and outcome prediction. We will discuss two traditional biomarkers, eGFR and urine albumin, and one new marker serum cystatin C [6, 7, 9, 14, 23, 27, 50–55]. Which of them is the most reliable and powerful marker in evaluating patients with MetS remains controversial.

3.2.1. eGFR. Among individuals with CKD, the stages are defined based on the level of GFR, which is estimated by a formula based on the value of creatinine [56]. CKD shares

TABLE 1: OR of CKD in MetS: population-based studies.



(b)

Study	Ethnicity	Adjusted risk factors	OR (95% CI)
(1) Hoehner et al. 2002 [13]	Americans	Age	1.8 (1.1-2.3)~2.3 (1.1-4.9) difference insulin resistance syndrome trait powerful traits hypertension, impair fasting glucose
		Sex	
		HTN	
		DM	
(2) Chen et al. 2004 [14]	American adults	Age	2.60 (1.68-4.03)
		Sex	
		HTN	
		DM	
(3) Kurella et al. 2005 [22]	Americans	Age	1.24 (1.01-1.51)
		Sex	
		HTN	
		DM	
(4) Choi et al. 2006 [23]	Korean	Age	1.53 (1.13-2.07) Powerful traits TG and waist circumference
		Sex	
		HTN	
		DM	
(5) Ninomiya et al. 2006 [24]	Japanese	Age	2.08 (1.23-3.52)
		Sex	
		HTN	
		DM	

(b) Continued.

Study	Ethnicity	Adjusted risk factors	OR (95% CI)
(6) Tanaka et al. 2006 [25]	Japanese	Age	1.54 (1.28–1.85)
		Sex	
		HTN	
		DM	
(7) Chen et al. 2007 [26]	Chinese adults	Age	1.64 (1.16–1.32)
		Sex	
		HTN	
		DM	
(8) Hao et al. 2007 [27]	Japanese	Age	1.99 (1.49–2.66)
		Sex	
		HTN	
		DM	
(9) Rashidi et al. 2007 [28]	Americans	Age	0.93 (0.45–1.92)
		Sex	
		HTN	
		DM	
(10) Tozawa et al. 2007 [29]	Japanese	Age	1.86 (1.43–2.41)
		Sex	
		HTN	
		DM	
(11) Zhang et al. 2007 [30]	Chinese	Age	2.03 (1.05–3.94)
		Sex	
		HTN	
		DM	
(12) Kawamoto et al. 2008 [31]	Japanese	Age	1.53 (1.1–2.13)
		Sex	
		HTN	
		DM	
(13) Lucove et al. 2008 [7]	American Indians	Age	1.3 (1.0–1.6)
		Sex	
		HTN	
		DM	
(14) Luk et al. 2008 [32]	Hong Kong	Age	1.31 (1.12–1.54) Powerful traits central obesity, hypertriglyceridemia, hypertension, and low BMI were independent predictors for CKD.
		Sex	
		HTN	
		DM	
(15) Ryu et al. 2009 [17]	Korean	Age	1.83 (1.34–2.49) Powerful traits increased TG and LDL cholesterol levels were associated with significantly increased risk of CKD
		Sex	
		HTN	
		DM	
(16) Sun et al. 2010 [12]	nondiabetic Taiwanese	Age	ATP-III-MetS1.3 (1.24–1.36) IDF –MetS 1.37 (1.30–1.44)
		Sex	
		HTN	
		DM	

TABLE 2: Definitions of metabolic syndrome and adjusted ORs of associated microalbuminuria.

	WHO 1998 [38]	EGIR 1999 [49]	NCEP ATP III 2001 [39]	IDF 2005 [40]	AHA 2005 [2]
Essential criteria Definition of MetS	IFG, IGT, or IR plus 2 of other 5 criteria	Insulin in top 25% plus 2 of other 4 criteria	Any 3 of 5 criteria listed below	Increased waist plus any of 2 of other 4 criteria	Any 3 of 5 criteria listed below
Abdominal obesity (men/women)	Waist-to-hip ratio >0.9/0.85 BMI > 30 (kg/m ²)	Waist ≥ 94/80	Waist > 90/80	Men ≥94 cm (European) ≥90 cm (Chinese) ≥90 cm (South Asian) ≥85 cm (Japanese) Women ≥80 cm (European) ≥80 cm (Chinese) ≥80 cm (South Asian) ≥90 cm (Japanese)	Waist ≥ 90/80
Triglycerides (nmol/L)	≥1.7 or drug treatment for this lipid abnormality	>2.0 or drug treatment for this lipid abnormality	≥1.7 or drug treatment for this lipid abnormality	≥1.7 or drug treatment for this lipid abnormality	≥1.7 or drug treatment for this lipid abnormality
HDL cholesterol (nmol/L) (men/women)	<0.9/1.0 or drug treatment for this lipid abnormality	<1.0 or drug treatment for this lipid abnormality	<1.0/1.3 or drug treatment for this lipid abnormality	<1.0/1.3 or drug treatment for this lipid abnormality	<1.0/1.3 or drug treatment for this lipid abnormality
Blood pressure (mmHg)	More than 140/90 or drug treatment for hypertension	More than 140/90 or drug treatment for hypertension	More than 130/85 or drug treatment for hypertension	More than 130/85 or drug treatment for hypertension	More than 130/85 or drug treatment for hypertension
Fasting glucose (nmol/L)	More than 6.1 HOMA-IR >2.53	More than 6.1	More than 6.1	More than 5.6	More than 5.6
Urinary albumin excretion	More than 30 mg/g creatinine	—	—	—	—
Adjusted ORs (95% CI) of microalbuminuria [41]	Men 4.44*** (2.85–6.91) Women 4.16*** (2.57–6.73)	Men 2.62*** (1.49–4.60) Women 1.80 (0.99–3.29)	Men 1.99 (1.31–3.03) Women 2.21*** (1.47–3.32)	Men 1.51 (0.97–2.35) Women 2.29*** (1.51–3.48)	Men 1.64* (1.08–2.50) Women 2.26*** (1.52–3.38)

World Health Organization (WHO), European Group for the Study of Insulin Resistance (EGIR), National Cholesterol Education Program (NCEP), Adult Treatment Panel III (ATP-III), International Diabetes Federation (IDF), American Heart Association and National Heart Lung and Blood Institute (AHA/NHLBI), Metabolic Syndrome (MetS); Body mass index (BMI); high-density lipoprotein (HDL); homeostasis model assessment of insulin resistance (HOMA-IR); insulin resistance (IR). Adjusted OR (95% CI) of microalbuminuria: a cross-sectional epidemiological study based on data from the Taichung Community Health Study [41]. *P < .05; **P < .01; ***P < .001.

many of the same risk factors as CVD, namely obesity [9, 57], high blood pressure [58–60], diabetes mellitus [51, 58], hypertriglyceridemia [61], low HDL level [18, 20, 51], and smoking [51]. These factors overlap with components of MetS [51]. Direct measurement of GFR value may be the most reliable measure of renal function. However, the obesity-related renal injury is also associated with glomerular hyperperfusion, hyperfiltration and causes slightly increases of GFR [9, 55].

3.2.2. Urine Albumin. Albuminuria is generally conceived as an attractive marker of MetS-related renal injury [6, 50]. According to the previous study, it is a better risk marker than low estimated GFR to identify individuals at risk for accelerated GFR loss [62] and even a target to improve cardiovascular and renal outcomes [63]. But some

limitations should be noted in evaluation about the urinary albumin excretion for it would be affected by infection, stress condition and needed to be repeatedly measured. In addition, while end-stage renal disease causes the reduction of urine volume, albuminuria may no longer be increased with renal function progression.

3.2.3. Cystatin C. Cystatin C is suggested to be a new biomarker for the early detection of acute renal injury, MetS, and cardiovascular risk [52–55, 64–66]. According to the results of the Chennai Urban Rural Epidemiology Study (CURES) (MetS was defined using National Cholesterol Education Program criteria for adults modified for waist measured using the World Health Organization Asia Pacific guidelines. Serum cystin-C was estimated by a high-sensitivity particle-enhancing nephelometry assay),

it showed that subjects with four or five metabolic abnormalities had the highest cystatin C level. With decreasing number of metabolic abnormalities, the cystatin C levels decreased linearly (P for trend $< .001$), and it concluded that Cystatin C levels are highly correlated with the number of metabolic abnormalities in Asian Indians [67]. Previous evidence suggested that the measurement of serum cystatin C may be useful for evaluating cardiovascular risk profile [54]. A study reported that the association of cystatin C level with all-cause and CVD mortality is even stronger than that of GFR with these outcomes in stage 3 or 4 CKD [66]. Furthermore, cystatin C is considered to be a marker of inflammation as well as renal function [64]. Among elderly persons without CKD, cystatin C is a prognostic biomarker of risk for death, CVD and CKD, and seems to identify a preclinical state of kidney dysfunction that cannot be completely detected by measurement of serum creatinine or eGFR [65]. However, more clinical studies will be required to evaluate the clinical usefulness and cost effectiveness as compared with traditional markers.

4. Plausible Biologic Links between MetS and CKD

4.1. Hyperinsulinemia, Central Obesity, Hypertension, Dyslipidemia (Figure 1)

4.1.1. Hyperinsulinemia. Hyperinsulinemia-related insulin resistance is suspected to be the most important link between obesity and other metabolic complications leading to renal injury [9]. Insulin resistance and associated hyperinsulinemia may lead to renal involvement and injury through several different pathways. For example, activation of the renin-angiotensin system (RAS) with elevated angiotensin II and aldosterone, which subsequently affect insulin/insulin-like growth factor-1 signaling pathways, reactive oxygen species formation to destroy endothelial function, would cause the development of CVD [68]. Hyperinsulinemia causes atherosclerosis through hyperglycemia and dyslipidemia and endothelial dysfunction by inducing oxidative stress and attenuating peroxisome proliferator-activated receptor (PPAR) gamma, and the downregulation of peroxisome proliferator-activated receptors (PPARs) was proved by several studies in vivo [69, 70]. Adipokines and proinflammatory cytokines play an important role in the regulation of endothelial atherosclerosis [71].

4.1.2. Central Obesity. It is well known that patients with atherosclerotic complications are at a higher risk of CKD. Abdominal obesity is especially related to incident CKD and mortality. Inflammatory genes and genes implicated in insulin resistance are overly expressed in glomeruli of patients with obesity-related nephropathy [34, 35, 72]. Adipose tissue is the source of a novel group of hormonally active substances known as adipokines. Adipokines including IL-6, TNF- α , and plasminogen activator inhibitor-1 (PAI-1) may cause tissue damage by a direct proinflammatory mechanism or insulin resistance (some adipokines improve

insulin resistance, for example, leptin, adiponectin, and Visfatin) (Table 3) [4, 73, 74] and can be translated into inflammatory changes in the kidney [48, 71].

4.1.3. Hypertension. Hypertension cause, nephrosclerosis by blood pressure-dependent and -independent mechanisms. In addition, adipokines is implicated in hypertension and sodium retention secondary to obesity because it potently activates the sympathetic system, including sympathetic activity in the kidney [21]. Because of the interference with glomerular hemodynamics and with inflammatory mechanisms, the RAS is of paramount importance in CKD generation, and the angiotensin-II blockade significantly reduces cytokines and oxidative stress [75]. Reduced GFR has been found in prehypertensive patients with high blood pressure load as well as increased proteinuria, suggesting that even mild elevated blood pressure puts patients at risk of developing renal injury [19, 76–78]. Evidence of relationship between hypertension and CKD is further supported by several clinical studies. Hypertension seems to be an important risk factor of CKD (detected by eGFR and albuminuria) for the elders [78]. A recent study, using NHANES 1999–2004 data ($n = 15,332$; age ≥ 20 years), indicated that the effects of CVD are less dramatic when hypertension and diabetes are considered [79].

4.1.4. Dyslipidemia. Dyslipidemia is related to the incidence and prognosis of CKD through the following mechanisms, such as inflammation and increased oxidative stress, which would cause endothelial damage and atherosclerosis diseases [80–82]. The mechanisms discussed above are congruent with some clinical evidences, for example, hypertriglyceridemia is an independent risk factor for CKD [61], and low HDL cholesterol predicts CKD progression [21].

4.2. Impact of Treating the MetS on the Risk of Kidney Injury or CKD Progress. The effects of MetS treatments in improving renal outcomes remain largely unexplored. We try to discuss the effects of the interventions in controlling MetS components based on limited evidence (Figure 1).

The adjusted ORs of renal injury associated with individual or multiple components of the MetS had ever been investigated. A cross-sectional survey conducted in a nationally representative sample of 15160 Chinese adults showed that the adjusted ORs of CKD with hypertension, impaired fasting glucose, waist >102 cm in men or >88 cm in women, high triglyceride, low HDL cholesterol were 1.17 (CI, 0.88 to 1.56), 1.93 (CI, 1.40 to 2.76), 1.95 (CI, 1.21 to 3.14), 0.92 (CI, 0.68 to 1.24), and 1.34 (CI, 0.98 to 1.83), and the ORs of renal injury increased with increasing the number of metabolic abnormalities [26].

4.2.1. Hyperglycemia. It is widely recognized that intensive treatment of hyperglycemia can significantly delay the onset of albuminuria and decrease the risk of diabetic CKD [83–85]. Some evidences about using insulin sensitizer (e.g., Thiazolidinedione and Metformin) suggested that

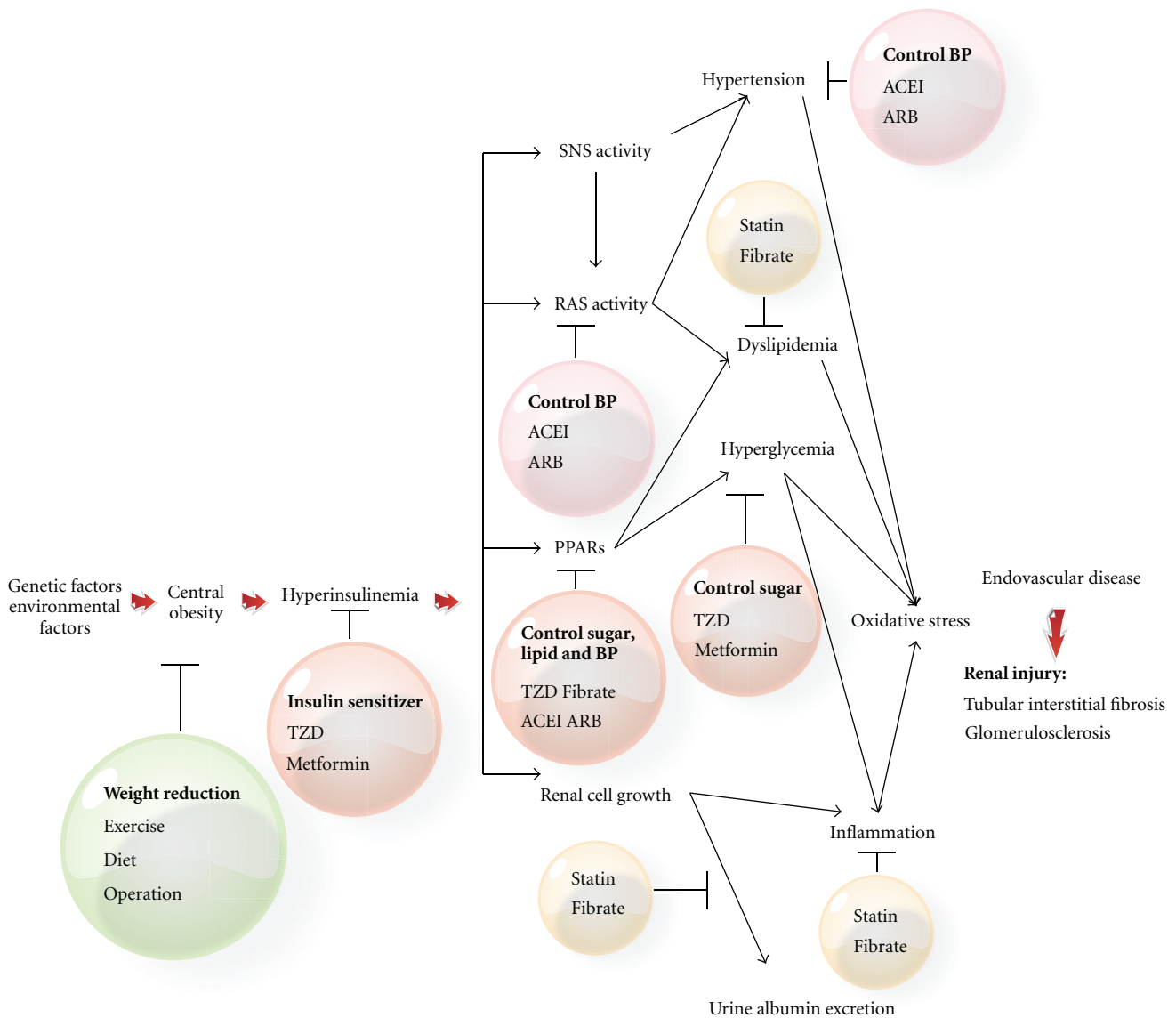


FIGURE 1: Mechanisms of insulin resistance with the consequent development of renal injury and the target of treatments. SNS: sympathetic nervous system, RAS: renin-angiotensin system, PPAR: peroxisome proliferator-activated receptors, ACEI: angiotensin-converting enzyme inhibitor, ARB: angiotensin II receptor blocker, TZD: thiazolidinediones.

improving endothelial function may be beneficial to renal injury [86, 87].

4.2.2. *Obesity.* Exercise improves insulin resistance, values of TG, HDL cholesterol, and blood pressure in patients with the MetS. A cross-sectional analysis showed that reduced renal function correlated with lower physical activity [88], and previous evidence reported the improvement of microalbuminuria after intense exercise in patients with MetS [89]. *Dietary changes* are as follows: a low-calorie diet can improve CKD while high protein intake may

worsen proteinuria and induce renal injury [90]. *Antiobesity drugs.* Orlistat blocks intestinal lipase and produces modest weight loss; it did not show obvious improvement on serum creatinine in 3 months of continuous study [91]. Sibutramine is a serotonin-norepinephrine reuptake inhibitor; it may improve insulin sensitivity [92], but a previous study reported that sibutramine exhibited weight loss and reductions of cystatin C levels at 6 months, while serum creatinine levels were not reduced [93]. It has a warning on its label from the US Food and Drug Administration because of cardiovascular risk. *Surgical treatment* includes a variety of procedures performed on people who are obese,

TABLE 3: The Adipokines effect on insulin sensitivity.

Adipokines (Adipose-derived protein)	Effect on insulin sensitivity [73]	Clinical significance in CKD [4, 74]
Resistin	Decline	Elevated serum levels Similar levels in both HD and PD Associated to heart disease in dialysis [4]
TNF- α	Decline	Elevated serum level Enhance gene expression of TNF- α in circulating blood cells in uraemia Elevated TNF- α associated to increased mortality in HD Anorexia and a poor nutritional status in PD [4]
IL-6	Decline	Elevated serum levels Reliable predictor of mortality Better mortality predictor than TNF- α in CKD and HD [4]
PAI-1	Decline	Elevated serum level Plasma PAI-1 levels increase in several chronic inflammatory states that are associated with CKD It may contribute to the pathogenesis of the accelerated vascular disease in this patient population [74]
Leptin	Improvement	Markedly elevated serum level Clinical marker of body fat content in dialysis Associated to inflammation, atherogenic lipid profile, and insulin resistance in CKD Low leptin is an independent risk factor for mortality in HD [4]
Adiponectin	Improvement	Elevated serum level Inversely associated with metabolic risk factors in uremia Inversely associated with CV events in HD Improved survival and better outcome in dialysis patients [4]
Visfatin	Improvement	Elevated serum level Anorexigenic Decreased circulating levels of amino acids and triacylglycerols Mortality predictor in CKD [4]

IL-6: interleukin-6, PAI-1: plasminogen activator inhibitor-1, TNF- α : tumor necrosis factor-alpha, HD: hemodialysis, PD: peritoneal dialysis.

reducing the size of the stomach with an implanted gastric banding or sleeve gastrectomy or biliopancreatic diversion with duodenal switch or gastric bypass surgery. Bariatric surgery may achieve long-term weight loss in patients with morbid obesity, improve the MetS, and reduce mortality, but the prevalence of microalbuminuria after surgery was only reduced in the diabetic group [91]. Reduction in albuminuria associated with improvement in glomerular hyperfiltration after gastroplasty has been reported [94]. However, we should notice the serious complications, such as oxalate nephropathy and nephrolithiasis, following bariatric surgery. Therefore, both surgical and nonsurgical approaches appear to be effective at reducing blood pressure and proteinuria [95]. A meta-analysis including thirteen studies reported that in smaller, short-duration studies in patients with CKD, nonsurgical weight loss interventions reduce proteinuria and blood pressure and prevent further decline in renal function; while in morbidly obese patients with glomerular hyperfiltration, surgical interventions normalize GFR and reduce blood pressure and microalbuminuria [96].

4.2.3. Hypertension. Blood pressure control helps in reducing CVD risk and CKD progression [97–101]. A continuous study of 8.8 to 12.2 years stint in evaluating the progression

of CKD, which was defined as a doubling of the serum creatinine level, a diagnosis of end-stage renal disease, or death, and showed that intensive blood-pressure control (the mean blood pressure was 130/78 mmHg in the intensive-control group and 141/86 mmHg in the standard-control group) had no effect on kidney disease progression but may lead to differential effects on intensive blood-pressure control in patients with and those without baseline proteinuria [100]. Different antihypertensive drugs may have different effects on the protection of CKD [101]. Angiotensin II signaling and subsequent oxidative stress in adipose tissue may be potential targets for the prevention of atherosclerotic cardiovascular disease in MetS and also in metabolic syndrome-based CKD [75], and a previous study reported that the Angiotensin-converting enzyme inhibitors (ACEIs) appear to be more effective than beta blockers or dihydropyridine calcium channel blockers in slowing GFR decline [101]. ACEI is recommended for the treatment of hypertension in patients with CKD and is considered a prognostic factor of CKD [102]. Previous evidences suggested that angiotensin-receptor blockers (ARBs) could reduce proteinuria, but the results are variable. A study provided that ARB inhibits albumin-elicited proximal tubular cell apoptosis and injury in vitro [103]. A meta-analysis from January 1990 to September 2006 also reported that the ARBs reduce proteinuria, and

the reduction in proteinuria from ARB and ACEI is similar [104].

4.2.4. Dyslipidemia. Fibrate therapy can decrease TG, increase HDL cholesterol, improve insulin sensitivity, and reduce the mesangium-induced glomerular matrix deposition [105]. Statin therapy can decrease LDL, TG, reduce inflammation, and improve endothelial function [106–109]. The current data are based on effects of proteinuria [110].

5. Relationship between MetS, Renal Injury, and CVD

It is known that CKD is associated with decreased cardiac function, ventricular hypertrophy, diastolic dysfunction, and increased risk of adverse cardiovascular events [111]. The components of MetS may contribute to the pathophysiological interactions between heart and kidney in type 4 cardiorenal syndrome and cause subsequent cardiac damage (traditional risk factors are diabetes, hypertension, low HDL cholesterol, and physical inactivity; nontraditional risk factors are albuminuria, oxidative stress, or high sympathetic tone) [111, 112]. A recent study reported the association between MetS, CKD, and left ventricular hypertrophy (LVH) and suspected that the combination of MetS and CKD is a strong risk for LVH as well as a strong and independent predictor of subsequent CVD [113]. Furthermore, a previous study indicated that the coexistence of early CKD with MetS could increase the accuracy of risk prediction for CVD mortality [114].

6. Conclusions

In addition to the effect of diabetes and hypertension, MetS is related to the incidence and prognosis of renal injury and CKD. MetS-associated renal injury may predict the subsequent CVD and even the mortality. Further studies about the MetS components that are implicated in renal damage can help to establish the targets in intervention of MetS in order to prevent CKD and CVD.

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