

Relationship between chronic kidney disease and metabolic syndrome: current perspectives

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Abstract: Both metabolic syndrome (MetS) and chronic kidney disease (CKD) are increasing in incidence and lead to significant cardiovascular morbidity and mortality. The relationship between these two entities is complex. Individual components of the MetS are known risk factors for incident kidney disease, but it is not clear how the clustering of these components is linked to the development and progression of kidney disease. Cross-sectional studies show an association of the MetS and prevalent CKD; however, one cannot draw conclusions as to which came first – the MetS or the kidney disease. Observational studies suggest a relationship between MetS and incident CKD, but they also demonstrate the development of MetS in patients with established CKD. These observations suggest a bidirectional relationship. A better understanding of the relationship between components of the MetS and whether and how these components contribute to progression of CKD and incident cardiovascular disease could inform more effective prevention strategies.

Keywords: obesity, insulin resistance, hypertension, oxidative stress, inflammation, adipokines

Introduction

The clustering of elevated blood glucose, hypertension, and hyperuricemia was first noted in 1923.¹ Subsequently, obesity, hypertension, and elevated blood glucose were observed in patients who were at risk of developing diabetes.²

The term syndrome X was first used in 1988.³ It was believed that insulin resistance was the pathophysiological common denominator underlying this cluster. The term metabolic syndrome (MetS) later replaced syndrome X. Several definitions were proposed for the MetS. The most widely accepted definition was issued by the Adult Treatment Panel III of the National Cholesterol Education Program (NCEP-ATPIII). According to the NCEP-ATPIII definition, MetS is defined as having three or more of the following five risk factors including: 1) abdominal obesity defined by waist circumference (men >102 cm; women >88 cm); 2) triglycerides ≥ 150 mg/dL; 3) low high-density lipoprotein (HDL) cholesterol levels (men <40 mg/dL; women <50 mg/dL); 4) blood pressure $\geq 130/\geq 85$ mmHg; and 5) fasting glucose ≥ 100 mg/dL.⁴

The MetS is linked prospectively with incident diabetes mellitus, stroke, and other cardiovascular events.⁵ Moreover, the MetS is also linked to the development of fatty liver, hyperuricemia/gout, polycystic ovarian syndrome, gallstones, and sleep disorders.⁶ According to the third National Health and Nutrition Examination Survey (NHANES III) criteria, about 47 million people have MetS. This is about 24% of the US adult population, including 44% in people over 50 years of age.⁷

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The prevalence of the MetS varies widely worldwide and rises with economic development and the associated overweight and obesity as seen among populations in Asia, South America, and Eastern Europe. MetS statistics depend on the definition used.⁸

The 2002 definition of chronic kidney disease (CKD) was recently updated by the Kidney Disease: Improving Global Outcomes (KDIGO) Group. CKD is classified based on cause, glomerular filtration rate (GFR) category, and albuminuria category (Tables 1 and 2).⁹

It is estimated that 26 million American adults have CKD and millions of others are at increased risk. In addition to leading to end stage renal disease (ESRD), CKD increases the risk of death, cardiovascular events, and hospitalization. This risk rises sharply with an estimated GFR (eGFR) less than 45 mL/min/1.73 m² with risk of mortality particularly high with eGFR values below 15 mL/min/1.73 m².¹⁰

In a systematic review of 39 studies that included a total of more than a million patients, Tonelli et al demonstrated an increased relative risk of all-cause mortality in nondialysis-dependent CKD patients. The absolute risk of death appeared to increase exponentially as renal function declined.¹¹

The MetS is associated with a twofold increase in cardiovascular events,¹² stroke,¹³ and in all-cause mortality.^{12,14} Outcomes studies in the setting of CKD and MetS comorbidity are limited. Data from the multiethnic study of atherosclerosis reported that the combination of CKD (defined as eGFR <60 mL/min/1.73 m²) and MetS (defined by the NCEP-ATPIII) is a strong predictor of incident cardiovascular events (myocardial infarction, cardiac arrest, angina, stroke, cardiovascular related death), adjusted hazard ratio (HR) 5.56 (95% confidence interval [CI] 3.72–8.12).¹⁵

In a study of 545 consecutive patients who underwent percutaneous coronary intervention, cardiovascular events (cardiovascular death, nonfatal myocardial infarction, revascularization for target and new lesions) occurred more frequently in patients with both MetS and CKD than those with CKD or MetS (51.4%) (log-rank $P<0.001$). After adjusting for confounders, both MetS and CKD

Table 2 GFR categories in CKD

GFR category	GFR (mL/min/1.732 m ²)	Terms
G1	≥90	Normal or high
G2	60–89	Mildly decreased
G3a	45–59	Mildly to moderately decreased
G3b	30–44	Moderately to severely decreased
G4	15–29	Severely decreased
G5	<15	Kidney failure

Abbreviations: CKD, chronic kidney disease; GFR, glomerular filtration rate.

appeared to be independent predictors of cardiovascular events ($P=0.018$).¹⁶

Similar findings were reported in the Korean Acute Myocardial Infarction Registry. In 11,462 patients with acute myocardial infarction, the 1-year mortality rate was higher in patients with both MetS and renal insufficiency than in those with MetS without renal insufficiency (HR 1.42; 95% CI 1.03–1.95; $P=0.033$) or in individuals without MetS (HR 1.42; 95% CI 1.03–1.95; $P=0.033$ and HR 1.08; 95% CI 0.77–1.51; $P=0.677$).¹⁷

Furthermore, insulin resistance in CKD patients is associated with increased arterial stiffness.¹⁸ The synergistic effect of decreased insulin sensitivity and CKD on mortality was demonstrated in a very recent study by Xu et al¹⁹ of 449 elderly men with stages 3–4 CKD, ages 70–71 years. After adjusting for confounders, glucose disposal rate (GDR) during euglycemic, hyperinsulinemic clamp was an independent correlate of all-cause mortality in smokers (adjusted HR 0.72; 95% CI 0.54–0.96 per 1 mg/kg per minute increase in GDR) and physically inactive individuals (HR 0.77; 95% CI 0.61–0.97) but not their matched controls. In other words, the higher the GDR (greater insulin sensitivity), the lower the all-cause mortality.¹⁹

Finally, the development of MetS in 200 patients with stage 4 and 5 CKD was an independent predictor of time to composite end-point of cardiovascular death, acute coronary syndrome, revascularization, nonfatal stroke, and amputation (adjusted HR 2.46; 95% CI 1.17–5.18).²⁰

Awareness of this relationship and implementing interventions that reduce incident MetS and manage MetS-related risk factors when present may decrease incident cardiorenal disease in CKD patients.

The link of MetS to CKD

Individual components of the MetS are associated with the development of albuminuria and decreased GFR. For example, hypertension alone may lead to glomerulosclerosis

Table 1 Albuminuria categories in CKD

Category	Albumin/creatinine ratio (mg/g)	Terms
A1	<30	Normal to mildly increased
A2	30–300	Moderately increased
A3	>300	Severely increased

Abbreviation: CKD, chronic kidney disease.

and mild proteinuria independently from hyperlipidemia and central obesity. However, an increasing body of evidence in the last decade suggests that MetS has an additive risk on the development and the progression of CKD.

In this review, we will focus on the literature linking the MetS (defined by NCEP-ATPIII) as a cluster to renal dysfunction defined by either albuminuria, decreased GFR, or both (Table 3).

Chen et al analyzed data on 7,800 participants with MetS in the NHANES III who were followed for over 21 years. Individuals with the MetS were at 2.6-fold greater risk of incident CKD (defined as eGFR <60 mL/min) than individuals without MetS. The risk of CKD increased with the number of MetS components from an odds ratio (OR) of 1.89 in adults with one MetS component to 5.85 in adults with all five components. The risk of microalbuminuria among adults with MetS was double that of adults without. The risk of microalbuminuria also increased in a step-wise fashion with the number of MetS components.²¹

In another analysis of the NHANES III data, incident microalbuminuria was greater in both women (OR 2.2; 95% CI 1.44–3.34) and men (OR 4.1; 95% CI 2.45–6.74) with MetS than without MetS.²²

Similar findings were reported in the Atherosclerosis Risk in Communities Study. In this study, 10,096 nondiabetic subjects with normal baseline GFR were followed for 9 years. The risk of developing CKD was 43% higher in subjects with the MetS than those without (OR 1.43; 95% CI 1.18–1.73). After adjusting for incident diabetes and hypertension, the risk of CKD remained higher in adults with MetS than without the MetS (OR 1.24; 95% CI 1.01–1.51).²³

Among 447 adults with untreated stage 1 and 2 essential hypertension, incident microalbuminuria was significantly greater in those with MetS than without the MetS after adjustment for systolic blood pressure.²⁴ In a cohort of 353 individuals without CKD, prevalent microalbuminuria was greater among patients with MetS than without the MetS (36.2% versus 19.3%; $P < 0.002$).²⁵

Other studies documented a close association between MetS and the development of CKD defined as decreased eGFR. In a cross-sectional study of 15,160 Chinese adults, Chen et al found that the multivariate-adjusted ORs (95% CI) of CKD and elevated serum creatinine in participants with MetS compared to those without the MetS were 1.64 (1.16–2.32) and 1.36 (1.07–1.73), respectively. Compared to those without any components 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 one, two, three, and four or five 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

The Strong Heart Study enrolled 1,484 Native Americans without diabetes between 1988 and 1999. The multivariable adjusted HR for CKD associated with MetS was 1.3 (95% CI 1.1–1.6). Equivalent HRs for albumin-to-creatinine ratio greater than 30 mg/g and eGFR less than 60 mL/min/1.73 m² were 1.4 (95% CI 1.0–1.9) and 1.3 (95% CI 1.0–1.6), respectively. The relationship between MetS and kidney outcomes was stronger in those who developed diabetes during follow-up.²⁷ In a similar study of 118,924 individuals in China, Sun et al reported that MetS was predictive of CKD defined by incident proteinuria (HR 1.39; 95% CI 1.24–1.36) and stage 3 or lower eGFR (1.37; 95% CI 1.3–1.44).²⁸

MetS predicted CKD in 6,980 Japanese adults participating in a screening program. There was a linear association between the number of MetS components and prevalent CKD (adjusted OR 1.54 and 95% CI 1.287–1.85; $P < 0.0001$).²⁹

Similar results were found in the Korean population, in a retrospective study of 60,921 healthy adults; prevalence of CKD was greater in those with MetS (11.0% versus 6.3%; $P < 0.001$) than those without MetS. This prevalence increased with the number of components of the MetS, and this association persisted after multivariate adjustment with OR was 1.680 (95% CI 0.566–1.801).³⁰

Surendar et al estimated GFR using cystatin C (cys-C) in a study of Indian Asians enrolled in the Chennai Urban Rural Epidemiology Study. Participants were divided according to the components of the MetS. Those with four or five metabolic abnormalities had the highest cys-C levels, and with a decreasing number of metabolic abnormalities, the cys-C levels decreased linearly (P for trend <0.001).³¹

In another study from Asia, Yang et al followed 4,248 Chinese adults in Taiwan for a median of 5.40 years. The multivariate-adjusted HR of CKD in participants with MetS compared with those without was 1.42 (95% CI 1.03–1.73). Additionally, there was a significantly graded relationship between the number of the MetS components and risk of CKD.³²

Ninomiya et al analyzed the association between the GFR slope and MetS by using a multiple regression model. In this study, 1,440 individuals over the age of 40 years, without CKD, were followed for 5 years. The multivariate-adjusted mean value for the GFR slope decreased significantly faster in subjects with four or more MetS components in comparison

Table 3 Risk of CKD in adults with and without the MetS

Study/author	Patients	Study design	Definition of CKD	Results
Cross-sectional studies of prevalent CKD Chen et al ²¹ NHANES III	6,217 US adults	Cross-sectional	eGFR <60 mL/min/1.73 m ² and/or Microalbuminuria urinary Alb/Cr ratio of 30–300 mg/g	OR for prevalent CKD 2.60 Two components of MetS 2.21 Three components of MetS 3.38 Four components of MetS 4.23 Five components of MetS 5.58 Prevalent microalbuminuria 1.89 Three components of MetS 1.62 Four components of MetS 2.45 Five components of MetS 3.19. OR for prevalent CKD One component of MetS 1.80 Two components of MetS 1.80 Three or more components 2.30. Microalbuminuria was more common in both women and men with MetS. OR 2.2 and 4.1, respectively. OR for CKD 1.64 One component of MetS 1.51 Two components of MetS 1.50 Three components of MetS 2.13 Four and five components of MetS 2.72. OR of prevalent CKD for those with four metabolic syndrome risk factors compared to those with no metabolic syndrome risk factors was 1.77. (The association was significant in participants <60 years only). Individuals with MetS had a multivariate adjusted OR of 1.680 for CKD compared with those without MetS. Increased risk of prevalent CKD in individuals with MetS (HR 1.99, 95% CI 1.46–2.73).
Hoehner et al ³⁹ Inter-Tribal Heart Project	934 Native Americans	Cross-sectional	Microalbuminuria Alb/Cr ratio of 30–299 mg/g	OR for incident CKD 1.43 Greater risk of CKD in patients with: Two components of MetS than without; OR 1.53 Three components of MetS 1.75 Four components of MetS 1.84 Five components of MetS 2.45. Greater risk incident CKD with than without MetS (HR 1.42, 95% CI 1.03–1.73).
Palaniappan et al ²² NHANES III	6,217 American adults	Cross-sectional	Microalbuminuria Alb/Cr ratio of 30–299 mg/g	
Chen et al ²⁶ Inter-Asia Study	15,160 Chinese adults	Cross-sectional	eGFR <60 mL/min/1.73 m ²	
Tanaka et al ²⁹	6,980 Japanese adults	Cross-sectional; hospital- based survey	eGFR <60 mL/min/1.73 m ² or proteinuria (+1 dipstick)	
Chang et al ³⁰	60,921 Korean adults	Retrospective analysis	eGFR <60 mL/min/1.73 m ² or proteinuria (+1 dipstick)	
Ryu et al ³⁴	10,685 Korean healthy men	Prospective cohort study; 3.8 years follow-up	eGFR <60 mL/min/1.73 m ²	
Prospective studies of incident CKD Kurella et al ²³ (ARIC Study)	10,096 US adults	Prospective; 9 years follow-up	eGFR <60 mL/min/1.73 m ²	
Yang et al ³²	4,248 Chinese adults	Prospective; 5.4 years follow-up	eGFR <60 mL/min/1.73 m ²	

Ninomiya et al ³³	1,440 adults ≥40 years; no CKD	Prospective; 5 years follow-up	eGFR <60 mL/min/1.73 m ²	Faster decline of eGFR in adults with none to one versus four to five MetS components.
Lucove et al ²⁷ (Strong Heart Study)	1,484 Native Americans	9 years follow-up	eGFR <60 mL/min/1.73 m ² or Albuminuria urinary Alb/Cr >30 mg/g	MetS was associated with a 30% increased risk of incident CKD. OR for decreased eGFR and albuminuria 1.3 and 1.4, respectively.
Sun et al ²⁸	118,924 Taiwanese	3.7 years follow-up	GFR <60 mL/min/1.73 m ² or proteinuria (+1 dipstick)	Incidence and HRs on CKD increased with the number of MetS components. The multivariable-adjusted HR for CKD associated with MetS was 1.30 (95% CI 1.24–1.36).
Ryu et al ³⁴	10,685 Korean healthy men	Prospective cohort study 3.8 years follow-up	eGFR <60 mL/min/1.73 m ²	The development of MetS during follow-up was associated with an increased risk of incident CKD (HR 1.75, 95% CI 1.28–1.39).
Thomas et al ³⁵	30,146 adults	Meta-analysis 11 prospective studies	eGFR <60 mL/min/1.73 m ² and/or Microalbuminuria or proteinuria	Greater CKD risk with than without MetS (OR 1.55, 95% CI 1.34–1.80).

Abbreviations: Alb, albumin; ARIC, Atherosclerosis Risk in Communities; CI, confidence interval; CKD, chronic kidney disease; Cr, creatine; eGFR, estimated glomerular filtration rate; HR, hazard ratio; MetS, metabolic syndrome; NHANES, National Health and Nutrition Examination Survey; OR, odds ratio.

with those who had one or no components, and the mean of the GFR slope showed a significantly greater decline in subjects with three MetS components in the group 60 years and older.³³

More evidence was provided in a prospective study of 10,685 Korean men who had no diabetes or hypertension and who were followed longitudinally over 3.8 years. It was found that individuals with preexisting MetS (n=787) were at increased risk for CKD (HR, 1.99; 95% CI 1.46–2.73). The development of MetS during follow-up was also associated with an increased risk of incident CKD (HR 1.75; 95% CI 1.28–1.39).³⁴

Thomas et al performed a meta-analysis that assessed the relationship between MetS and CKD in eleven prospective observational studies with 30,146 individuals. OR for the association of the MetS (using NCEP-ATPIII definition) and CKD (defined as eGFR <60 mL/min per 1.73 m²) was 1.55 (95% CI 1.34–1.80). The strength of the association increased as the number of MetS components increased (trend *P*-value =0.02).³⁵

In another prospective study, Rashidi et al reported an 88% (OR 1.88, 1.26–2.8) increased risk for CKD in patients with MetS compared to those without, within a 3-year follow-up. In a multivariate analysis, hypertension was the strongest predictor of CKD among the components of the MetS (OR 3.4; 95% CI 2.2–5.4; *P*<0.001). When patients with hypertension were excluded, the incidence of CKD after 3 years was not statistically significant (OR 0.925; 95% CI 0.446–1.917; *P*=0.844).³⁶

The prospective studies in Table 3 demonstrate a clear epidemiological link between the MetS and incident kidney disease. Despite differences in the follow-up times, populations, and methodology, these studies agree on a close relationship between MetS and both prevalent and incident kidney disease.

The link between kidney disease and the MetS was further established by histopathology. Alexander et al retrospectively evaluated the records of 146 patients from the Brigham and Women's Hospital who underwent elective nephrectomy for renal cell carcinoma between 2005 and 2007. Twelve patients who met the NCEP-ATPIII definition of MetS were matched with twelve patients who did not have MetS. Pathologists were blinded to the clinical diagnosis of these patients. Compared with healthy controls, patients with MetS had higher prevalence of tubular atrophy (*P*=0.0006), interstitial fibrosis (*P*=0.001), and arterial sclerosis (*P*=0.001). Patients with MetS had more global glomerulosclerosis and segmental glomerulosclerosis (*P*=0.04 and *P*=0.05, respectively).

Moreover, the eGFR 1 year after nephrectomy was significantly lower in patients with MetS than in controls (44.0 ± 20 versus 62.0 ± 11 mL/min/1.73 m²; $P=0.027$).³⁷

Several studies documented the presence of renal dysfunction prior to the onset of diabetes mellitus. Kohler et al conducted a cross-sectional analysis to describe the prevalence of and risk factors for microalbuminuria among blacks with newly diagnosed type 2 diabetes. Risk factors associated with increased albumin/creatinine included male sex, poor glycemic control, endogenous hyperinsulinemia, high blood pressure, elevated triglyceride levels, and obesity.³⁸

Insulin resistance and CKD

While there is significant overlap between MetS and insulin resistance, the two terms are not synonymous. Several observational and prospective studies have suggested a relationship between insulin resistance and incident kidney disease (Table 4).^{39–43} In a cross-sectional survey of nondiabetic Native Americans enrolled in the Inter-Tribal Heart Project, insulin resistance was associated with twofold greater prevalence of microalbuminuria. OR for microalbuminuria was 1.8 (95% CI 1.0–3.2) for two components and 2.3 (95% CI 1.1–4.9) for three or more components versus no traits after controlling

age, sex, smoking, body mass index (BMI), education, and family histories of diabetes and kidney disease.³⁹

In an observational study of 133 middle-aged patients, hyperglycemia and insulin resistance in prediabetes stages was thought to be the main risk factor for renal dysfunction in diabetic patients.⁴⁰

Chen et al demonstrated a step-wise increase in prevalent CKD as glucose tolerance decreased. In their study of 6,453 US adults without diabetes mellitus, the prevalence of CKD, defined as a GFR less than 60 mL/min, increased from 1.2% with fasting plasma glucose levels of 89–95 mg/dL to 4% with fasting glucose levels of at least 102 mg/dL.⁴¹

In the Uppsala longitudinal study of adult men, glycemic clamps was employed to examine insulin sensitivity in >1,000 older community-dwelling men who were followed for over 7 years. This study showed a direct positive association between insulin sensitivity and eGFR (95% CI 0.69–1.68; $P<0.001$); this association was still significant after adjustment for age, glucometabolic and cardiovascular risk factors. Furthermore, in longitudinal analyses, higher insulin sensitivity at baseline was associated with lower risk of impaired renal function (GFR <50 mL/min/1.73 m²) during follow-up, independently of glucometabolic variables (multivariable-adjusted OR for

Table 4 Studies that evaluated the association between insulin resistance and CKD

Study/author	Patients	Study design	Definition of CKD	Results
Cross-sectional studies of prevalent CKD				
Hoehner et al ³⁹	934 Native Americans	Cross-sectional	Microalbuminuria Alb/Cr ratio of 30–299 mg/g	OR for CKD Two components of MetS, 1.8 Three or more components, 2.3.
Chen et al ⁴¹	6,453 US adults without diabetes	Cross-sectional	eGFR <60 mL/min/1.73 m ²	OR of CKD Serum insulin 4.03 (CI 1.81–8.95; $P=0.001$) C-peptide 11.4 (CI 4.07–32.1; $P<0.001$) HbA _{1c} 2.67 (CI 1.31–5.46; $P=0.002$) HOMA-insulin resistance 2.65 (CI 1.25–5.62; $P=0.008$).
Prospective studies of incident CKD				
Niskanen et al ⁴⁰	144 middle-aged adults	Prospective observational 10 years follow-up	Microalbuminuria: urinary albumin excretion of 30–300 mg/24 hour Macroalbuminuria: >300 mg/24 hour	The development of both micro and macroalbuminuria was strongly associated with hyperglycemia and fasting insulin levels (trend $P<0.001$).
Nerpin et al ⁴²	1,070 elderly men	Prospective 7 years follow-up	Cystatin C-based eGFR <50 mL/min/1.73 m ²	Higher insulin sensitivity at baseline was associated with lower risk of impaired renal function; OR for 1-unit higher of insulin sensitivity 0.58 ([95% CI 0.40–0.84]; $P<0.004$).
Li et al ⁴³	2,696 Chinese adults	Prospective 7 years follow-up	Decline in renal function defined as drop in eGFR by 25% or >5 mL/min/1.73 m ² /year	Insulin resistance was NOT associated with decline in renal function OR 0.97 (0.79–1.19).

Abbreviations: Alb, albumin; CI, confidence interval; CKD, chronic kidney disease; Cr, creatine; eGFR, estimated glomerular filtration rate; HbA_{1c}, hemoglobin A_{1c}; HOMA, hemostasis model assessment; MetS, metabolic syndrome; OR, odds ratio.

1-unit higher of the insulin sensitivity index (M/I) 0.58 [95% CI 0.40–0.84]; $P<0.004$).⁴²

The effect of MetS versus insulin resistance on renal function was evaluated in a recent study of 2,696 Chinese adults. After a follow-up period of 7 years, subjects with MetS were found to be at an increased risk of renal function decline (defined by drop in eGFR by 25% or sustained decline in eGFR of more than 5 mL/min/1.73m²/year); OR 1.77 (95% CI 1.25–2.52). However, insulin resistance at baseline (defined as > the sex-specific percentiles of hemostasis model assessment [HOMA]-insulin resistance) was not associated with renal function decline; OR 0.97 (0.79–1.19).⁴³

In summary, fewer studies evaluated the relationship between insulin resistance and CKD, and methods to assess insulin resistance varied. The majority of studies pointed toward a possible link between insulin resistance and incident CKD.

MetS and kidney disease: a bidirectional relationship?

In this section, we will review the evidence linking CKD to the development of both insulin resistance and the MetS. Evidence from animal studies has shown that kidney failure led to hyperglycemia and hyperinsulinemia.^{44,45}

In humans, the development of insulin resistance and hyperinsulinemia in patients with CKD was recognized decades ago.^{46–48} DeFronzo et al were first to demonstrate this by assessing tissue sensitivity to insulin with the euglycemic insulin clamp technique in patients with renal insufficiency.⁴⁹

Other observational studies showed that insulin resistance is present in mild kidney disease, irrespective of its etiology, and progresses as kidney function diminishes. Fliser et al demonstrated an association between insulin resistance and the degree of renal dysfunction in patients with polycystic kidney disease and immunoglobulin A nephropathy.⁵⁰

Kato et al investigated insulin sensitivity in 18 young, lean nondiabetic male patients with biopsy-proven chronic glomerulonephritis. They found that GFR was notably lower in individuals with insulin resistance compared to those who were insulin sensitive ($P=0.0003$); eGFR correlated significantly with insulin sensitivity ($r=0.58$, $P<0.02$).⁵¹

Among 6,453 adults with diabetes in the NHANES III survey, Chen et al reported that prevalent CKD was significantly and progressively higher with increasing levels of serum insulin, C-peptide, hemoglobin A_{1c}, and HOMA-insulin resistance. The OR of CKD for the highest compared with

the lowest quartile was 4.03 (95% CI 1.81–8.95; $P=0.001$), 11.4 (95% CI 4.07–32.1; $P<0.001$), 2.67 (95% CI 1.31–5.46; $P=0.002$), and 2.65 (95% CI 1.25–5.62; $P=0.008$) for serum insulin, C-peptide, hemoglobin A_{1c} levels, and HOMA-insulin resistance, respectively.⁴⁰

In fact, insulin resistance increases progressively and linearly with declining renal function. In a study by Kobayashi et al, the hyperinsulinemic euglycemic glucose clamp technique was used to examine insulin sensitivity in 29 patients without diabetes but with different stages of renal function. It was found that insulin sensitivity was diminished in patients with CKD. The GDR of patients with CKD (6.91 ± 2.46 mg/kg/min) was significantly less than that of healthy subjects (9.93 ± 1.33 mg/kg/min; $P<0.01$). A negative correlation between GDR and serum creatinine level ($r=-0.449$; $P<0.05$) and positive correlations between GDR and creatinine clearance ($r=0.549$; $P<0.01$) and Apo A-1/B levels ($r=0.396$; $P<0.05$) were noted.⁵²

In a study of septuagenarians, stage 3 CKD was associated with a 40% increased odds of insulin resistance and was associated with higher visceral fat mass. This was the first prospective study to evaluate whether kidney disease predicted the development or worsening of insulin resistance.⁵³

The effect of insulin resistance on progression of CKD was evaluated in 1,456 elderly individuals from Taiwan. Using the HOMA formula, each unit increment of insulin resistance was associated with 1.16-fold increase in the HR (95% CI 1.06–1.26; $P<0.01$) of decline in renal function.⁵⁴

It appears that uremia-induced insulin resistance resolves at the initiation of renal replacement therapies. This may suggest the presence of dialyzable substances that mediate this process.⁵⁵

Similarly to insulin resistance, the development of MetS in patients with CKD was demonstrated in prospective studies. In a study from Hungary, among 223 patients with immunoglobulin A nephropathy, MetS was diagnosed in 107 patients at the time of diagnosis or during follow-up. There was significant association between MetS and doubling serum creatinine in these patients 95% CI 1.96 (1.17–1.33; $P=0.011$). The association remained significant after adjustment for confounders: 1.70 (1.02–3.83; $P=0.040$).⁵⁶

Not only is MetS associated with incident CKD but also with its progression. In a single center study from Japan, MetS predicted a composite outcome of progression of CKD, ESRD and death in 213 Japanese subjects. In this study MetS was associated with higher urinary albumin-to-creatinine

levels, and survival was significantly higher among individuals without MetS ($P=0.0086$).⁵⁷

Mechanisms of the interrelationship between MetS and CKD

The exact mechanism that links the MetS to renal damage has not yet been completely elucidated. The pathophysiological factors contributing to renal disease in patients with MetS are complex and include insulin resistance, adipocytokines, endothelial dysfunction, renin-angiotensin-aldosterone-system (RAAS) activation, and oxidative stress.

Oxidative stress

The role of oxidative stress was documented in animal studies. In a study by Wang et al, 4-week old, obese Zucker rats were randomized into three groups: control, vehicle dimethyl sulfoxide, and acetaminophen treated. Lean Zucker rats were considered healthy controls. Tubulointerstitial fibrosis, inflammation, and atrophy were significantly more evident in the obese rats compared with the lean ones. Treatment with acetaminophen reduced markers of tubular injury, suggesting a role for oxidative stress via decreasing tissue superoxide and macromolecular oxidation.⁵⁸

Johnson et al reported that MetS in patients with advanced CKD correlated with oxidative stress and reduced adiponectin levels.²⁰

The role of inflammation

The constellation of insulin resistance, hypertension, and inflammation releases inflammatory cytokines, including interleukin-6 and tumor necrosis factor- α , which cause renal fibrosis.⁵⁹ The role/association of inflammation and CKD was implicated in a cross-sectional study by Lee et al, who studied the interrelationships between elevated C-reactive protein (defined as >3), MetS (NCEP-ATPIII definition), and CKD (eGFR <60 mL/min/1.73 m² or albuminuria) in 9,586 subjects without diabetes mellitus or hypertension. Subjects with high C-reactive protein and MetS had a greater likelihood of having CKD (OR 3.26; 95% CI 2.00–5.31).⁶⁰

The role of angiotensin II

Visceral adipocytes secrete angiotensinogen and thus stimulate the renin-angiotensin-aldosterone pathway to cause hypertension, hyperfiltration, and renal injury.⁶¹ Insulin resistance is associated with a more active RAAS.⁶² This may contribute to the enhanced oxidative stress vascular

remodeling and pressor responses to exercise, a predictor of both cardiovascular and renal risk.^{63,64}

Additionally, angiotensin II levels are considered to be potent activators of transforming growth factor β 1 (TGF- β 1) expression, a fibrogenic cytokine that contributes to glomerular injury.⁶⁵

The role of adipokines

Adipose tissue is a highly active endocrine organ, secreting numerous factors that contribute to renal and cardiovascular complications. These factors regulate glucose and lipid metabolism. Leptin, a small peptide produced mainly in adipocytes of white fat tissue, is increased in patients with MetS. Leptin is cleared by the kidneys and has numerous effects on the kidney, which were summarized by Wolf et al.⁶⁶ Leptin mediates sympathetic nerve activation, and infusion of leptin into rats increases renal sympathetic nervous activity. The role of sympathetic renal nerves in the development and course of hypertension has been proven in both animal experimental models and in human studies.^{67,68} Additionally, leptin stimulates the proliferation of cultured glomerular endothelial cells, increases TGF- β 1 synthesis in endothelial cells, and upregulates TGF- β type II receptor expression. TGF- β is a fibrogenic mediator in various renal diseases. Some authors suggest that leptin also may have profibrotic effects on mesangial cells, independent of the TGF- β pathway.⁶⁹ Finally, leptin was linked to increased production of oxidative stress in human endothelial cells.⁷⁰ High levels of leptin after a nephrectomy may be responsible for the development of glomerulosclerosis in the remaining kidney.⁷¹

Similar to leptin, resistin is another adipokine which appears to participate in insulin resistance and kidney disease. Resistin is markedly increased in obese experimental animals, and its levels are lowered by thiazolidinediones (TZD). TZDs are drugs currently used to treat type 2 diabetes by increasing insulin sensitivity. TZDs also inhibit leptin production and ameliorate microalbuminuria, both in the streptozotocin-induced diabetic rat and type 2 diabetic patients.⁷²

Adiponectin is an adipokine that is synthesized and secreted by adipocytes. It is known to have strong anti-inflammatory and antiatherosclerotic properties. Deficiency of adiponectin plays an important pathophysiologic role in patients with impaired glucose homeostasis.⁷³

Adiponectin deficiency is linked to the development of albuminuria in obese patients. This may help explain the link between obesity and kidney disease. In animal models, adiponectin knockout mice exhibited increased albuminuria and fusion of podocyte foot processes. In cultured podocytes,

the infusion of adiponectin reduced podocyte permeability to albumin and podocyte dysfunction. The presumed mechanism is reduction of oxidative stress, as adiponectin regulated an isoform of NADPH oxidase through the ADP-activated protein kinase pathway.⁷⁴

In a large prospective trial of patients with mild to moderate kidney disease, insulin resistance was associated with low adiponectin levels similar to what is found in patients with the MetS.⁷⁵ In this prospective study, adiponectin levels were inversely related to cardiovascular events. Furthermore, in an earlier study of patients with advanced kidney disease, low adiponectin values were significantly related to cardiovascular events (HR 1.56; 95% CI 1.12–1.99).⁷⁶

The role of overweight and obesity

The link between obesity and CKD has been recognized for nearly a century.⁷⁷ However, there is little published information on the relationship between renal dysfunction and total or regional body fat.

Perhaps one of the strongest epidemiological studies associating obesity (defined by BMI >25 kg/m²) and CKD comes from the Kaiser Permanente database. Hsu et al evaluated over 320,000 members of the Kaiser Permanente healthcare system who volunteered for screening and were followed for 15–35 years. The risk of ESRD increased in a step-wise fashion as BMI rose, even after adjusting for blood pressure, diabetes, smoking, and cardiovascular disease.⁷⁸

In a multivariate analysis of the NHANES III data, it was found that risk of prevalence for CKD was more than twice as high in patients with an increased waist circumference, suggesting that abdominal obesity may be an independent risk factor for CKD.²¹

In a cohort of 1,683 nondiabetic Chinese adults, insulin resistance, assessed by HOMA, was not associated with CKD (eGFR <60 mL/min/1.73 m²) in those with normal weight (BMI <24 kg/m²) (relative risk 1.43, 95% CI 0.87–2.36, *P*=0.16), comparing the highest to the lowest quartile of HOMA. However, HOMA was associated with prevalent decline in eGFR in the overweight/obese subpopulation (*R* 2.10, 95% CI 1.11–3.97; *P*=0.02).⁷⁹ One can perhaps conclude that obese subjects are at increased risk of declining eGFR at levels of HOMA-insulin resistance that have no effect in lean individuals.

In another study, 8,792 healthy Korean men, who had no known risk factors for CKD, were followed longitudinally. Weight gain greater than 0.75 kg/year was associated with

a 3.74 higher HR for developing CKD compared to weight gain less than 0.75 kg/year.⁸⁰

Praga et al reported that obese patients are at high risk for developing proteinuria and CKD after unilateral nephrectomy. Among 14 obese patients with a BMI greater than 30 kg/m², 13 patients (92%) developed proteinuria and renal insufficiency. Conversely, among 59 patients with a BMI less than 30 kg/m², only seven patients (12%) developed these complications.⁸¹

The term “obesity-related glomerulopathy” (ORG) was first established by Kambham et al to describe a distinct histopathologic pattern characterized by glomerulomegaly with or without classical focal segmental glomerulosclerosis in obese patients (BMI >30 kg/m²). Compared with idiopathic focal segmental glomerulosclerosis, ORG has a lower incidence of nephrotic syndrome, more indolent course, consistent presence of glomerulomegaly, and milder foot process fusion. This was based on 6,818 native renal biopsies received from 1988–2000. During this period, a 10-fold increase in this biopsy diagnosis incidence was noted. This is alarming and consistent with the increase in the prevalence of obesity.⁸²

Obesity is not only implicated in the development of CKD but also with a faster progression. Influence of obesity on progression of nondiabetic CKD was evaluated in a retrospective cohort study by Othman et al. One hundred twenty-five nondiabetic patients with stage 3 CKD were followed at a single center for 10 years. Higher baseline BMI and younger age were strongly and independently associated with faster CKD progression (fall in eGFR >1 mL/min/1.73 m²/year) (*R*²=0.122; *P*<0.001).⁸³

Obesity results in kidney disease beyond just CKD. In a meta-analysis examining the association between obesity and kidney disease, Wang et al reported >60% increased risk for any kidney disease including nephrolithiasis, renal cancer, CKD, and ESRD in BMI >30 kg/m² (relative risk =1.83 [1.57–2.13]).⁸⁴

The synergistic effect of obesity and hypertension on kidney function was examined by Munkhaugen et al who followed 74,986 adults participating in a Norwegian registry with a 20-year follow-up study. They found that prehypertension in nonobese patients was not a risk factor for incident kidney disease, whereas it was in obese patients.⁸⁵

Obesity: does it matter where the fat is?

It is important to note that studies on obesity and outcomes did not always distinguish the fat distribution pattern. Abdominal obesity is considered the most important feature of the MetS.⁸⁶

Abdominal obesity results from sedentary lifestyle and overeating. Additional genetic and environmental factors also play a role. Abdominal obesity results in insulin resistance. Visceral adipose tissue releases cytokines and free fatty acids responsible for insulin resistance.^{87,88} Abdominal fat can accumulate either subcutaneously or in the visceral compartments. It is not entirely proven which pattern is more predictive of insulin resistance; however, some studies have shown greater risk with visceral adiposity than abdominal subcutaneous fat.^{89,90} These considerations should be taken into account when investigating the clinical impact of MetS.^{87–90}

The role of hypertension

Another component of MetS is hypertension. Hypertension alone is a known cause of CKD and proteinuria, typically <500 mg/day. In fact, hypertension is the second leading cause of ESRD.⁹¹

It is associated with an approximately 2- to 3-fold increased risk of microalbuminuria. The development of microalbuminuria in hypertension is perhaps related to increased intraglomerular pressure and resultant injury to the epithelial lining leading to leakage of albumin.^{92,93}

In a study discussed earlier by Rashidi et al,³⁵ controlling for hypertension eliminated the statistical association between MetS and renal disease. This study suggests that hypertension is the key player in the MetS renal disease association; however, these results need to be replicated before a conclusion is drawn.

CKD and the MetS – which component of the MetS is the main culprit?

Since every component of the MetS is a risk factor for the development and progression of CKD, it would be helpful to know which components of the MetS contribute the most to CKD. Epidemiologic studies have demonstrated greater risk for renal dysfunction with specific components of the MetS. For example, hypertension and fasting plasma glucose levels of >110 mg/dL were associated with the greatest risk for microalbuminuria and low GFR in the NHANES III data.²¹

Mänttari et al tested the hypothesis that hyperlipidemia might also add a greater risk for accelerated renal dysfunction in patients with hypertension. A total of 2,702 dyslipidemic, middle-aged men without kidney disease participating in the Helsinki Heart Study were studied. Subjects with an elevated ratio of low-density lipoprotein to HDL cholesterol (>4.4) had a 20% faster decline in eGFR than those with a ratio less than 3.2.⁹⁴

In the Atherosclerosis Risk in Communities Study, reduced HDL cholesterol or elevated triglycerides levels were independently associated with a significantly increased risk for CKD (defined by increase serum creatinine >0.4 mg/dL). The adjusted relative risk for the highest versus lowest quartile of triglycerides was 1.65 (95% CI 1.1–2.5; $P=0.01$) and for HDL was 0.47 (95% CI 0.3–0.8; $P=0.003$).⁹⁵

Observations in the Modification of Diet in Renal Disease Study cohort indicated that low levels of high-density lipoprotein HDL cholesterol predicts faster CKD progression in 840 patients with diverse renal diseases.⁹⁶

To the contrary, data from 2,141 patients with diabetes mellitus and CKD stages 3–5 enrolled in the Kidney Early Evaluation Program showed that overall glycemic control but not lipids were associated with abnormal urinary albumin excretion, a marker of increased risk for progressive disease.⁹⁷ In summary, it is not entirely clear whether one component of the MetS has more significance than the others in the development of CKD.

Potential therapeutic interventions

Well-designed studies that aim at evaluating potential interventions to improve renal outcomes in patients with MetS are lacking. Available studies are often small and short term or post hoc analyses of large trials. Furthermore, many studies do not evaluate hard renal outcomes like progression to ESRD.⁹⁸

There is no doubt that controlling the metabolic abnormalities in the MetS is important to cardiovascular disease prevention.⁹⁹ It is well established that controlling these abnormalities delays renal disease in patients with diabetes; however, clinical trials in patients with the MetS are scarce.¹⁰⁰ This is partially due to the fact that the mechanism of renal injury in MetS is not fully understood. Table 5 summarizes potential interventions from clinical trials.

Increased physical activity improves cardiovascular outcomes in patients with MetS. Although no prospective studies were undertaken on the effect of increased physical activity on renal function in individuals with the MetS, its positive effects on glucose and lipids metabolism, reduced inflammation, and improved endothelial function are well established.¹⁰¹

In a cross-sectional study, Finkelstein et al¹⁰² evaluated data from NHANES III and found a clear association between physical activity and eGFR. However, conclusion on causality could not be drawn given the nature of the study.

Several studies found that weight loss achieved by surgical and medical therapies resulted in decreased proteinuria

Table 5 Summary of potential interventions in MetS and CKD

Intervention	Effect(s)
Physical activity	Improves glucose and lipids metabolism Reduces inflammation Improves endothelial function
Weight loss	Decreases proteinuria Increases GFR in obese patients Delays progression to ESRD in CKD patients
Blood pressure control <140/90 mmHg	Decreases the risk of CKD progression Reduces risk of cardiovascular events
Sibutramine	Decreased Cystatin C but not creatinine in clinical trials of obese women with polycystic ovaries Increases blood pressure
Orlistat	No effect on renal function in clinical trials
Metformin	Improves insulin sensitivity Improves endothelial function
RAAS inhibitors	Decrease proteinuria Decrease inflammation Lowers markers of oxidative stress Increase adiponectin
HMG-CoA reductase inhibitors	Preserve renal function and decrease proteinuria in CKD patients

Abbreviations: CKD, chronic kidney disease; CoA, coenzyme A; ESRD, end stage renal disease; GFR, glomerular filtration rate; HMG-CoA, 3-hydroxy-3-methylglutaryl-CoA; MetS, metabolic syndrome; RAAS, renin-angiotensin-aldosterone system.

and improved GFR in obese patients.¹⁰³ Chagnac et al¹⁰⁴ found that weight loss ameliorates obesity-related glomerular hyperfiltration. The improvement in hyperfiltration may prevent the development of overt ORG.

Weight loss may be beneficial in delaying the progression of CKD to ESRD, but it is not indicated once renal replacement therapies are started. This is due to the paradoxical effect renal replacement therapies have on survival.¹⁰⁵

The effect of several obesity drugs on renal function was evaluated in clinical trials. Sibutramine, a serotonin–norepinephrine reuptake inhibitor, which acts on the hypothalamic satiety center to reduce hunger, was used along with lifestyle modification for 6 months to reduce weight in obese women with polycystic ovary syndrome. The intervention resulted in weight loss and reduction in serum cys-C levels but not creatinine. It should be noted that sibutramine can raise blood pressure.¹⁰⁶ Orlistat showed no improvement in renal function assessed by serum creatinine after 3 months of use.¹⁰⁷

The role of RAAS inhibition is well established in delaying the progression of renal disease in diabetics (75% have MetS). However, studies of RAAS inhibition and progression of renal disease have not been done specifically in MetS patients. Nonetheless, their antiproteinuric effect is

well established. In a mouse model of obesity, olmesartan, an angiotensin II type 1 receptor blocker, significantly reduced inflammatory cytokines and markers of oxidative stress and increased adiponectin levels.¹⁰⁸

Statins decrease proteinuria in renal disease. A meta-analysis of clinical trials indicates that lipid lowering preserves GFR and decreases proteinuria level in patients with renal disease.¹⁰⁹

The management of lipid disorders was addressed in the 2014 KDIGO guidelines. The guidelines state that monitoring of lipid profiles might improve the health of people with secondary dyslipidemia and CKD. At the same time, it was acknowledged that no direct evidence indicates that following the recommendations will lead to better outcomes. The guidelines recommend that patients ≥ 50 years of age with an eGFR < 60 mL/min/1.73 m² not on dialysis receive a statin or statin/ezetimibe combination. Those with a higher eGFR should receive a statin.¹¹⁰

However, it remains unknown whether statin therapy is also effective in the prevention of the onset of renal dysfunction in patients with normal kidney function.

Discussion

In this review, cross-sectional studies show a close association of the MetS and CKD. The strength of association between MetS and CKD increased as the number of components increased from one to five. However, one cannot draw a conclusion as to which came first – the MetS or the kidney disease.

One of the challenges in this analysis is the multiple definitions for the MetS. In fact, a study of Kitiyakara et al¹¹¹ has even suggested that the risk of CKD associated with the MetS was different depending on the definition of MetS used.

The components of the MetS individually are risk factors for cardiorenal disease; however, it remains unclear how much additive risk the clustering of these components contributes to the risk of individual traits. Clinical studies disagree on which combination of MetS components is more predictive of CKD.¹¹¹ This uncertainty probably accounts for skepticism among some nephrologists on the significance of clustering of the MetS over the individual components in the pathogenesis of kidney disease. The dichotomization of continuous MetS variables may contribute to attenuation of predictive power.¹¹²

Similarly to cross-sectional studies, observational studies suggest a relationship of MetS with incident CKD. They also demonstrate the development of MetS in patients with established CKD, which suggests a bidirectional causal relationship between CKD and MetS. Regardless

Table 6 Clinical summary

1. CKD is associated with MetS and its individual components in cross sectional studies.
2. Incident CKD is associated with MetS and vice versa, which suggests a bidirectional relationship.
3. An improved understanding of the pathogenesis of this relationship is needed to design clinical trials aiming toward therapeutic interventions.

Abbreviations: CKD, chronic kidney disease; MetS, metabolic syndrome.

of which comes first, both the MetS and CKD are strongly associated with cardiovascular and overall morbidity and mortality (Table 6).

The implications of CKD in patients with the MetS were significant enough to lead some investigators to propose including CKD in the definition of MetS.¹¹³ On the other hand, other authors suggest that perhaps the MetS is a marker and not a causative factor in the development of CKD.¹¹⁴

The relationship between MetS and CKD is complex. In order to assess renal outcomes in MetS, more studies on the mechanism of linkage are needed. Treating hypertension and hyperglycemia reduce kidney disease, as does treating lipids with statins. However, large randomized controlled trials of therapeutic regimens designed to prevent the onset and progression of cardiorenal disease in MetS are critical. Moreover, validated CKD risk score in patients with MetS similar to other scores used to stratify cardiovascular disease risk need to be formulated.¹⁰⁸

Understanding the genetic and environmental factors that impact the relationship between CKD and MetS is also important. The clinical effects of MetS vary among ethnic groups. Race and sex affect the calculations used to estimate GFR. Lea et al¹¹⁵ outlined ethnic differences in the association between MetS and renal disease. In African Americans, MetS was not independently associated with CKD progression but was associated with proteinuria, suggesting the later as a confounding variable to explain the renal damage in MetS.

While awaiting further studies, awareness of the association between MetS and CKD is important. This awareness should prompt early implementation of lifestyle changes and aggressive control of blood pressure and lipids, which may improve cardiovascular outcomes.

Disclosure

The authors report no conflicts of interest in this work.

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