Metabolism and Translational Medicine

REVIEW ARTICLE

Correlation between renal metabolism and cardiovascular disease

Siying Deng[1], Wei Huang[2,3,4,*]

[1]China National Clinical Research Center for Neurological Diseases, Beijing Tiantan Hospital, Capital Medical University, Beijing 100070, China
[2]Department of Cardiology, General Hospital of Central Theater Command of PLA, Wuhan 430070, Hubei Province, China
[3]Division of Cardiology, Hubei Key Laboratory of Genetics and Molecular Mechanisms of Cardiological Disorders, Tongji Hospital, Tongji Medical College, Huazhong University of Science and Technology, Wuhan 430030, Hubei Province, China
[4]Wuhan Clinical Medical Research Center for Hypertension, Huazhong University of Science and Technology, Wuhan 430030, Hubei Province, China

ABSTRACT

Cardiovascular disease is the main medical burden in the world, and coronary heart disease and heart failure are the main reasons for the increase of all-cause mortality and cardiovascular mortality year by year. There is a synergistic effect between cardiovascular and kidney diseases. Under pathological conditions, there is a significant correlation between various cardiovascular diseases and kidney diseases. In this review, we discussed the effects of metabolite accumulation caused by kidney disease on multiple mechanisms of atherosclerosis from the whole process of the formation and development of atherosclerosis. These metabolites can be mainly divided into uremic toxins, intestinal metabolites, fibroblast growth factor 23, and advanced glycosylation end products. Then we summarized the effects of metabolites related to renal metabolism on heart failure according to the biological changes of patients with heart failure at three different levels.

Key words: cardiovascular disease, atherosclerosis, heart failure, chronic kidney disease, renal metabolism

INTRODUCTION

Cardiovascular diseases (CVDs) are the main cause of death and burden of disease globally.[1] Due to various types and multiple related risk factors, the research on CVDs has never been overlooked. A study evaluated the trend of the burden of CVDs around the world from 1990 to 2019.[2] This article introduced 13 CVDs such as ischemic heart disease (IHD), stroke, hypertensive heart disease and rheumatic heart disease, and analyzed the epidemiology and indicators of burden of disease regarding 9 risk factors including high systolic blood pressure, high low-density lipoprotein cholesterol (LDL-C), high body mass index (BMI), and renal function impairment. Compared with the past, due to the change of lifestyle and the aging of society, the diagnosis, treatment, and prevention of CVD, we are facing are still full of challenges even if the medical conditions continue to be optimized.

The heart is the organ with the highest requirement for metabolism in the human body.[3] As the basis of most CVDs,[4] the disorder of heart energy metabolism can directly lead to cardiac dysfunction and eventually form organic changes. Utilizing the most advanced metabolomics techniques allows us to measure thousands of metabolites in biological fluids or living tissues, providing us with an individual's metabolic

***Corresponding Author:**
Wei Huang, Department of Cardiology, General Hospital of Central Theater Command of PLA, No.627, Wuluo Road, Wuchang District, Wuhan 430070, Hubei Province, China. Email: huangwei0521@126.com; https://orcid.org/0000-0001-6136-6653
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fingerprint.[3] Under different physiological and pathological conditions, these metabolites can reflect changes in the metabolism of various organs and tissues of the body. Further analysis can reveal the connection between cardiac metabolism and metabolism of other organs and tissues.

Among various metabolites, some link cardiovascular events with impaired renal function. As early as 1836, Bright[5] proposed a link between chronic kidney disease (CKD) and cardiovascular abnormalities. Since then, many studies have confirmed and extended this association, and given different explanations. Patients with a glomerular filtration rate (GFR) less than 60 mL/min/1.73 m² have approximately double the risk of developing heart failure compared with those with preserved GFR.[6] There is also an increased risk of stroke,[7] peripheral artery disease,[8] coronary artery disease (CAD), and atrial fibrillation.[9]

On the one hand, the kidneys excrete metabolites and harmful substances in the body through the production of urine to keep the internal environment of the body stable. Therefore, when the kidney function gradually loses, it is accompanied by the retention of a large number of metabolites. Many of these metabolites have been shown to be biologically active, thereby affecting cellular functions and metabolic processes, leading to uremic syndrome.[10] On the other hand, the kidneys can secrete renin and prostaglandins to regulate blood pressure, secrete erythropoietin to act on the bone marrow hematopoietic system, and promote the activation of vitamin D to promote calcium and phosphorus absorption and bone growth. In summary, the excretory function and endocrine function of the kidney play a key role in regulating the metabolic state of the body. However, only a few national and international guidelines on cardiovascular risk management pay special attention to CKD as a significant risk factor,[11] and the link between renal metabolism and CVD deserves greater attention.

This review will start with several classic CVDs such as CAD and heart failure. Then, the review demonstrates how several important metabolites related to renal metabolism affect the occurrence, development, and outcome of CVDs. The review is intended to provide reference for the development and application of therapeutics.

EPIDEMIOLOGY DEMONSTRATES SIGNIFICANT ASSOCIATION BETWEEN CARDIOVASCULAR DISEASE AND RENAL INSUFFICIENCY

Previous epidemiological surveys have pointed out that patients with CKD have increased cardiovascular risk and mortality, and conversely, cardiovascular events are the most common cause of death in patients with CKD.[12] The nature and extent of CVD of individuals with CKD have been considered distinct from those of individuals without renal disease, including atherosclerosis, arteriosclerosis, calcified arterial and valvular disease, left ventricular remodeling and dysfunction, cardiac arrhythmias, and sudden cardiac death.[10] In 2004, Go *et al.*[13] evaluated a longitudinal GFR of 1,120,295 adults who measured serum creatinine between 1996 and 2000 and did not undergo dialysis or kidney transplantation in a large general health care system. Multivariate associations were found between estimated GFR and risk of death, cardiovascular events, and hospitalization. Kottgen *et al.*[6] pairs of 14,857 participants, from 1987 to 2002, followed up the events of heart failure hospitalization or death and found that middle-aged people with moderate or severe renal dysfunction are high-risk groups for heart failure. Reboldi *et al.*[14] analyzed 8794 participants with a mean age of 52 in 8 prospective studies. In a multivariate Cox model including age, sex, 24-hour mean blood pressure, smoking, diabetes, and cholesterol, and high estimated glomerular filtration rate (eGFR), the risk of cardiovascular events in participants with low eGFR was significantly higher than that in participants with normal eGFR, which further verified the conclusion that the curves describing the relationship between GFR and cardiovascular outcomes and GFR and all-cause mortality were u-shaped.[15–17] It shows that the rise and decline of GFR increase CVD risk and total mortality to the same extent. Compared with long-term dialysis treatment, successful kidney transplantation significantly reduces the risk of death from cardiovascular events.[18]

CORONARY HEART DISEASE AND RENAL METABOLISM

CAD is an important component of morbidity and mortality around the world.[19] According to Global Burden of Diseases (GBD) data, the global prevalence of CAD in 2016 was 154 million, accounting for 32.7% of the global burden of CVD and 2.2% of the total global burden of disease.[20] In 2019, the number of patients with IHD reached 197 million and the number of deaths was 9.14 million, and the absolute number is still increasing.

Atherosclerosis, as one of the main causes of CAD,[21] refers to the damage of the arterial intima due to various reasons, with lipid deposition, foam cell formation, and smooth muscle cell and fiber component proliferation, gradually forming plaques in the arterial wall. In the plaque, tissue necrotizes and disintegrates, and then combines with deposited lipids to form atheroma.[22] Clinical studies point out that renal insufficiency is

associated with the severity of coronary atherosclerosis, the incidence of coronary events, and the mortality rate after myocardial infarction. Nakano *et al.*[23] investigated the relationship between CKD and severity of coronary atherosclerosis in a population-based autopsy sample. According to the research, a progressive increase in the frequency of advanced atherosclerotic lesions and an increase in the frequency of coronary calcified lesions are noticed as eGFR decreases. Bae *et al.*[24] conducted a retrospective cohort study to eGFR in 12,636 patients with acute myocardial infarction (AMI) and concluded that eGFR was independently associated with mortality and complications after AMI. Interpretation of the epidemiology of CAD is complicated due to the frequent coexistence of CKD and diabetes, which is also a predisposing factor for cardiac events.[25] Nevertheless, even with modest impairment of eGFR, the risk of myocardial infarction is still increased in nondiabetic patients.[26] Epidemiological evidence suggests that the progression of atherosclerosis in CKD cannot be fully explained by traditional CVD risk factors such as hypertension, diabetes, and dyslipidemia, meaning that there are also nontraditional risk factors that contribute to atherosclerosis in CKD Sclerosis formation, including proteinuria, accumulation of uremic toxins, *etc.*[25]

Atherosclerosis is a dynamic process, and changes in the microenvironment at each time point can affect the occurrence of outcome events. Therefore, when we explore the relationship between renal metabolism and CAD under pathological conditions, we can find the key points more carefully and logically according to the occurrence process of atherosclerosis.

Renal insufficiency can induce dyslipidemia

One of the mechanisms of atherosclerosis is lipid infiltration. Many factors can cause endothelial damage and increase the permeability of low-density lipoprotein (LDL), which accumulates under the endothelium. The combination of excessively deposited LDL and proteoglycans makes it easier to be oxidized or chemically modified in other ways to facilitate macrophage recognition and phagocytosis, and eventually get removed. Monocytes are stimulated by oxidized LDL and other stimuli to migrate to the subendothelium to differentiate into macrophages, and further recognize and phagocytize the modified oxidized LDL particles through scavenger receptors. Finally, foam cells are formed. A large number of foam cells die to form lipid pools and develop into typical atheromatous plaque.[22]

In previous studies, it has been reported that patients with chronic renal failure and experimental animals often have elevated plasma triglycerides, impaired clearance of very low-density lipoprotein (VLDL) and chylomicrons, sustained reduction in plasma high-density lipoprotein (HDL) concentration, and impaired maturation of cholesterol-ester-rich cardioprotective HDL-2 from HDL-3 with low level of cholesterol ester.[27–29] In addition to changes in the content of plasma protein itself, its composition has also changed. A decrease in cholesteryl ester content and a relative increase in triglyceride content in several lipoproteins suggests a redistribution of cholesterol from HDL to VLDL and LDL, as well as a defect in the removal of triglyceride from LDL and HDL particles. However, other factors that accompany CKD, such as diabetes, insulin resistance, metabolic syndrome, obesity, and overt proteinuria, may enhance dyslipidemia and high triglyceride lipoprotein cholesterol, making it difficult to determine a causal independent effect of CKD on lipid abnormalities.[30]

Studies have indicated that strategies to reduce traditional risk factors for cardiac adverse events in the general population, such as LDL-C, do not benefit patients with CKD.[31] According to the Study of Heart and Renal Protection (SHARP), compared with placebo, although simvastatin plus ezetimibe reduces the composite cardiovascular outcome in subjects with CKD by 17%, it does not reduce all-cause mortality or CAD mortality.[32] A sub-study of the Treating to New Targets (TNT) trial shows that lowering LDL cholesterol with atorvastatin in CKD reduces the relative risk of major cardiovascular events in CKD patients.[33] Triglyceride-lowering drugs such as gemfibrozil and fenofibrate have been shown to be cardioprotective in patients with non-dialysis CKD.[34,35] These results suggest that LDL plays a more important role than high-density lipoprotein cholesterol (HDL-C) in CVD in CKD. Besides, triglyceride may also play a role, but there is no evidence to prove it. Studies of cholesteryl ester transfer protein (CETP) inhibition, such as torcetrapib and dalcetrapib, fail to demonstrate improved cardiovascular outcomes, although they successfully increase HDL-C levels.[36,37] The recently completed Heart Protection Study 2-Treatment of HDL to Reduce the Incidence of Vascular Events (HPS2-THRIVE) study is the largest prospective randomized trial testing niacin in patients at high risk of cardiovascular events. However, it failed to demonstrate a reduction in the risk of major vascular events.[38]

Renal insufficiency promotes the development of insulin resistance

Insulin resistance is a core characteristic of several common human diseases such as type 2 diabetes and primary hypertension, which are potential risk factors for coronary heart disease. Epidemiological studies have shown that up to 40% of patients with coronary heart disease in whites may have diseases related to insulin

resistance, while in South Asia, nearly 60% of the risk of coronary heart disease may be associated with insulin resistance.[39] Dugani *et al.* explored the baseline risk status of female coronary heart disease development based on the age of onset and found that insulin resistance appears to be one of the strongest risk factors for early-onset coronary heart disease.[40] In different community populations, insulin resistance is associated with an increased risk of cardiovascular disease events, regardless of whether it is directly measured, estimated using fasting insulin concentration (such as in homeostatic model assessment), or calculated through dynamic tests (such as the oral glucose tolerance test).[41] In recent years, Derek Klarin's team conducted a genome-wide association study, testing the association between approximately 9 million DNA sequence variations and CAD, and identified a new gene locus *CCDC92* that may affect CAD through the insulin resistance pathway.[42]

In physiological conditions, insulin plays a regulatory role in cellular metabolism by enhancing glucose utilization in insulin-sensitive tissues, and also regulates vascular relaxation of small blood supplying arteries by activating endothelial nitric oxide synthase (eNOS) through the phosphatidylinositol-3-kinase (PI3K)/Akt signaling pathway.[43] Insulin resistance is defined as a decreased tissue response to insulin stimulation and is thus characterized by defects in glucose uptake and oxidation, decreased glycogen synthesis, the ability to inhibit lipid oxidation to a lesser extent, and vasoconstriction.[44] Insulin resistance is closely associated with mitochondrial dysfunction, reactive oxygen species (ROS) production, endothelial dysfunction, and other cardiovascular risk factors, although it is difficult to disentangle the causal relationships between these processes.[45]

Research has shown that patients with CKD begin to develop insulin resistance before the onset of a decrease in GFR,[46] but the specific cause is not yet determined. Renal function impairment may be promoted by residual uremic toxins, acidosis, and deficiency of active vitamin D, while insulin resistance can lead to renal function impairment by damaging glomerular endothelial and epithelial cells.[41,47] In one epidemiological study, insulin resistance was found to be an independent risk factor for the development of CKD and the rapid decline of eGFR in the Korean population.[48]

Metabolic disorders caused by renal insufficiency can lead to endothelial dysfunction and can aggravate inflammation and oxidative stress

The functions of the endothelium in a healthy state include dynamic maintenance of vascular tone, angiogenesis, hemostasis, and providing an antioxidant, anti-inflammatory, and antithrombotic interface. Vascular endothelial dysfunction is manifested by impaired endothelium-dependent vasodilation, enhanced oxidative stress, chronic inflammation, leukocyte adhesion and hyperpermeability, and endothelial cell senescence.[49] In a cross-sectional study of patients with peripheral arterial disease (PAD), endothelial function is assessed by flow-mediated vasodilation in the brachial artery. It is estimated that GFR was significantly correlated with endothelial function. Under such a background, renal function can be described as one of the determinants of endothelial dysfunction.[50]

Uric acid (UA)

UA is the final product of purine metabolism in higher animals. It is mainly synthesized in the liver, intestine, and vascular endothelium. The kidney plays a leading role in the excretion of UA. The kidney excretes about 70% of the daily UA produced, and the rest 30% of UA is excreted by the gut.[51] When UA production exceeds UA excretion, hyperuricemia, defined as a serum UA concentration > 7.0 mg/dL, occurs. Various transporters expressed in the renal proximal tubules mediate UA exchange. These molecules include glucose transporter 9 (GLUT9), uric acid transporter 1 (URAT1), the human adenosine triphosphate-binding cassette subfamily G 2 (ABCG2), organic anion transporter (OAT) 1, 3, and 4.[52] A meta-analysis[53] including 15 studies shows that the carotid intima-media thickness (CIMT) in the high UA group is significantly higher than that in the control group, and further studies indicate that high UA is significantly correlated with the presence of carotid atherosclerotic plaques.[52] Based on a meta-analysis of 29 prospective cohort studies, Li *et al.*[54] verified that hyperuricemia may increase the risk of CAD events. For every 1 mg/dL increase in UA level, the pooled multivariable relative risk of CAD mortality is 1.13 (95% confidence intervals [CI] 1.06–1.20). Dose-response analysis shows that the combined relative risk for CHD mortality is 1.02 (95% CI 0.84–1.24) for a 1 mg UA increase per liter. There is research incubating human umbilical vein endothelial cells (HUVECs) with UA, ROS scavenger polyethylene glycol superoxide dismutase (PEG-SOD), endoplasmic reticulum (ER) stress inhibitor 4-phenylbutyric acid (4-PBA), and the protein kinase C (PKC) inhibitor polymyxin B. The research assesses nitric oxide (NO) production, eNOS activity, intracellular ROS, ER stress levels, and the interaction between eNOS and calmodulin (CaM) and cytosolic calcium levels. It is demonstrated that UA triggers oxidative stress and ER stress through PKC/eNOS-mediated eNOS activity and NO production, thereby inducing HUVEC apoptosis and endothelial dysfunction.[55] It is reported that high concentrations of UA can induce endothelial dysfunction through the high

mobility group protein B1/receptor for advanced glycosylation end-product (HMGB1/RAGE) signaling pathway.[56] In addition, hyperuricemia-induced endothelial dysfunction is also been validated in many clinical studies.[57,58]

Urea

Urea is a toxic end product produced when amino acids and other nitrogen-containing metabolites are broken down in the liver. It is normally excreted by the kidneys. However, patients with end-stage renal disease (ESRD) are unable to urinate and thus have continuously increased blood urea concentrations. This condition can only be treated with intermittent hemodialysis or kidney transplantation. Although hemodialysis can improve uremia in patients with ESRD, it can only replace about 10% of normal renal function. Therefore, these patients still suffer from chronic urea overload.

As kidney function declines, accumulated urea spontaneously decomposes to form cyanate, which undergoes an irreversible non-enzymatic reaction with proteins and free amino groups, called carbamylation.[59] There is evidence that protein carbamylation induced by chronically elevated blood urea is associated with the risk of CVD in patients.[60] Studies with tissue culture and animal models also show that urea and protein carbamylation may contribute to CVD.[59] Carbamylated albumin has pro-inflammatory properties and is more nephrotoxic than albumin and traditional albumin modifications.[61] Apostolov *et al.*[62] demonstrated that carbamylated low-density lipoprotein (cLDL) can promote atherosclerosis by causing dysfunction of human endothelial cells through the lectin-like, oxidized low-density lipoprotein receptor-1 (LOX-1) and partially CD36, scavenger receptor expressed by endothelial cells 1 (SREC1) and scavenger receptors A1 (SR-A1) receptors. The research team also demonstrate that intercellular adhesion molecule-1 (ICAM-1) and vascular cell adhesion molecule-1 (VCAM-1) play important roles in cLDL-activated human vascular endothelial monocyte adhesion *in vitro*.[63] Schreier *et al.*[64] found that carbamylation completely abolishes the proteolytic and cytoprotective effects of threonine against hypochlorous acid (HOCl) challenge, thus carbamylation may contribute to oxidative stress. Urea itself is also shown to induce ROS in cell culture studies.[25]

Free amino acids are competitive inhibitors of protein carbamylation. Studies manifest that amino acid scavenger therapy can reverse protein carbamylation.[65] Intensification of hemodialysis treatment also reduces protein carbamylation and may partly explain the benefit seen when dialysis dose (*i.e.*, frequency) is increased. The impact of reduced protein carbamylation on clinical outcomes awaits further study and is a promising target for intervention.

Indoxyl sulfate (IS)

IS is a uremic toxin metabolized by dietary tryptophan. In tubular epithelial cells, IS is excreted from blood into urine by OATs and organic anion-transporting polypeptides (OATPs).[66] Clinical evidence suggests that IS is an independent risk factor for cardiovascular morbidity and mortality in patients with CKD.[67] Itoh *et al.*[68] revealed elevated levels of 11 protein-bound uremic toxins in the serum of hemodialysis patients. IS, p-cresol sulfate, and 3-carboxy-4-methyl-5-propyl-2-furan propionic acid (CMPF) cannot be effectively removed by hemodialysis due to high protein binding, among which indoxyl phenyl sulfate has the strongest induction effect on ROS production in endothelial cells. Ito *et al.*[69] demonstrated that IS enhances leukocyte-endothelial cell interaction and promotes vascular inflammation by upregulating E-selectin, possibly through c-Jun N-terminal kinase (JNK)- and nuclear factor κB (NF-κB)-dependent pathways. Matsuo *et al.*[70] exposed THP-1 cell-differentiated macrophages to IS *in vitro*. The result shows that IS reduces the viability of THP-1-derived macrophages and promotes generation of inflammatory cytokines such as interleukin-1 beta (IL-1β), tumor necrosis factor (TNF)-α, and ROS. Nakano *et al.*[71] proved that human and mouse macrophages express OAT and OATP family transporters through *in vivo* and *in vitro* experiments. Additionally, this family of proteins mediates the IS-induced pro-inflammatory activation of macrophages *in vitro* and *in vivo*, and accelerates the development of cardiovascular metabolic disorders. The activation of this inflammatory response is achieved through the organic anion transporting polypeptide 2B1 (OATP2B1)-Delta-like 4 (Dll4)-Notch axis.

P-cresol sulfate (PCS)

PCS is a major uremic toxin derived from tyrosine and phenylalanine *via* hepatic metabolites. It circulates primarily in combination with albumin and is taken up by body cells *via* OAT1 and/or OAT3.[72] Wu *et al.*[73] use a prospective cohort study to investigate how serum IS and PCS are related with all-cause mortality and cardiovascular mortality in elderly hemodialysis patients. It is concluded that serum free PCS levels can help predict all-cause and cardiovascular mortality risk in elderly hemodialysis patients beyond traditional and uremia-related risk factors. It is also reported that PCS is associated with adverse clinical effects.[74] Lin *et al.*[75] demonstrated that serum PCS and IS levels are associated with PAD. *In vitro* cell experiments reveal that p-cresol's major *in vivo* metabolite, p-cresol sulfate, has a pro-inflammatory effect on unstimulated leukocytes.[76] Gross *et al.*[72] demonstrated that PCS induces ROS production in vascular smooth muscle cells (VSMCs), confirming its prooxidative effect on endothelial cells. They also point out that PCS can directly activate Rho kinase to induce constriction of mouse thoracic aorta.

Pletinck *et al.*[77] assessed the effects of acute and sustained exposure to uremic levels of IS, PCS, and p-cresol glucuronide (PCG) on the recruitment of circulating leukocytes in rat peritoneal vascular bed in rats using intravital microscopy. The results show that IS, PCS, and PCG exert pro-inflammatory effects by stimulating crosstalk between leukocytes and blood vessels, leading to vascular injury.

Phosphate

Hyperphosphatemia is very common in patients with ESRD. For many years, hyperphosphatemia has been recognized as an important cause of high CVD morbidity and mortality in CKD patients.[78,79] However, its common pathogenicity of promoting vascular calcification does not explain recent epidemiological findings that higher serum phosphate levels within the normal range may also be a risk factor for CVD in individuals with normal renal function.[80,81] Six *et al.*[78] found that phosphate had a rapid, concentration-dependent vasoconstrictive effect on the mouse aorta and that this constriction is abrogated by the hydroxyl radical scavenger dimethylthiourea. Furthermore, phosphate increases H_2O_2 production in human vascular smooth muscle cells (HVSMCs). Thus, uremic toxins such as phosphate can enhance vasoconstriction by releasing oxygen free radicals. Shuto *et al.*[80] studied the acute effects of phosphorus loading on endothelial function *in vitro* and *in vivo*. It is found that exposure of bovine aortic endothelial cells to phosphorus loading increases production of ROS dependent on phosphorus influx through the sodium-dependent phosphate transporter, and meanwhile, reduces NO through inhibition of phosphorylation of eNOS generation. Further studies by Peng *et al.*[82] pointed out that both hyperphosphatemia and hypophosphatemia decrease eNOS activity by decreasing intracellular calcium and increasing PKCβ2. Hyperphosphatemia also decrease eNOS transcription *via* signaling through the PI3K/Akt/NF-κB and mitogen-activated protein kinases (MAPK)/NF-κB pathways. It also shows that hyperphosphatemia can increase oxidative stress through increased ROS generation leading to apoptosis of endothelial cells, a process that compromises endothelial cell integrity.[83] Di Marco *et al.*[84] demonstrated that high phosphate levels unrelated to vascular calcification play a role in the pathophysiology of cardiovascular burden by interfering with endothelial function, thereby impairing microvascular function, angiogenic capacity, and inducing endothelial stiffness.

Sevelamer is a calcium-free phosphate binder that lowers blood phosphate and has pleiotropic effects including correction of lipid abnormalities and reduction of oxidative stress and inflammation. Caglar *et al.*[85] conducted a small, randomized, prospective study showing that short-term treatment with sevelamer significantly increases fetuin A levels and improves flow-mediated dilation (FMD) in nondiabetic stage 4 CKD patients. Six *et al.*[78] use multiple approaches to test the therapeutic potential of Sevelamer to prevent phosphate- and CKD-induced endothelial dysfunction and reveal that it can reduce the expression of adhesion molecules (ICAM-1 and VCAM-1).

Fibroblast growth factor 23 (FGF-23)

FGF-23, a bone-derived phosphoturic hormone, reduces renal synthesis of 1,25-dihydroxy vitamin D3 (1,25[OH]2D3). FGF-23 acts primarily by binding to a receptor complex consisting of fibroblast growth factor receptors (FGFRs) and a co-receptor α-Klotho (known as Klotho).[86] In CKD, FGF-23 serum levels gradually increase with a decline in GFR and renal phosphate excretion capacity.[87] Several epidemiological studies note an association between serum FGF-23 levels and systemic atherosclerosis.[88–90] Animal experiments show that FGF-23 increases superoxide, inhibits the bioavailability of NO, and affects endothelial vasodilation, leading to aortic endothelial dysfunction in mice.[91] Klotho deficiency in mice can also lead to decreased level of NO synthesis in vascular endothelial cells, affecting endothelial function and causing arteriosclerosis.[86,92]

Asymmetric dimethylarginine (ADMA)

ADMA is an endogenous inhibitor of eNOS. It is that elevated ADMA levels during CKD may be associated with decreased renal excretion and increased production due to dysfunction of the endothelial L-arginine/NO pathway.[93] Meinitzer *et al.*[94] noted that ADMA concentrations can predict all-cause and cardiovascular mortality in patients with CAD. Mangiacapra *et al.* demonstrated that serum ADMA levels are an independent predictor of the extent of coronary atherosclerosis. Lee *et al.*[95] reported that pathological concentrations of UA increase intracellular levels of ADMA, disrupt the balance of the ADMA/dimethylarginine dimethylaminohydrolase 2 (DDAH-2) axis, and result in endothelial cell dysfunction, thereby accelerating atherosclerosis. Several *in vitro* cell experiments prove that ADMA can enhance the adhesion of monocytes to endothelial cells *in vitro* and mediate the proinflammatory state of endothelial cells.[96–99] There are also animal cell studies showing that ADMA contributes to eNOS suppression through multiple mechanisms, increases ROS burden, and can also reduce ROS disposal, thereby establishing a pathogenic redox state in the vasculature.[100–104] Furthermore, studies show that ADMA can significantly upregulate the expression of LOX-1 in monocytes, upregulate cholesterol acyltransferase (ACAT), elevate the uptake of oxidized low density lipoprotein (oxLDL), and drive the formation of

foam cells in atherosclerotic plaques.[99,103]

Gut microbiome-related metabolites

Trimethylamine N-oxide (TMAO) is a gut microbiota-derived metabolite formed from the conversion of trimethylamine (TMA) by hepatic flavin monooxygenase 3 (FMO3). Mammals cannot metabolize TMAO, and about 95% of it are excreted by the kidneys. Multiple epidemiological investigations in recent years show that the serum TMAO concentration of CKD patients is elevated, which is strongly negatively correlated with eGFR, indicating that the long-term survival rate is reduced.[105–108]

Multiple studies show that TMAO can promote the progression of atherosclerosis.[109] A large clinical cohort study is the first to establish that TMAO can predict CVD risk,[110] and in subsequent animal experiments, a significant increase in atherosclerosis is observed in mice supplemented with TMAO.[110,111] Wang *et al.*[112] noted that diet-induced atherosclerosis can be affected by using specific inhibitors of TMAO's precursor metabolites, further supporting the pro-atherogenic properties of TMAO. Dietary supplementation of the TMAO precursor choline results in increased atherosclerotic lesion burden, increases aortic expression of scavenger receptors (CD36 and scavenger receptor A), and increases foam cell formation by cholesterol-rich macrophages.[113] Studies show that TMAO can promote vascular endothelial cell pyroptosis through ROS induced by upregulation of succinate dehydrogenase complex subunit B (SDHB),[114] and can also induce vascular injury by affecting the distribution of bile acids.[115] Interestingly, although TMAO has increasing evidence of its association with CVD events, its role in atherosclerosis remains controversial. In two acknowledged mouse models of atherosclerosis, apolipoprotein E $(ApoE)^{-/-}$ and low density lipoprotein receptor $(Ldlr)^{-/-}$ mice, dietary choline supplementation does not alter atherosclerotic lesion size.[116,117] In addition, in some recent population-based clinical studies, the positive association between cardiovascular risk and TMAO levels is not confirmed.[118,119] There are many reasons for the controversy, such as the difference in animal cells used by different research groups, the duration of the experiment, *etc.*, which are also affected by many factors in human research. Overall, TMAO is only one of many factors that affect atherosclerosis and its complications.

Phenylacetylglutamine (PAGln) is also a metabolite produced by intestinal microorganisms and mainly excreted by the kidneys. When the kidney function is impaired, it can accumulate in the body. Like TMAO, it belongs to the gut-derived uremic toxin (GDUT).[120,121] Multiple epidemiological studies point out an independent association between PAGln and the burden of coronary atherosclerosis, as well as its correlation with major adverse cardiovascular events.[122–124]

Advanced glycation end products (AGEs)

AGEs are a heterogeneous group of compounds. They are representative metabolites of T2DM and are derived from non-enzymatic glycosylation of proteins, lipids, and nucleic acids through a complex reaction called the Maillard reaction, followed by further sugar oxidation reactions under oxidative stress conditions.[125] AGEs are metabolized and cleared by the kidneys, filtered through the glomeruli, and reabsorbed by the renal proximal tubules, so the gradual retention of AGEs that occurs with the decline of renal function will cause a vicious cycle of renal damage and accelerated decline of renal function.[10] Epidemiological investigations show that AGE and circulating receptor for AGEs (RAGE) levels are independently associated with decreased GFR.[126]

Several studies manifest that AGEs are highly correlated with adverse cardiovascular events caused by atherosclerosis.[127,128] Modifications of extracellular proteins such as collagen, elastin, and laminin by AGEs can alter the structure, function, and properties of normal tissues and trigger inflammatory responses. Haitoglou *et al.*[129] demonstrated that glycosylation of laminin and collagen IV impairs endothelial cell adhesion and migration by disrupting cell attachment sites. The formation of AGEs on vascular wall and myocardial collagen leads to mutual cross-linking of collagen molecules, which leads to the loss of collagen elasticity, which in turn leads to a decrease in vascular wall flexibility and vascular stiffness.[130] In cells, AGEs can accumulate in the ER and bind to mitochondrial proteins, increasing superoxide and ROS production.[131,132]

Metabolic disturbance caused by renal insufficiency can induce vascular smooth muscle cell type transformation and abnormal function

VSMCs reside in the media of arterial vessels, maintaining arterial structural integrity and vascular tone. A range of phenotypes are identified in VSMCs, exhibiting a contractile phenotype under physiological conditions. When challenged with noxious stimuli, VSMCs lose their contractile properties and switch to a synthetic phenotype, which is critical for atherosclerotic plaque formation and progression.[133]

Ok *et al.*[134] demonstrated that cLDL induces dose-dependent vascular cell injury associated with atherosclerosis, including vascular smooth muscle cell proliferation and endothelial cell death. Yuan *et al.*[135] use *in vitro* cell experiments to prove that AGEs can activate the PI3K/Akt pathway through RAGE, thereby promoting the proliferation and migration of human aortic vascular smooth muscle cells (HASMC). Studies by Xing *et al.*[133] showed that AGEs can induce M1-type polarization of plaque macrophages through activation

of the RAGE/toll-like receptor 4 (TLR4) pathway. In this process, activated RAGE/TLR4 signaling promotes Dll4 expression in this plaque M1 macrophage subset through the extracellular regulated protein kinases/forkhead box protein c2 (ERK/FOXC2) pathway. Through direct cell-to-cell contact, Dll4 is expressed on macrophage-mediated VSMCs to achieve contractile phenotype switching through the Notch pathway, thereby promoting atherosclerosis.

Metabolic disorders caused by renal insufficiency can lead to vascular calcification and thrombosis

Vascular calcification is a mineral metabolism disorder that is very common in patients with CKD,[136] occurring in the early stages of CKD and becoming increasingly severe as the disease progresses. It can lead to the development of atherosclerosis and plaque rupture,[137,138] and is one of the main risk factors for cardiovascular death.[139] Vascular calcification is the abnormal deposition of phosphate (Pi) salts in vascular tissue (including blood vessels, valves, and the heart), and its development involves complex pathological mechanisms, including osteogenic differentiation and apoptosis of vascular smooth muscle cells, instability and release of calcium and phosphate from extracellular vesicles, and elastic fiber degradation.[136]

Multiple studies have shown that there is a pathogenic link between hyperphosphatemia and the associated development of vascular calcification.[140,141] Phosphate-induced endothelial dysfunction and vascular calcification are considered key inducing factors for atherosclerosis in patients with CKD.[142] With the decline in renal function and glomerular unit mass, parathyroid hormone (PTH) and FGF-23 are synthesized and secreted as early as CKD stages 2 and 3 in response to relative phosphate overload. Although it is widely believed that FGF-23 levels are elevated in CKD and are associated with renal function impairment and mineral metabolism disorders, the role of FGF-23 in vascular smooth muscle cell (SMC) matrix calcification remains controversial.[136,143] Zhao *et al.*[139] demonstrated that tumor necrosis factor (TNF) activates NF-κB promotes inorganic phosphate induced calcification of human aortic smooth muscle cells. Thi Nguyen's team demonstrated that high Pi increases mitochondrial phosphate carrier (PiC) abundance by activating protein translation dependent on ERK1/2-mechanistic target of rapamycin (mTOR) signaling.[144] High Pi can upregulate the abundance of plasma cell Pi transporter PiT-1/2 through ERK1/2, mTOR, and p70 ribosomal protein S6 kinase (p70S6K), and can also stimulate its plasma membrane transport.[145] Upregulation of Pi transporter protein can increase cytoplasmic and mitochondrial ROS, which helps NF-κB inhibitor alpha (inhibitor kappa B alpha, IKB-α) release NF-κB. Enable its transport to the nucleus of VSMCs. NF-κB, as a transcription activator of many osteogenic genes, including Runt-related transcription factor 2 (Runx2) and Osteopontin, plays a core role in vascular calcification.[144]

Multiple clinical studies demonstrate a significant association between circulating TMAO levels and the risk of thrombotic events.[146,147] The mechanism of TMAO in thrombus formation has been studied a lot in recent years. Skye *et al.*[148] found that transplantation of a subject's human fecal microbiota produces differential TMA and TMAO in the host, accompanying increased platelet aggregation assay reactivity and *in vivo* thrombotic potential. Zhu *et al.*[149] pointed out that direct exposure of platelets to TMAO can enhance multiple agonist stimulus-dependent platelet activation by increasing the release of intracellular calcium ions. It is also demonstrated that the key enzyme FMO3, which regulates the last step of the TMAO pathway, can affect platelet reactivity and thrombosis rate.[150] However, since the nature, if any, of the "TMAO receptor" remains unknown, more detailed molecular mechanisms of the exact pathways by which TMAO exerts its pro-inflammatory and pro-thrombotic effects remain elusive.[151] There is also a positive correlation between PAGln levels and thrombotic events in humans. On the basis of previous studies, Nemet *et al.*[124] verified that PAGln can enhance platelet activation-related phenotypes and thrombosis potential in animal models of arterial injury, and that PAGln can mediate cellular events through G protein-coupled receptors including α 2A, α2B, and β2-adrenergic receptors.

HEART FAILURE AND RENAL METABOLISM

Heart failure is a chronic and progressive disease resulting from structural or functional cardiac abnormalities that lead to reduced pumping capacity. It can be categorized as either reduced or preserved left ventricular ejection fraction (LVEF).[152,153] Heart failure, as the primary syndrome, can accompany secondary CKD, and vice versa. Both can coexist based on shared risk factors or systemic disease. In a recent international academic conference on the relationship between heart failure and CKD, it was pointed out that as the severity of CKD increases, the prevalence of heart failure also increases, and that the decrease in eGFR is associated with all-cause mortality, cardiovascular mortality, and an increased risk of hospitalization in patients with heart failure with preserved ejection fraction (HFpEF) or heart failure with reduced ejection fraction (HFrEF).[154]

Heart failure is a multi-dimensional lesion. Changes in systemic circulation volume and blood pressure, organic changes in the heart itself, and abnormalities in

circulating endocrine metabolites are all part of it. CKD, which occurs bidirectionally with heart failure, effects all three levels above. In CKD and ESRD, as CKD progresses, blood pressure control is generally disrupted. Simultaneously, salt and water retention leading to excessive preload, and left ventricular hypertrophy (LVH) and fibrosis are expected to develop sequentially. In addition, there are CKD- and end-stage kidney disease (ESKD)-specific factors that affect cardiac systolic and diastolic capacity.[154–156] Next, we will mainly explore the mechanism of heart failure due to altered renal metabolism.

The influence of abnormal renal metabolism on circulating volume

Hypertension is one of the main causes of heart failure. Studies show that long-term hypertension (refractory hypertension/renal hypertension) is an important factor leading to heart failure,[157] and one of the most common complications of CKD is renal hypertension.[158] The retention of water and sodium caused by renal insufficiency can cause increased blood volume and increased blood pressure. In addition, the metabolites retained by the decreased renal clearance rate are also confirmed to cause hypertension. Previously, we have discussed that various kidney-related metabolites can cause endothelial dysfunction through impaired NO production. Studies show that endothelial dysfunction, oxidative stress, and elevated endothelin levels are all associated with the pathogenesis of hypertension in CKD patients.[158] Angiotensin II (Ang II) can directly constrict blood vessels, increase systemic vascular resistance and blood pressure. Jiang *et al.*[159] demonstrated that TMAO promotes Ang II-induced vasoconstriction and the consequent hypertension, which involves the protein kinase R-like endoplasmic reticulum kinase/ROS/calcium–calmodulin dependent protein kinase II/phosphatidylinositol specific phosphoesterase Cβ3 (PERK/ROS/CaMKII/PLCβ3) axis.

Anemia is a common feature of CKD, and the kidney is the main source of erythropoietin. For many years, the hypothesis that erythropoietin deficiency or resistance is the main cause of anemia in CKD patients has been confirmed.[160] Several studies show that anemia affects the prognosis of patients with heart failure.[161–163] Thus, under such pathophysiological background, several small clinical studies show that the administration of erythropoietic-stimulating agents (ESAs) to patients with anemic heart failure improves outcome events.[162] However, ESAs do not improve systolic heart failure in a large randomized, double-blind trial.[164] This indicates that anemia may not be a mechanism causing heart failure, but just a mark of heart failure.

Abnormal metabolism of the kidneys can lead to organic changes in the heart

LVH is not a disease in essence. It can be a natural response of the myocardium to aerobic exercise and strength training, but it is often a precursor to heart disease and a pathological response to CVD and hypertension. LVH is an important manifestation in the progression of heart failure, and multiple studies have shown a strong correlation between CKD and LVH.[165] Anemia, as well as sodium and water retention secondary to decreased renal function contribute to volume overload. Metabolic abnormalities associated with CKD are also shown to be risk factors for LVH. In the early stage of CKD, FGF-23 prevents the increase in serum phosphate levels, thereby attenuating phosphate-induced vascular calcification. Whereas in ESRD, FGF-23 can no longer maintain serum phosphate homeostasis. Hyperphosphatemia and elevated FGF-23 levels can promote the development of hypertension, vascular calcification, and LVH through different mechanisms.[166,167] Faul *et al.*[168] reported that chronically elevated FGF-23 level directly contributes to high LVH morbidity and mortality in CKD patients in a large, ethnically diverse CKD cohort. As renal function declines, serum phosphate levels rise, which in turn induces the secretion of the phosphate hormone FGF-23. This further stimulates FGFR, which can lead to cardiac hypertrophy, alter cardiomyocyte contractility, and increase the risk of cardiac arrhythmic events in cardiomyocytes.[169] Bao *et al.*[170] found that CKD-related factors such as FGF-23, uremic toxin, and Ang II inhibit the expression of cardiac microRNA-30, an important regulator affecting LVH. This could serve as a new therapeutic target for LVH in CKD, which is beneficial to block the induction of CKD on ventricular hypertrophy.

Another aspect of the organic change of the heart is interstitial fibrosis. Interstitial fibrosis reduces the compliance of the ventricle Since the myocardial contractility cannot exert its proper ejection effect, a vicious circle is formed. Eventually, it leads to irreversible end-stage heart failure. In clinical and animal studies, the severity of renal failure is closely and directly correlated with the degree of cardiac fibrosis.[171,172] Extensive studies point out that transforming growth factor-β1 (TGF-β1) promotes renal fibrosis through the TGF-β1/Smad signaling pathway in CKD.[173] Plus, its elevated level also induces cardiac fibrosis. Targeted therapy for this mechanism can attenuate CKD-induced cardiac fibrosis.[172]

The influence of abnormal renal metabolism on endocrine regulation

In the process of heart failure, the activation of the renin-angiotensin-aldosterone system (RAAS) is one of the neurohumoral regulation mechanisms in the compensatory period of heart failure. Although the RAAS has a compensatory effect, it will also activate and promote the remodeling of the heart and blood vessels.

This can aggravate myocardial injury and worsen cardiac function.[174] RAAS activation in CKD also increases absolute mortality and the occurrence of high-risk adverse events.[175] RAAS activation leads to increased aldosterone secretion, and aldosterone-induced downregulation of transient receptor potential melastatin 7 (TRPM7) and associated hypomagnesemia can cause CVD and kidney injury.[176] According to previous studies, TRPM7 mediates anti-inflammatory and anti-fibrotic effects through magnesium ions.[177] In recent years, there have been many studies on targeted therapy for RAAS. Chung *et al*.[178] pointed out that aldosterone antagonists can reduce proteinuria and systolic blood pressure in adults with mild to moderate CKD, but may increase the risk of hyperkalemia, acute kidney injury, and gynecological coma if combined with angiotensin converting enzyme inhibitors (ACEI) and/or angiotensin II receptor blockers (ARB). It is proved that aldosterone is an enhancer of vascular calcification progression. Hammer *et al*.[179] noticed a protective effect of aldosterone on vascular calcification in CKD in a prospective randomized controlled clinical trial. Since aldosterone acts as a mineralocorticoid, the mineralocorticoid receptor antagonists, spironolactone and eplerenone, are proved to improve both heart failure and CKD.[180] Another factor in the RAAS that can induce heart failure progression is Ang II. Studies indicate that Ang II can regulate ROS production, mitochondrial dysfunction, expression of pro-inflammatory cytokines, autophagy, apoptosis, and cardiovascular system pathogenesis including hypertension and heart failure.[181] Several clinical studies evaluate the therapeutic effect of angiotensin-neprilysin inhibition.[182,183]

There are two forms of vitamin D in the human body, vitamin D3 (cholecalciferol) and vitamin D2 (ergocalciferol). Vitamin D3 is converted to 25-hydroxyvitamin D3 (25-OH-D3) by hydroxylation in the liver, and then converted to active 1,25-(OH)2D3 in the kidney. Therefore, when kidney function is impaired, vitamin D activation will be severely affected. The role of 1,25-(OH)2D in the regulation of calcium and phosphate homeostasis is central. Heart failure is associated with decreased circulating 1,25-(OH)2D and elevated FGF-23 level.[184] Raising serum vitamin D level have beneficial effects on proteinuria, blood pressure, inflammation, and cardiovascular outcomes.[185–187] It is also pointed out that one of the mechanisms of action of vitamin D is that it serves as a negative regulator of the RAAS.[188] Another metabolic disorder brought about by CKD is secondary hyperparathyroidism.[189] Serum parathyroid hormone level correlates significantly with the severity of heart failure.[190,191] Clinically, drug treatments for this symptom, such as the benefits and harms of calcimimetic agents, are also being evaluated continuously.[192]

CONCLUSION

The synergistic effect between cardiovascular and kidney is prominent. Under pathological conditions, there is a significant correlation between a variety of CVDs and renal diseases. This pathophysiological connection between the heart and kidneys led to the first proposal of the concept of "Cardiorenal Syndrome (CRS)" by Bongartz *et al*.[193] A few years later, European scholars from many countries further refined the definition of CRS, which was divided into five subtypes. In this review, we discussed the multi-mechanism effects of the accumulation of metabolites caused by kidney disease on atherosclerosis from the whole process of atherosclerosis formation and development. These metabolites can be mainly divided into uremic toxins including UA, urea, IS, p-cresol sulfate, phosphate, and ADMA, gut-derived metabolites including TMAO and PAGln, as well as FGF-23 and the end product of advanced glycation. Then we summarized the impact of renal metabolism-related metabolites based on three different levels of biological changes manifested in patients with heart failure.

In fact, besides CAD and heart failure, metabolic abnormalities caused by kidney disease are also risk factors for other CVDs. CKD confers a risk of uremic cardiomyopathy, which is characterized by cardiac hypertrophy, fibrosis, and functional impairment.[194] Accumulating evidence suggests that increased production of FGF-23 and Klotho deficiency are potential major drivers of cardiac remodeling in patients with uremic cardiomyopathy.[195,196] Due to the adverse cardiomyopathy and vasculopathy environment in CKD, the occurrence of arrhythmias, conduction abnormalities, and sudden cardiac death may be exacerbated by electrolyte shifts, divalent ion abnormalities, diabetes, sympathetic overactivity, and inflammation and iron deposition.[197]

Cardiovascular problems and kidney diseases significantly contribute to the global medical burden. Although the etiology and pathogenic mechanism are constantly improving, there is still a long way to go for diagnosis, treatment, and prevention. Because of the inextricable connection between the heart and the kidneys, reasonable and effective treatment should be taken into consideration. A recent meta-analysis indicates a significant benefit of sodium-glucose cotransporter-2 inhibitors (SGLT2i) in reducing both heart failure hospitalizations and renal disease progression.[198] In the future, the development and application of drugs should reduce the types and quantities while achieving more comprehensive, more precise, and longer-lasting clinical effects.

DECLARATION

Author contributions

Deng SY: Conceptualization, Investigation, Resources, Writing—Original draft. Zheng LM: Writing—Review and Editing, Visualization, Supervision. Huang W: Writing—Review and Editing, Visualization, Supervision.

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The authors declare no conflict of interest.

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