REVIEW

Metabolic syndrome and chronic kidney disease: Current status and future directions

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Core tip: Metabolic syndrome is associated with chronic kidney disease but its role in chronic kidney disease incidence and progression has not been established. When both these conditions are present, management should be targeted to individual risk factors for kidney disease progression and cardiovascular disease.

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Abstract

Metabolic syndrome (MetS) is a term used to denote a combination of selected, widely prevalent cardiovascular disease (CVD)-related risk factors. Despite the ambiguous definition of MetS, it has been clearly associated with chronic kidney disease markers including reduced glomerular filtration rate, proteinuria and/or microalbuminuria, and histopathological markers such as tubular atrophy and interstitial fibrosis. However, the etiological role of MetS in chronic kidney disease (CKD) is less clear. The relationship between MetS and CKD is complex and bidirectional, and so is best understood when CKD is viewed as a common progressive illness along the course of which MetS, another common disease, may intervene and contribute. Possible mechanisms of renal injury include insulin resistance and oxidative stress, increased proinflammatory cytokine production, increased connective tissue growth and profibrotic factor production, increased microvascular injury, and renal ischemia. MetS also portends a higher CVD risk at all stages of CKD from early renal insufficiency to end-stage renal disease. Clinical interventions for MetS in the presence of CKD should include a combination of weight reduction, appropriate dietary modification and increase physical activity, plus targeting of individual CVD-related risk factors such as dysglycemia, hypertension, and dyslipidemia while conforming to relevant national societal guidelines.

INTRODUCTION

Metabolic syndrome (MetS), previously called "syndrome X" is a term in popular use for the past quarter century, having first been described in 1988 by Reaven[1] to denote a combination of selected, widely prevalent cardiovascular disease (CVD)-related risk factors. Although the general principle behind using the MetS concept is to denote an increased CVD or diabetes risk, the MetS definition itself is ambiguous through the inclusion of different criteria and assigning them different levels of importance[2-6]. Furthermore, some MetS definitions have been revised over the years, leading to the multiple definitions in current use[2-6]. The four most common definitions are summarized in Table 1. Nonetheless, the general concept is that a MetS patient will have some combination of conditions, among which are insulin resistance or hyperglycemia, dyslipidemia, hypertension, and obesity. Identifying such combinations should add meaningfully to the long-term clinical management of

Table 1 Criteria in definitions of the metabolic syndrome[2-6]

Definition and its criteria	Values
World Health Organization 1998	
Insulin resistance	Type 2 diabetes mellitus or impaired fasting glucose (> 100 mg/dL per 5.6 mmol/L) or impaired glucose tolerance
Plus two of the following:	
Abdominal obesity	Waist-to-hip ratio > 0.9 in men or > 0.85 in women or BMI > 30 kg/m^2
Triglycerides and/or HDL cholesterol	> 150 mg/dL (1.7 mmol/L) and/or < 35 mg/dL (0.9 mmol/L) in men and < 39 mg/dL (1.0 mmol/L) in women respectively
Blood pressure	⩾ 140 mmHg systolic; ⩾ 90 mmHg diastolic
Microalbuminuria	Urine albumin ⩾ 20 μg/min or albumin-to-creatinine ratio ⩾ 30 mg/g
American Heart Association/National Heart, Lung, and Blood Institute (2004)	
Any three of the following:	
Waist circumference	> 102 cm in men and > 88 cm in women
Triglycerides	⩾ 150 mg/dL (1.7 mmol/L)
HDL cholesterol	< 40 mg/dL (1.03 mmol/L) in men and < 50 mg/dL (1.29 mmol/L) in women
Blood pressure	≥ 130 mmHg systolic; ≥ 85 mmHg diastolic
Fasting glucose	⩾ 100 mg/dL (5.6 mmol/L)
International Diabetes Federation 2005	
Central obesity based on ethnicity	Waist circumference for Europeans > 94 cm in men and 80 cm in women; South Asians, Chinese, and Japanese > 90 cm in men and > 80 cm in women; ethnic South and Central Americans use South Asian data; for sub-Saharan Africans and Eastern Mediterranean and Middle East (Arab) populations use European data.
	Can be assumed if BMI > 30 kg/m^2
Plus two of the following:	
Triglycerides	⩾ 150 mg/dL (1.7 mmol/L)
HDL cholesterol	< 40 mg/dL (1.03 mmol/L) in men and < 50 mg/dL (1.29 mmol/L) in women
Blood pressure	⩾ 130 mmHg systolic; ⩾ 85 mmHg diastolic; treatment of previously diagnosed hypertension
Fasting glucose	⩾ 100 mg/dL (5.6 mmol/L), in which case oral glucose tolerance test is recommended
Harmonized (Consensus) Definition incorporating IDF and AHA/NHLBI definitions (2009)	
Any three of the following:	
Waist circumference	According to population and country-specific definitions
Triglycerides	⩾ 150 mg/dL (1.7 mmol/L)
HDL cholesterol	< 40 mg/dL (1.03 mmol/L) in men and < 50 mg/dL (1.29 mmol/L) in women
Blood pressure	⩾ 130 mmHg systolic; ⩾ 85 mmHg diastolic
Fasting glucose	⩾ 100 mg/dL (5.6 mmol/L) or use of medication

IDF: International Diabetes Federation; AHA/NHLBI: American Heart Association/National Heart, Lung, and Blood Institute.

MetS.

MetS is known to be with increased CVD risk in the general population[7,8]. It has also been associated with incident overt type 2 diabetes[9,10], in those previously without diabetes contributing to their MetS definition. Other MetS associations include non-alcoholic fatty liver disease[11], and hyperuricemia[12]. In addition, the association of MetS with chronic kidney disease (CKD) is receiving increased attention in selected populations[13-15]. CKD however is also a long-term illness, just like MetS, and often progresses over many years from mild reductions in glomerular filtration rate to more advanced pre-uremic states and eventual renal replacement therapy. CKD is asymptomatic until very late in its course, when symptoms such as fatigue, nausea and anorexia, itching, cramping and muscle twitching, and edema occur. The relationship between MetS and CKD is typically approached as snapshots in isolation during each CKD stage. The major purpose of this review is to approach the MetS-CKD relationship from the standpoint of each stage as points along the CKD spectrum where the diagnosis of MetS may be raised. This may help to better determine whether MetS is either in fact part of the etiology of CKD, the end result of risk factors common to both MetS and CKD, or a completely unrelated entity.

METABOLIC SYNDROME AS AN ASSOCIATION WITH CKD

Many studies associate MetS with CKD. This is perhaps the lowest level of evidence for causation. Each component of MetS has been associated with both CKD incidence and progression. MetS and CKD share a complex, bidirectional relationship. Obesity is associated with CKD[16-18]. Both obesity and CKD are increasing in prevalence, at least in the United States[19]. The earliest stages of CKD are typically missed because of its asymptomatic nature and lack of screening in annual physical examinations. It is therefore difficult to assemble sufficiently large cohorts known to be without CKD based on the appropriate baseline data and then follow them over a sufficient length of time in order to determine whether they have developed early (i.e., stages I or II) CKD or not. This will require measurements of renal function in the normal range that tools such as the Modification

Table 2 Renal associations of metabolic syndrome	
Renal outcome	**Ref.**
eGFR < 60/mL/min per 1.73 m^2	[15,19]
Proteinuria and/or microalbuminuria	[13,22,23,29,30]
Histopathological abnormalities (tubular atrophy, interstitial fibrosis, arterial sclerosis)	[31]
Ultrasound abnormalities (increased intra-renal resistive indices)	[32]

of Diet in Renal Disease (MDRD) equations[20] were not designed to handle.

A meta-analysis of eleven studies[13,14,21-29] of 30146 subjects reported that MetS was associated with development of an estimated GFR (eGFR) < 60 mL/min per 1.73 m^2, (Stage III CKD) with odds ratio (OR) 1.55 (95%CI: 1.34-1.80)[19]. Many of these studies specifically excluded those with diabetes[21,22,26-28], which is not only a potential component of MetS, but a major cause of CKD. Not included also was a study[15] from the National Health and Nutrition Examination Survey (NHANES III) database of 7800 subjects followed for 21 years, who having had normal renal function at baseline, were found to have an OR of 2.6 (95%CI: 1.68-4.03) for CKD if MetS was present. These authors[15] also determined a relationship between the number of MetS components present and risk. Sometimes, surrogate markers of CKD such as microalbuminuria or proteinuria are used instead[13,22-23,29] using varying definitions for both protein loss and MetS[19]. A small number of studies showed an increase in albumin or protein excretion associated with MetS[19]. Another study from the NHANES database also showed an increase in microalbuminuria with MetS[30].

Despite the large number of such associative studies between MetS and CKD, causality remains unproven[19]. The time-to-onset of both MetS and CKD are equally difficult to determine. Since individual components of MetS are prone to fluctuating values and are sensitive to unmeasured lifestyle modifications, medication effects, or acute illness, it is possible that some proportion of subjects experience change with respect to their MetS status overall during follow-up. Similar changes may occur with eGFR and a CKD diagnosis that is based on arbitrary eGFR cut-offs. Over-simplification of MetS criteria (such as using only body mass index (BMI) while ignoring waist and hip circumference, or systematically ignoring ethnicity), further limits making firm conclusions about associations. Obesity and CKD are increasing in prevalence[19] and this could obfuscate the relationship between two common disease entities. Investigation at the level of the individual subject may help shed light on the association of MetS with CKD.

A histopathology-based cross-sectional report of 146 patients undergoing nephrectomy showed a higher prevalence of CKD features, including global as well as segmental glomerulosclerosis in those with MetS. Other features noted included a higher prevalence of tubular atrophy, interstitial fibrosis, and arterial sclerosis[31]. Loss of renal function post-nephrectomy was more pronounced[31], but sequential biopsy studies are of course not feasible. Another approach is to study intra-renal hemodynamics by ultrasound, wherein renal parenchymal damage in MetS may be reflected by increased intra-renal resistive indices[32]. These novel studies may help us progress beyond making simple associations, but will need prospective evaluation in larger numbers of patients for validation. A summary of important renal associations with MetS is provided in Table 2.

METABOLIC SYNDROME AS AN ETIOLOGY OF CKD

More convincing than association alone would be a mechanistic explanation for MetS as a cause for CKD. The search for mechanisms is essential to remove the "black boxes" that exist along any proposed causal pathway between MetS and CKD. It may be all one linear mechanism that leads from MetS to CKD, or it may equally likely be a number of distinct but inter-dependent mechanisms set in motion by MetS and operating simultaneously to result in significant renal impairment. The mechanisms leading to MetS may also be the same ones causing CKD. In this context, there may be a "perfect storm" of multiple risk factors including insulin resistance, inflammation, abnormal lipid metabolism, and hypertension leading to increased expression of pro-fibrotic factors[33]. Finally, we still cannot exclude chance associations between two otherwise common diseases.

Insulin resistance may be the most important MetS-related etiological factor for CKD. Insulin is an anti-inflammatory hormone. Insulin resistance, which is typical of type 2 diabetes, leads to inflammation, leading to oxidative stress and renal insufficiency[34]. Raised insulin levels stimulate insulin-like growth factor 1 (IGF-1) production, which increases connective tissue growth factor, thus causing fibrosis in the diabetic state[35]. Furthermore, and possibly independently, obesity may lead to increased secretion by adipose tissue of pro-inflammatory cytokines such as leptin, interleukin-6, and tumor necrosis factor-alpha (TNF-α)[36]. Leptin may lead to increased intra-renal expression of transforming growth factor-beta (TGF-β), leading to glomerulosclerosis[37]. It may also promote type IV collagen production[38,39]. TNF-α may lead to the production of reactive oxygen species (ROS) that can in turn lead to renal endothelial cell dysfunction, mesangial expansion and fibrosis[40]. Anti-inflammatory hormones like adiponectin may be reduced[36,41], contributing to insulin resistance as well. Adiponectin deficiency is associated with vascular intima thickening and smooth muscle cell proliferation[42]. Its vascular effects may even be independent of insulin sensitivity[43], and so may extend to CKD. Obesity also leads to increased glomerular volume, podocyte hypertrophy, and mesangial matrix expansion preceding CKD[44]. Triglycerides and free fatty acids may themselves be nephrotoxic by

Table 3 Potential mechanisms of chronic kidney disease in metabolic syndrome

Mechanism	Ref.
Oxidative stress	[34,40]
Increased pro-inflammatory cytokines (leptin, interleukin 6, tumor necrosis factor α)	[36]
Increased connective tissue growth and/or fibrosis factors (connective tissue growth factor, transforming growth factor β, type IV collagen)	[35,37-39]
Increased glomerular volume and podocyte hypertrophy	[44]
Triglyceride- and free-fatty acid induced injury	45
Increased ischemia and microvascular injury (angiotensin II)	[46,47]
Hyperuricemia	[48,49]

promoting pro-inflammatory cytokine production[45]. In association with hypertension, another MetS component, angiotensin II stimulates ROS production, in turn decreasing nitric oxide synthase production and causing renal microvascular injury, ischemia, and tubulointerstitial damage[46,47]. Dissecting out the relative contribution of insulin resistance, obesity, and hypertension to these findings versus the composite of MetS however is difficult. In this regard, the presence of early arterial hyalinosis[31] which is more typical of diabetes but not MetS, may point towards MetS being a distinct risk factor for CKD independent of its individual components. One more somewhat provocative hypothesis is that hyperuricemia, not a "traditional" MetS component but associated with MetS[12], is a promoter of CKD through the inhibition of nitric oxide production[48] or even recurrent nephrolithiasis[49]. Another limitation to be pointed is that most mechanistic explanations have been derived from animal models, and so their importance in human patients with MetS and CKD, with their different lifespans and disease profiles remains to be demonstrated. A summary list of possible mechanisms for CKD in MetS is shown in Table 3. Studies mostly support the direction of the relationship to be from MetS to CKD and not vice versa, but this is unconfirmed.

METABOLIC SYNDROME AND PROGRESSIVE CKD

Once CKD is identified, with the understanding that the definition is somewhat arbitrary, monitoring progression becomes more straightforward. Several population-based studies have identified MetS with CKD progression. Once stage III or IV CKD has been reached, the presence of MetS has been associated with a hazard ratio of 1.33 (95%CI: 1.08-1.64) for end-stage renal disease (ESRD) over a follow-up period of just 2-3 years in a cohort of over 15000 patients[50]. In particular, impaired glucose metabolism, hypertriglyceridemia, and hypertension were associated with an increased risk of ESRD. Similarly, an incremental increase in insulin resistance was associated with a greater rate of decline in renal function in a cohort of elderly patients with CKD[51]. On the other hand, it

was demonstrated that the relationship of MetS to CKD may not be constant over the progression through CKD stages. In the later stages of CKD, MetS as a risk factor for progression may become less important[52], perhaps because CKD itself leads to rapid progression in a form of vicious circularity. Also, greater attention may be paid to MetS in the later stages of CKD, so that its impact becomes less prominent. Another study showed that even though MetS was associated with albuminuria, the effect of MetS on CKD progression was independent of this[53]. This is controversial however, since proteinuria is a known risk factor for CKD progression to ESRD and is also a component of some MetS definitions. Despite the greater than 30% risk with MetS, adjustment for proteinuria attenuated the risk for development of a composite endpoint of significant decrease in GFR, ESRD, or death in the African American Study of Kidney Disease and Hypertension trial[54].

The distinction between CKD incidence and progression may be arbitrary since renal insufficiency must first progress to the point where CKD is diagnosed at some threshold level of renal function. If the underlying progression is left unchecked however and the new pathophysiology of CKD becomes established, then the risk factors common to CKD and MetS combine to accelerate CKD progression. First, obesity-related glomerular hyperfiltration could combine with that induced by CKD itself, leading to accelerated glomerulosclerosis. Second, inflammation and oxidative stress are worsened in CKD[55]. Hypertension and hypertriglyceridemia are worsened[55], and insulin resistance may be promoted by the undernourished state that can be caused by CKD as well as lead to CKD[56,57]. This relationship is thus bidirectional. Third, this insulin resistance may combine with inflammation to cause "endoplasmic reticulum stress". According to this theory, misfolded proteins accumulate in the lumen of the endoplasmic reticulum, suppressing insulin secretion through phosphorylation of the insulin receptor substrate (IRS-1)[58]. Finally, insulin resistance also worsens renal hemodynamics through increasing sodium retention, and affecting the transport of other cations and anions[59]. Hypertension is worsened, leading to further renal damage. Similarly, the sympathetic nervous system is activated[60], leading to unfavorable renal hemodynamics, proteinuria, and ischemia. Proteinuria itself may lead to podocyte injury, and eventually lead to chronic tubulointerstitial injury, thereby worsening CKD[61]. Unless cardiovascular mortality intervenes, progression to ESRD may occur.

Role of cardiovascular disease in progression of metabolic syndrome-related CKD

Even mild CKD has been associated with increased CVD risk[62]. CVD mortality also increases with increasing serum creatinine concentrations[62]. Advanced CKD is also a high risk situation for cardiovascular events and mortality. In one study of stage IV or V CKD patients, MetS was predictive of a composite of CVD mortality, acute coronary syndrome (ACS), revascularization, non-

fatal stroke, and amputation (hazard ratio 2.46, 95%CI: 1.17-5.18)[63]. In this study of 200 patients, intensive risk factor modification was not effective[63]. Coronary heart disease is promoted by the components of MetS. Patients with both MetS and CKD exhibit greater coronary artery plaque burden with higher lipid content, as demonstrated by intravascular ultrasound[64]. With renal insufficiency, myocardial infarction (MI) in the context of MetS is associated with higher mortality at one year[65]. In over 900 patients undergoing carotid revascularization where 14% had some degree of CKD, MetS increased the risk for stroke, MI, and death[66].

The patient with MetS and progressive CKD treads a dangerous path towards ESRD. Besides being simply associated with CKD, MetS may also lead to CKD through a variety of pathophysiological mechanisms. MetS may also lead to more rapid CKD once it is established. Both MetS and CKD in turn are associated with increased risk for CVD events, and when both occur together the effect may be additive. It stands to reason that ACS and MI are major contributors to all-cause mortality seen when these two common conditions are combined, regardless of whether MetS leads to CKD or both are independently acquired. Furthermore, it is likely that ACS and MI themselves lead to acute kidney injury and acceleration of CKD. This could happen as a result of acute shifts in effective intravascular volume or contrast exposure, for example. Increased mortality effectively prevents progression of CKD to ESRD, so it is reasonable to speculate that fewer patients with MetS will actually reach ESRD.

METABOLIC SYNDROME AND RENAL REPLACEMENT THERAPY

Many patients receiving hemodialysis (HD) also have MetS. The mortality rate is very high in the initial few months after HD initiation both in the United States[67] and worldwide[68]. A significant proportion of this mortality is attributable to CVD, related to existing cardiovascular comorbidities[69]. Therefore, patients with MetS starting chronic HD are at increased risk for major cardiovascular events and mortality. The prevalence of MetS is quite high (often exceeding 50%) in HD cohorts worldwide[70-72]. Interestingly, the presence of MetS has even been extended to their relatives[73]. Longer-term follow-up also indicates a higher incidence of cardiovascular events[74] and high rate of hospitalization[75]. Other co-morbid conditions may co-exist with MetS in HD patients. A higher prevalence of moderate-to-severe periodontal disease has been reported[76]. However, significant correlations were not noted in dialysis patients with reduced bone mineral density[77], quality of life[78], or mood[78].

Several pathophysiological mechanisms may be operational during hemodialysis that could further exacerbate the effects of MetS. Besides insulin resistance, hyperlipidemia, and hypertension carried over from the pre-dialysis

phase of CKD, further inflammation and oxidative stress may result from dialysis treatment itself. There is a loss of antioxidants and increase in leukocyte activation during dialysis[79-82]. This may occur through loss of vital antioxidants through the hemodialysate, or reactions to semi-synthetic dialysis membranes, or both. Dialysis patients are also prone to infections further promoting inflammatory stress. Logistical difficulties in hemodialysis in obese patients, such as vascular access difficulties leading to suboptimal renal functional replacement may promote inflammation. Chronic volume expansion promotes worsening hypertension, further adding to morbidity. Insulin resistance, even in those without diabetes, may also lead to chronic malnutrition as part of an overall catabolic condition[83].

MetS has an impact on patients on peritoneal dialysis (PD) as well. When glucose-containing solutions are used there is systemic glucose absorption via the peritoneal membrane, leading to increased intra-abdominal fat[84] consistent with MetS. The increased glucose load increases serum LDL cholesterol and triglyceride concentrations, which when combined with hypertension and volume overload, may increase CVD[85]. MetS increases patient mortality on PD[86,87] and also decreases PD technique survival in patients on PD for at least three months[87]. Technique failure and subsequent conversion to HD is also a stressful state that can cause inflammation. MetS has been associated with an elevated white blood cell count and C-reactive protein level, independently of infection but consistent with inflammation[88]. MetS is also associated with lower circulating adiponectin levels in PD[89], and this may increase CVD risk.

TREATING THE METABOLIC SYNDROME IN THE PRESENCE OF CKD

There is an obvious clinical need to reduce CKD morbidity and mortality, and MetS seems to be an easily identified target for intervention. However, the approach is far from precise. Randomized clinical trials in CKD patients are few and are limited by small sample sizes. Renal outcomes are often not described as the primary outcomes. Studies of CKD prevention or progression require large numbers of patients followed over long periods of time to gather sufficient CVD or ESRD outcomes, and if MetS is added as an inclusion criterion, recruitment difficulties are exacerbated. There is a shortage of high quality randomized, controlled trials in nephrology generally[90]. Nonetheless, targeting MetS as a risk factor for CVD, for which CKD patients are at risk is certainly reasonable.

An initial approach should include some combination among weight reduction, dietary modification, and increased physical activity[91], preferably all three. A small clinical trial of 38 patients with MetS but without CKD, randomized to dietary weight loss, weight loss plus aerobic exercise, or no treatment was able to dem-

Table 4 Possible clinical interventions for metabolic syndrome in chronic kidney disease[a,b]

Clinical intervention	Ref.
Lifestyle modification: weight reduction, dietary adjustment (calorie and phosphate reduction), increased physical activity, and/or smoking cessation	[91-94]
Weight loss medication (orlistat) or surgery	[95,97]
Lipid-lowering medication (statins, fibrates)	[96,104,105]
Blood pressure-lowering medication (renin-angiotensin system antagonists)	[100]
Blood glucose-lowering medication (metformin, thiazolidinediones)	[102,103]

[a]It is recommended that individual national society guidelines be followed in the management of individual metabolic syndrome components; [b]Interventions are individualized and used in combination.

onstrate a relationship between weight loss, albuminuria reduction, and improvement in eGFR, augmented by exercise[92]. An observational analysis of PREMIER, a randomized trial of blood pressure lowering in obese subjects but again without CKD, showed a relationship between reduction in waist circumference and urinary albumin excretion[93]. A decrease in phosphate intake may be beneficial as well[93]. It is unclear if these results indicate an improvement in incipient renal disease, or an improvement in systemic endothelial dysfunction manifest as microalbuminuria. Achieving weight loss without a corresponding loss in muscle mass may be difficult to achieve in CKD, especially ESRD. In a sample of 2288 participants with CKD from the NHANES III survey, regular physical activity but not diet was associated with decreased mortality[94]. Although unproven, it is likely that patients with both CKD and MetS will especially benefit. A multi-disciplinary approach that involves an exercise specialist to ensure regular physical activity and a dietician to achieve the goal of weight loss through reduced calorie intake, while avoiding malnutrition at the same time is preferable. Hospitalizations are likely to lead to setbacks. Smoking cessation has been associated with reduced mortality in CKD[94]. Measurement of waist circumference or the waist-to-hip ratio may allow for better compliance with existing MetS definitions[2-6] both for diagnosis and follow-up.

Both pharmacotherapy and surgical procedures for weight loss in patients with MetS have been explored. It is unclear if drugs prescribed for weight loss have significant adverse effects on renal function. Orlistat may be beneficial for MetS in the general population[95]. Fibrates on the other hand may worsen renal function[96], and could be harmful in patients with MetS and CKD. Pharmacotherapy needs to be combined with lifestyle modification in order to have significant effect, and would not be recommended in the absence of clinical trial data pertinent to CKD. Bariatric surgery has been shown to improve MetS parameters and also decrease mortality in the general population[97], and also reduce albuminuria[98]. However, the ability of CKD patients to recover from major surgery needs to be considered. Clinical trials in CKD patients are needed before this can be recommended.

Blood pressure control reduces CVD risk and CKD progression, and so relevant national guidelines for blood pressure targets and therapeutic agents should be followed depending on the presence or absence of CKD and/or diabetes, in the absence of specific guidelines for MetS patients. Thiazides may worsen MetS, perhaps through hyperuricemia, hypokalemia, and diabetes[99]. Renin-angiotensin system antagonists may prevent new-onset diabetes[100]. This may be considered for those with MetS who have not yet developed diabetes. MetS is associated with increased sympathetic activity, and so renal denervation has been considered when hypertension is part of MetS[101]. However, the value of this procedure for achieving sustained blood pressure reduction is controversial.

Management of dysglycemia requires special attention in the context of MetS. Metformin is associated with improved insulin resistance and endothelial function[102]. However, metformin is not used in more advanced CKD due to concerns surrounding lactic acidosis. Thiazolidinediones may also be considered[103], but their side effect profile deserves special attention. They may improve endothelial function as well as have anti-inflammatory effects[103]. Weight loss may also help improve glycemic control, but dietary conflicts among diabetes-related restrictions (such as carbohydrates) and CKD-related restrictions (potassium and phosphorus) may be especially problematic in MetS where total caloric intake must also be reduced and protein intake maintained. Specialized dietician input is again required.

Finally, the use of statins in MetS requires consideration. Statins may reduce proteinuria[104], either through improved endothelial function or reduction in systemic inflammation[104,105]. Success with statins in reducing cardiovascular events in ESRD[106] has been variable.

A summary of possible therapeutic interventions for MetS in the context of CKD is provided in Table 4. In the absence of firm data, relevant national guidelines should be followed for each individual cardiovascular or CKD-related risk factor.

CONCLUSION

At this point, it remains unclear whether MetS adds further cardiovascular risk to that conferred by CKD alone. Further research is first required to firmly establish the link between MetS and incidence of CKD in the first instance, and then between MetS and the progression of CKD. A single large, prospective clinical trial in human subjects that addresses both CKD incidence and progression in established CKD will help to provide the necessary justification for MetS intervention. However, the major clinical concern surrounding MetS is its association with CVD. A prospective clinical trial of intervention targeted to multiple MetS parameters in CKD would help address whether MetS is more than the sum of its parts in the context of CKD. Until then, we are

left with using surrogate markers such as proteinuria or microalbuminuria for both CKD and CVD. Statins, fibrates, and renin-angiotensin system antagonists allow for targeting specific MetS components including diabetes, hyperlipidemia, hypertension, and microalbuminuria. In combination with aggressive lifestyle modification, there is potential in the meantime for reducing MetS, CKD, and CVD mortality. Beneficial snapshot effects may be found in the literature for a particular intervention in one CKD sub-population and not another, such as in the case of statins. However, viewing CKD as a longitudinal construct allows for better understanding of the pathophysiology of CVD and CKD progression with MetS, and may thus allow for more rational therapeutic choices.

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