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Review

Chronic kidney disease combined with metabolic syndrome is a non-negligible risk factor

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***Abstract*:** Metabolic syndrome (MetS) is a group of conditions characterized by hypertension (HTN), hyperglycaemia or insulin resistance (IR), hyperlipidaemia, and abdominal obesity. MetS is associated with a high incidence of cardiovascular events and mortality and is an independent risk factor for chronic kidney disease (CKD). MetS can cause CKD or accelerate the progression of kidney disease. Recent studies have found that MetS and kidney disease have a cause-and-effect relationship. Patients with CKD, those undergoing kidney transplantation, or kidney donors have a significantly higher risk of developing MetS than normal people. The present study reviewed the possible mechanisms of MetS in patients with CKD, including the disorders of glucose and fat metabolism after kidney injury, IR, HTN and the administration of glucocorticoid and calcineurin inhibitors. In addition, this study reviewed the effect of MetS in patients with CKD on important target organs such as the kidney, heart, brain and blood vessels, and the treatment and prevention of CKD combined with MetS. The study aims to provide strategies for the diagnosis, treatment and prevention of CKD in patients with MetS.

Keywords: chronic kidney disease, glucose metabolic disorders, metabolic syndrome, pathological characteristics, therapeutics

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Introduction

Metabolic syndrome (MetS) is a group of conditions characterized by metabolic abnormalities. The World Health Organization proposed the diagnostic criteria for MetS in 1998[1]; however, the diagnostic criteria and evaluation components for MetS proposed by various countries and related organizations are not uniform.[2] Nonetheless, the criteria mainly include serum glucose levels, body mass index (BMI), waist circumference (WC), waist–hip ratio, hypertension (HTN), central adiposity, high-density lipoprotein (HDL), cholesterol and triglyceride (TG) levels and impaired glucose tolerance.[3–7] These risk factors independently or cooperatively participate in or aggravate the damage to important target organs such as the heart, brain, blood vessels and kidney.[8–12] MetS can lead to changes in the structure and function of the kidneys in patients with no underlying kidney disease and can result in proteinuria and a decrease in the glomerular filtration rate (GFR). These findings have been confirmed in a large number of clinical studies in different countries.[13–16] Recent studies have found that the prevalence of MetS in patients with kidney disease is significantly higher than that in patients without kidney disease. To date, the mechanism of MetS in patients with chronic kidney disease (CKD) is not completely clear. The present study summarizes the mechanisms of MetS in patients with CKD, the effect of MetS on the kidney, heart, brain, blood vessels and other important target organs and the treatment and prevention of MetS.

Epidemiological characteristics of MetS in patients with CKD

The prevalence of MetS is not the same in patients of different races, sex and ages. It is estimated that the global prevalence of MetS is 20–25%,[16] and the prevalence of CKD in patients with MetS

Table 1. The prevalence of Mets in CKD patients.

Author	Years	Country/region	Object	Prevalence (%)	Subgroup	Reference
Pammer	2021	German	CKD	64.30	–	19
Chen	2017	China	CKD	58.40	–	17
Hana'a	2018	Israel	CKD	82.10	–	20
Li	2022	China	Non-dialysis CKD	62.60	–	21
Chang	2021	Taiwan, China	CKD3–5	64.70	CKD3 (63.5%), CKD4 (66.7%), CKD5 (64.8%)	22
Tsai	2018	Taiwan, China	CKD3–5	42.00	CKD3a (39.0%), CKD3b (49.0%), CKD4 (57.0%), CKD5 (46%)	23
Boronat	2016	Spain	Non-diabetes CKD	68.90	Chronic interstitial nephropathy (80%), CKD of uncertain aetiology (76.7%) and CKD related to vascular causes (76.2%)	24
Hung	2022	Taiwan, China	Non-diabetic CKD1–4	50.55	–	25
Kittiskulnam	2018	Thailand	Diabetic CKD	71.30	CKD3a (70.1%), CKD3b (72.3%), CKD4 (73.4%), CKD5 (72.7%)	26
Alswat	2017	Saudi Arabia	HD	38.60	–	27
AlShelleh	2019	Jordan	Transplant patients and dialysis	34.0, 55.7	–	28
Maduram	2010	USA	Paediatric renal transplant recipients	68.00	–	29

CKD, chronic kidney disease; HD, haemodialysis.

is twice that in patients without MetS.[17] A meta-analysis of 66 studies involving more than 30 countries revealed that MetS increases the risk of CKD by 50%.[18] Recent studies have found that patients with CKD have a higher risk of MetS. Studies from different countries on patients with different CKD stages, dialysis treatment and renal transplantation revealed that the prevalence of MetS in non-dialysis patients with CKD was 42.0–82.1%,[17,19–25] and in CKD stages 3–5 was 39.0–72.3%, 57.0–73.4% and 46.0–72.7%, respectively.[22,23,26] The prevalence of MetS in non-dialysis patients with CKD was different due to various causes, such as chronic interstitial neuropathy (80%), CKD of uncertain aetiology (76.7%), CKD related to vascular causes (76.2%) and diabetic nephropathy (71.3%).[24,26] The prevalence of MetS in patients undergoing dialysis was relatively low (38.6–55.7%),[27,28] which may be related to malnutrition in these patients. Higher age, female sex, being married, higher BMI, larger WC, Type 2 diabetes (T2D) and HTN, shorter haemodialysis (HD) duration, longer interval after placement of arteriovenous fistula, high post-HD creatinine levels, inadequate HD and hyperparathyroidism are risk factors of MetS.[27] The probability of MetS in patients undergoing renal transplantation was found to be 34–68%, and the difference was closely related to the types of immunosuppressant drugs received after transplantation.[28,29] Table 1 shows the prevalence of Mets in CKD patients.

The mechanism of MetS in patients with CKD

The kidney is an important organ that maintains the balance of glucose and lipids and has been proven to participate in the pathogenesis of MetS

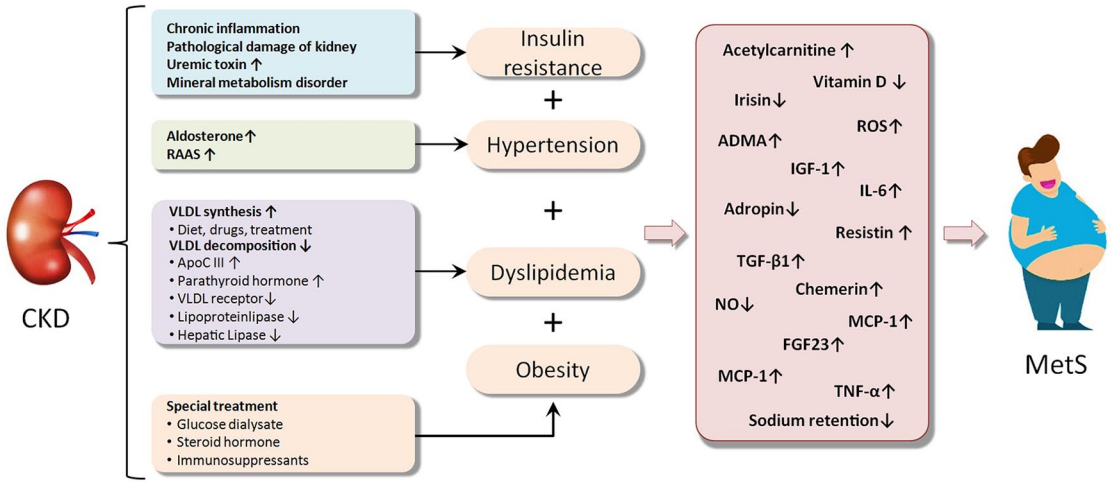

Figure 1. The pathogenesis of MetS in CKD patients.
CKD, chronic kidney disease; MetS, metabolic syndrome.

through a variety of mechanisms. Studies have reported that it can cause haemodynamic changes, sympathetic nerve excitation, increased reactive oxygen species (ROS) production, activation of the Renin Angiotensin Aldosterone System (RAAS) system and adipokine abnormalities through insulin resistance (IR), obesity, HTN and hyperlipidaemia.[30–33] IR appears to be the central mechanism of MetS. The risk of MetS in patients with CKD is approximately twice as high as that in non-CKD patients. The increased risk of MetS in patients with CKD can be attributed to a variety of pathophysiological mechanisms. CKD itself can lead to multiple metabolic abnormalities that are characteristic of MetS, including IR, HTN and dyslipidaemia.[34–37] In addition, CKD patients often have decreased physical activity and poor dietary habits, which can further contribute to the development of MetS. Inflammation and oxidative stress, which are common in CKD, can also play a role in the development of MetS by promoting IR and endothelial dysfunction. The pathogenesis of MetS in CKD patients is shown in Figure 1.

Insulin resistance

IR plays a predominant role in MetS.[38] Studies have reported an obvious IR, which is linearly related to the estimated GFR (eGFR) in patients with non-diabetic nephropathy, even in the early stage of CKD with normal eGFR. Similarly, patients on continuous ambulatory peritoneal dialysis (CAPD) and those who have undergone kidney transplantation have IR.[39–41] Chronic inflammatory state, mitochondrial damage, accumulation of uremic toxins, renal tubulointerstitial and renal arteriolar lesions, bone mineral metabolism disorder in CKD patients, etc. through oxidative stress, ROS, interleukin-6, monocyte chemotactic protein 1, tumour necrosis factor α and transforming growth factor-β1 IR in CKD patients are caused by the increase of ROS activity, the activation of RAAS system, the increase of proinflammatory factors release and the lack of vitamin D, which cause IR.[42–48] Recent studies have found that the renal–brain peripheral sympathetic reflex may also mediate IR in patients with CKD. Local inflammation and high salt intake after activation of RAAS/ROS may reduce glucose transporter 4 (GLUT4) output, thus triggering IR in patients with CKD.[49]

Lipoprotein abnormalities

Studies have reported that abnormal blood lipids in patients with CKD manifest as high TG and low HDL levels, which were not significantly higher than total cholesterol and low-density lipoprotein (LDL) levels.[50–52] CKD patients generally have IR, hepatic lipoprotein and dialysis with glucose lead to increased synthesis of free fatty acids and very low density lipoprotein (VLDL), resulting in high TG levels.[53] In addition, the decreases in the liver lipoprotein lipase and hepatic lipase levels and VLDL receptor expression, as well as

the increase in Apolipoprotein CIII (ApoC Ill) and parathyroid hormone levels, decrease the decomposition of VLDL. This leads to the accumulation of a large amount of VLDL in the body, which is an important reason for the increase in TG levels in patients with CKD.[54–57] In recent years, studies have found that the level of irisin is significantly lower in patients with CKD than that in normal people, and the decline is more obvious with the progression of CKD.[58] However, the level of irisin has been shown to increase in patients undergoing renal replacement therapy.[59] Studies have also reported decreased serum irisin levels in patients undergoing HD, and it is related to the increased mortality rate in cardiovascular and cerebrovascular diseases.[60] In conclusion, irisin plays an important role in maintaining the levels of HDL and cholesterol as well as lipid metabolism in patients with CKD.[61]

Hypertension

HTN is very common in patients with CKD. Many mechanisms lead to the persistence of HTN in patients with CKD and play an important role in various cardiovascular events. Similarly, HTN promotes the occurrence of MetS in patients with CKD through various mechanisms. The main mechanisms are as follows: (1) In HTN, the increase in aldosterone level leads to the activation of the RAAS that induces IR.[32,37,62] (2) Renal tubulointerstitial injury leads to renal ischaemia, hypoxia, the release of proinflammatory factors and inflammatory reaction, with an increase in Angiotensin II (AngII) production.[63–66] (3) The lower levels of leptin, adiponectin, Klotho and adropin[67–70] in patients with CKD may be involved in the development of MetS. Leptin is closely associated with HTN, which is induced by upregulating the renin–angiotensin system and inflammation.[71] The clearance of leptin is reduced in patients with CKD due to renal dysfunction, and lipid metabolism is disturbed due to hyperinsulinaemia and chronic inflammation, among other factors.[72–74] Adropin is a new polypeptide involved in energy metabolism and stability. Adropin regulates energy metabolism and protects the cardiovascular system by producing nitric oxide and regulating blood pressure.[75] Studies have reported significantly reduced serum adropin levels in patients with primary HTN, those on maintenance HD and kidney transplant recipients.[70,76,77]

Specific treatment for CKD

The specific treatment mode of CKD may lead to an increased risk of MetS. For example, continuous absorption of glucose in the dialysate through the peritoneum leads to abnormal glucose and lipid metabolism.[78] The rate of increase in fasting blood glucose levels reached 23.4% in patients on CAPD.[79] However, some studies have shown that new diabetes in patients with peritoneal dialysis is not closely related to the glucose load or peritoneal transport but to IR and obesity.[80] Immunosuppressive agents are an important cause of CKD, especially MetS, in renal transplant patients. Glucocorticoids mediate the rise in blood glucose levels through the following mechanisms: (1) increasing glucose resistance, (2) reducing insulin secretion and (3) inducing apoptosis of beta cells in the islets of Langerhans.[81] A meta-analysis showed that the incidence of new abnormalities in glucose metabolism in renal transplant patients treated with steroids was significantly higher than in those who did not undergo transplantation.[82] In addition, an increase in the activity of 11-β-hydroxysteroid dehydrogenase and the production of active glucocorticoids are closely related to MetS.[83] The calcineurin inhibitors (CNI) (cyclosporin and tacrolimus) can mediate abnormal glucose and lipid metabolism through the following mechanisms: (1) Direct toxic effect on cells to reduce insulin secretion.[84] (2) By affecting glucokinase function, cyclosporine causes decreased insulin secretion and apoptosis of islet β cells.[85] (3) CNI inhibits glucose uptake in peripheral tissues through the endocytosis of GLUT4, leading to increased blood glucose.[86] (4) CNI can cause hypomagnesaemia, increase cell calcium levels and reduce insulin secretion.[87] The effect of CNI on the metabolism of patients is dose-dependent.[84] The mammalian target of rapamycin inhibitor sirolimus can cause apoptosis of pancreatic β-cells and proliferation of the pancreatic duct cells,[88,89] leading to impaired insulin secretion and insulin signal transduction. In addition, long-term use of sirolimus leads to an increase in hepatic gluconeogenesis and IR.[90] In summary, various immunosuppressants lead to weight gain in patients with CKD by increasing appetite and fat distribution. Moreover, immunosuppressants increase blood pressure *via* retention of water and sodium, stimulation of the RAAS system, increasing sympathetic activity and direct contraction of blood vessels, among other mechanisms. These

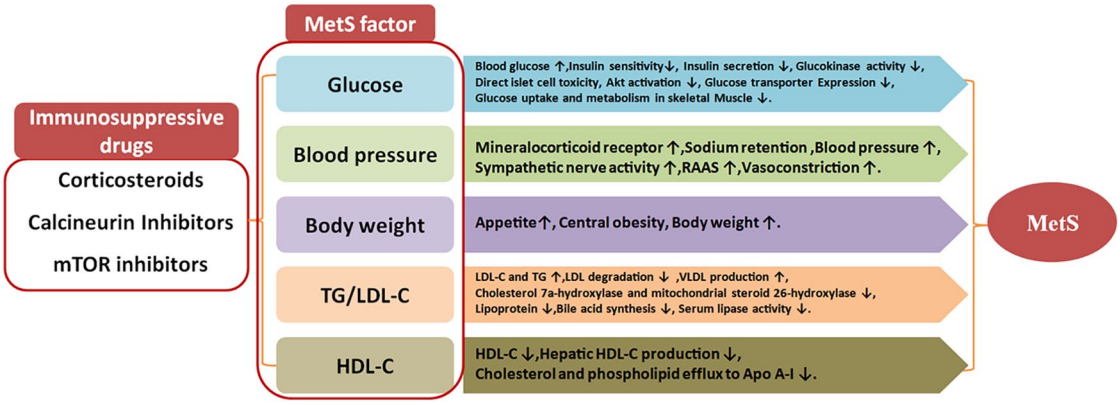

Figure 2. The mechanism of immunosuppressive drugs inducing MetS.
MetS, metabolic syndrome.

drugs lead to abnormal glucose metabolism by directly acting on the β cells in the islets of Langerhans, reducing insulin secretion and sensitivity, inhibiting the expression of the GLUT, reducing the muscle uptake and utilization of glucose and inhibiting glucokinase activity. Furthermore, immunosuppressants reduce the abnormalities in lipid metabolism caused by HDL[91,92] by increasing the activity of lipase, stimulating the liver to synthesize TG and VLDL, reducing the degradation of LDL, reducing the production of HDL-C and reducing the combination of cholesterol efflux and Apolipoprotein A, ultimately leading to MetS. The mechanism of immunosuppressive drugs inducing MetS is shown in Figure 2.

Effect of MetS on target organs in patients with CKD

CKD and MetS are associated with a high incidence of cardiovascular events and mortality.[93–95] When two types of diseases exist simultaneously in patients, large-sample studies must be conducted to verify whether they will aggravate target organ damage. The animal study discovered that obesity lasting for just 2 months can induce albuminuria, potentially because of elevated inflammation or oxidative stress.[96] MetS can lead to proteinuria and a decline in renal function.[97] A Korean study on patients with CKD and MetS found that obesity and metabolic abnormalities (1.41 and 1.38 times, respectively) were significantly related to adverse renal outcomes [eGFR reduction >50% or progression to end-stage renal disease (ESRD)] after 3.1 years of follow-up. Patients with obesity and metabolic abnormalities had a 1.53 times increased risk of CKD progression.[98] A study conducted in China reported a significantly increased risk of CKD progression in patients with MetS (Odds Ratio (OR) = 1.4).[30] Similarly, a study conducted in Taiwan found that the renal survival time of patients with stage 3–5 CKD and MetS was significantly lower than that of patients without complications.[23] Similar results were reported by studies conducted in the United States on patients with stage 3–4 CKD. Furthermore, the risk of ESRD in patients with MetS increased 1.33 times. HTN, abnormal glucose and lipid metabolism were closely related to the increased risk of ESRD (OR values 1.83, 1.67 and 1.07, respectively).[99] The GFR of children with MetS decreased faster each year than those without the syndrome (65 *versus* 88 mL/min/1.73 m^2).[29] The GFR of patients with MetS was lower 1.5 years after transplantation; however, there was no difference compared with patients without MetS 5 years after transplantation.[100] A German study found that the risk ratios of all-cause death and cardiovascular events in patients with CKD and MetS were 1.26 and 1.48, respectively. The risk ratio of all-cause death and cardiovascular events caused by abnormal glucose metabolism was the highest. The study found that the risk ratio increased to 1.50–2.50 with an increase in the components of MetS.[19] A study conducted on patients with stage 3–5 CKD found that central obesity and all-cause mortality showed a U-shaped curve.[101] Left ventricular hypertrophy in children with MetS who underwent kidney transplantation was found to be independently related to MS with elevated LDL cholesterol.[102] Another study reported that the incidence of left ventricular hypertrophy and left

ventricular eccentric hypertrophy was 2.6–3.0 times higher than that in patients without MetS.[103] Similarly, MetS has been reported to cause significant thickening of the carotid intima-media in African American renal transplant recipients.[104] These findings demonstrate that patients with MetS who have CKD and those who have undergone kidney transplantation have poor renal prognoses and experience cardiovascular complications.

Treatment of CKD combined with MetS

The chief goal of the treatment of CKD combined with MetS is to control each component of MetS. For obese patients, lifestyle interventions, such as diet restriction and aerobic exercise are conducive to weight control and an improvement in renal prognosis to achieve the standard wei ght.[105–107] A randomized controlled study reported that after an average follow-up of 1 year of patients following a Mediterranean diet,[108] the decline rate of eGFR was significantly lower (0.66 *versus* 1.25 ml/min/1.73 m^2) and the incidence of eGFR $<$60 mL/min/1.73 m^2 was significantly lower than that of the control group.[109] Among morbidly obese patients, bariatric surgery is the best method for long-term weight loss.[110] A study conducted 1 year after bariatric surgery on 30 obese patients with CKD revealed that proteinuria decreased by 63.7%, and the GFR after surgery was significantly higher than that before surgery (94 *versus* 79 ml/min).[111] Alex *et al.*[112] reported the same findings and concluded that the renal protective effect of weight loss surgery was significantly greater than the damage caused by the surgery to the kidney. In adolescents with a history of kidney disease, a study reported that urinary microalbuminuria/creatine decreased by 17 mg/g and eGFR increased by 26 ml/min/1.73 m^2 3 years after weight loss surgery. The renal function and albuminuria of patients with no history of nephrosis before surgery remained stable.[113] The findings show that surgery can effectively reduce the weight of all patients and delay or reverse the progression of kidney disease.

Pharmacological and non-pharmacological treatments should be combined for controlling blood pressure in patients with CKD and MetS. The Dietary Approaches to Stop Hypertension diet has been recommended,[114] which comprises more fruits and vegetables, and the minimum sodium intake (1200 mg/day) is conducive to controlling HTN and reducing the risk of kidney disease progression.[115–117] The renin–angiotensin system in patients with MetS is closely related to IR.[118] Blocking RAAS has a positive effect on the control of HTN and an effect on glucose metabolism. Therefore, RAAS inhibitors are the preferred antihypertensive agents for the treatment of patients with MetS.[119,120] The study found that irbesartan and telmisartan could significantly improve IR and increase the level of adiponectin, in addition to demonstrating a good antihypertensive effect.[121,122] RAAS inhibitors combined with high-intensity interval training (HIIT) can significantly reduce mean arterial pressure.[119] β-blockers and thiazide diuretics are not recommended for blood pressure control in MetS, and calcium channel blockers can be used under special circumstances; however, they do not offer any other benefits. Therefore, these agents are not recommended for patients with MetS.[63] Recent studies have shown that reserpine can effectively treat MetS by inhibiting soluble epoxide hydrolase.[123]

Statins have been listed as the first choice for treating hyperlipidaemia in patients with MetS as these agents inhibit the inflammatory reaction, improve endothelial dysfunction, stabilize atherosclerotic plaques, inhibit platelet aggregation and have antioxidant properties. In addition, statins can reduce proteinuria in patients with MetS and delay the progression of kidney disease.[124] Among the seven commonly used statins, rosuvastatin can not only reduce TG and LDL levels but also induce a significant increase in HDL levels,[125] which is a good choice for patients with CKD and elevated TG and decreased HDL levels as the main lipid metabolism abnormalities. However, some studies have found that high-dose atorvastatin has a significant effect on lipoprotein and apolipoprotein levels in women with MetS but has no significant effect on reducing inflammation, thrombosis or platelet aggregation.[126] Atorvastatin combined with silymarin was found to enhance the anti-lipid, anti-oxidation and anti-inflammatory effects in a rat model.[127] A study reported improved efficacy of statins combined with HIIT in MetS.[128] However, rosuvastatin should be used with caution in patients undergoing renal replacement therapy and patients with CKD having eGFR $<$30 ml/min/1.73 m^2. Ezetimibe, cholestyramine and other drugs can be used to control blood lipids in patients with MetS who cannot tolerate statins.[129,130] A study

found that the combination of niacin and cholestyramine has a positive effect on blood lipid and weight control in patients with MetS.[131] Most of the drugs for diabetes can be used for patients with abnormal glucose tolerance in MetS. Presently, metformin, pioglitazone, dipeptidyl peptidase-4 inhibitors, glucagon-like peptide 1 receptor agonists (GLP-1RAs) and sodium–glucose cotransporter 2 inhibitors have been studied for the treatment of MetS, and reduced the hazard ratio for a composite renal and cardiovascular death endpoint in patients with CKD attributed to various causes, with or without type 2 diabetes.[132] GLP-1RAs are the latest group of antidiabetic drugs. A large number of studies have shown that GLP-1RAs have multiple effects, with outstanding advantages in controlling blood glucose, lowering lipid levels and blood pressure, helping in weight loss, preventing atherosclerosis and inhibition of Ang II actions.[133–139] Linagliptin affects Insulin receptor substrate1/serine/threonine protein kinase B (IRS1/Akt) signalling and prevents high glucose-induced apoptosis in podocytes.[140] Among incretin-based therapeutic agents, tirzepatide was associated with a significantly reduced risk of diabetic kidney disease.[141] Imeglimin, as the first member of a new class of oral antidiabetic drugs, exhibits unique mechanisms that can potentially benefit patients with diabetes. By reducing ROS production and increasing mitochondrial DNA synthesis, imeglimin has the potential to mitigate the occurrence of diabetic nephropathy.[142] Thiazolidinedione, an insulin sensitizer, can improve insulin sensitivity and IR in patients with MetS, improve HDL levels and reduce TG levels.[143–145] Metformin plays an important role in improving insulin sensitivity and is safe for adolescents and children.[146] In cases of CKD combined with MetS, drugs for blood glucose control should be selected according to the patient's renal function. For example, it is recommended to select linagliptin, repaglinide and rosiglitazone for patients with stage 5 CKD.

Discussion

The prevalence of MetS in patients with CKD is significantly higher than that in patients without CKD due to renal tubulointerstitial injury, accumulation of uremic toxins, abnormal bone mineral metabolism and the use of specific drugs. Presently, the treatments for MetS in patients with CKD aim to manage the components of MetS reach the standard components of MetS. In the future, studies should focus on the specific mechanisms of MetS in patients with CKD for effective intervention. The interventions can include selecting immunosuppressants, such as mycophenolate mofetil that have less effect on glucose and lipid metabolism, correcting acidosis, eliminating asymmetric dimethylarginine in the serum and supplementing active vitamin D to reduce IR.[147–149] In addition, considering the effect of CKD, appropriate drugs and dosage should be selected based on the level of renal function. Finally, the chief issue in MetS is IR. IR leads to increased levels of inflammatory mediators in the body, increased ROS production and the activation of the RAAS system, among other changes. Some new treatment options that need to be explored for MetS in patients with CKD, such as fasting to change the intestinal flora,[150] garlic,[151] *Azadirachta indica*,[152] cardamom,[153] ginkgo leaf,[154] *Scutellaria baicalensis*, onion, turmeric and their active ingredients,[155–158] have been explored. These treatments are expected to improve the inflammatory status, reduce ROS production and RAAS activation and become a new therapeutic target for MetS.

Conclusion

In conclusion, the incidence of MetS is significantly higher among patients with kidney disease compared to those without, primarily due to disturbances in glucose and fat metabolism, IR, HTN and the utilization of glucocorticoids and CNIs following kidney injury. The implementation of blood pressure control, statins and novel blood glucose-regulating drugs can mitigate the occurrence of MetS in kidney disease patients, thereby reducing kidney damage. However, there are also some limitations in this manuscript, such as some new therapeutic strategies, and new therapeutic schemes of traditional Chinese medicine require is warranted through large-scale studies.

Declarations

Ethics approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

Author contributions

Lirong Lin: Writing – original draft.

Xianfeng Pan: Data curation.

Yuanzheng Feng: Writing – review & editing.

Jurong Yang: Project administration; Supervision.

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Competing interests
The authors declare that there is no conflict of interest.

Availability of data and materials
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Appendix

Abbreviations

BMI	body mass index
CAPD	continuous ambulatory peritoneal dialysis
CKD	chronic kidney disease
CNI	calcineurin inhibitors
eGFR	estimated glomerular filtration rate
ESRD	end-stage renal disease
GLP-1RAs	glucagon-like peptide 1 receptor agonists
GLUT4	glucose transporter 4
GFR	glomerular filtration rate
HD	haemodialysis
HDL	high-density lipoprotein
HIIT	high-intensity interval training
HTN	hypertension
IR	insulin resistance
LDL	low-density lipoprotein
MetS	metabolic syndrome
RAAS	Renin Angiotensin Aldosterone System
ROS	reactive oxygen species
TG	triglyceride
TGF-β	transforming growth factor-β
TNF-α	tumour necrosis factor α
VLDL	very low density lipoprotein
WC	waist circumference