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## **Renoprotective strategies**

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### **Abstract**

Kidney disease remains a condition with an increasing incidence, high morbidity and mortality associated with cardiovascular events. The incidence of end-stage renal disease is expected to increase. Despite of the technical improvement, dialysis never achieved a full clearance of the blood dialysis. Therefore, the demand for new renoprotective measures has never been greater. Here, we report new strategies for preventing renal damage.

### **INTRODUCTION**

Chronic kidney disease (CKD) is a common condition in which the renal function is gradually decreased in process of time. The declining renal function is a main risk factor for increased morbidity and mortality including the cardiovascular disease (CVD) and thend-stage of kidney disease (ESRD). Furthermore, despite the increased improvement, dialysis never achieved a full clearance of the blood. CKD is defined by the presence of some criteria, including one or more structural or functional abnormalities, such as <sup>1</sup>estimated glomerular filtration rate (eGFR) < 60 mL/min/1.73 m<sup>2</sup>, urine albumin-to-creatinine ratio (UACR) > 30 mg/g or urine albumin excretion rate > 30 mg/24 h, urine sediment abnormalities and renal tubular disorders for more than 3 mo<sup>[1,2]</sup>.

Renal insufficiency is on the rise worldwide and it is reflected on costs, which must be covered by society. In Germany have been recorded 109031 cases in 2013 *vs* 60451 cases

in 2003. Moreover, according to 2021 data, the prevalence of CKD in the United States is estimated equal to 15% (37 million adults), and older individuals (aged 65 years or more) more usually suffer from CKD comparatively to younger patients and in non-Hispanic Black people versus non-Hispanic White people or Asians<sup>[3]</sup>. CKD is usually underestimated and patient and physician awareness is observed to be low. In the ADD-CKD study of diabetic adults, primary care physician indentified only 22% of patients with stage 3–5 CKD as having CKD<sup>[4]</sup>. The potential role of both characteristics of CKD (eGFR < 60 mL/min/1.73 m<sup>2</sup> and UACR > 30 mg/g) on CKD progression, development of ESKD, CVD and mortality is also under appreciated<sup>[5,6]</sup>. Therefore, new renoprotective strategies are greatly required.

Renal damage is complex and frequently multi-factorial. A deep understanding of the underlying pathophysiological mechanisms could obtain the highlights of the acute and chronic renal injury<sup>[7]</sup>. Environmental factors including metabolic, haemodynamic perturbations<sup>[8]</sup> and drugs in combination with a genetic susceptibility promote the activation of pro-oxidative, pro-inflammatory<sup>[9]</sup> and pro-fibrotic underlined pathophysiological mechanisms<sup>[10]</sup>. The acute renal disease is closely related to the primary injury, whereas in chronic renal disease may contribute common pathways including elevated levels of reactive oxygen species, activation of protein kinase C $\beta$ , promotion of transforming growth factor $\beta$ 1, disorder of vascular growth factors (e.g. VEGF-A, angiopoietins), increased advanced glycation end products and adipocytokines. A such procedure results in increased extracellular matrix deposits, thickening of the glomerular basement membrane along with mesangial expansion. Finally, glomerular sclerosis is activated and tubulointerstitial fibrosis is elevated.

### **RENOPROTECTIVE APPROACHES**

Current renoprotective therapies leave much space for innovation. Acute kidney insufficiency (AKI) can be slowed by volume loading before contrast media exposure. Nevertheless, current approaches targeting in specific mechanisms of disease are proved unsatisfactory and therapeutic options for treating AKI still fail to significantly improve

outcomes. This may need basic research obtained by isolated cells and tissue preparation using animal models on the bedside.

In CKD, one of the major renoprotective strategy may be the strict control of hypertension, a common disorder in renal disease population. In the last 20 years, the only categories of recommended agents for diabetic or non-diabetic patients with CKD and hypertension, were angiotensin-converting enzyme inhibitors and angiotensin receptor blockers (ARBs) mainly in terms of reducing albuminuria caused by the reduction of glomerular hypertension<sup>[2]</sup>. The usage of low dietary sodium is often overlooked, but can improve BP control, especially for patients treated with the above reported agent, which blocks the renin-angiotensin system. The effect of diuretics on cardiovascular morbidity and mortality has been previously established. Chlorthalidone therapy improved blood-pressure control at 12 wk among patients with advanced CKD and poorly controlled hypertension<sup>[11,12]</sup>. Hypokalemia, hyperglycemia and hyperuricemia more frequently occurred in the group of patients with chlorthalidone compared to control group. However, hypokalemia is considered to be a desired condition in CKD patients.

Renal disorders are common in diabetics and an analysis of the United States Diabetes Collaborative Registry revealed that 20% of diabetic patients presented CKD<sup>[13]</sup>. The progression of diabetic nephropathy in patients with T2D treated with angiotensin receptor blockers was estimated to be closed to 15%–27% comparatively to placebo-treated patients over 2 years, depending on the level of baseline risk<sup>[14]</sup>. Moreover, the improved control of both hyperglycemia and hypertension and the usage of renin-angiotensin system blockers did not achieve to protect the kidney function of people with T2D<sup>[15]</sup>. Evidence is now accumulating to suggest some drugs to be potential treatments for chronic kidney disease, even though these initially were developed to treat other diseases. The sodium-glucose cotransporter 2 inhibitors, which are commonly used to lower blood sugar levels in diabetic patients, are examples of such drugs. SGLT2 inhibitors reduced the risk of deterioration of renal outcomes (permanent loss of kidney function, eGFR decline, worsening of albuminuria, new ESKD, and death from renal

causes) additionally to significant reduction of cardiovascular events risk than placebo, indicating that SGLT2 inhibitors are associated with significantly lower risk of deterioration of kidney function, due mainly to reducing of glomerular hypertension and hyperfiltration<sup>[16,17]</sup>. However, the initial studies were enclosed only 7%–26% of participants who had an eGFR less than 60 mL/min/1.73 m<sup>2</sup> and could not evaluate treatment benefits in patients with CKD<sup>[16,17]</sup>. Secondly, newer trials showed a significant reduction in the risk of CKD worsening with SGLT2 inhibitors in patients with diabetic kidney disease using canagliflozin in CREDENCE<sup>[18]</sup> and diabetic as well as nondiabetic CKD using dapagliflozin in DAPA-CKD<sup>[19]</sup>. More recently, EMPA-KIDNEY trial showed that empagliflozin therapy <sup>8</sup>resulted in a lower risk of progression of kidney disease or death from cardiovascular events compared to placebo, enrolling patients with a high risk for renal disease progression<sup>[20]</sup>.

Increased plasma aldosterone levels have been reported to be a main risk factor for renal injury and it could be improved by mineralocorticoid receptor (MR) antagonist therapy<sup>[21]</sup>. Renal endothelial dysfunction characterized by inflammatory activation, impaired vasodilation and fibrosis were induced by MR activation. <sup>2</sup>MR-mediated glomerulosclerosis may decrease the ability of capillary oxygen offer, which could finally lead in ischemic renal injuries<sup>[22]</sup>. MR blockers (spironolactone and eplerenone) may <sup>2</sup>attenuate the declined eGFR and severity of histopathological lesions resulting to an eventual protection of the patients from potential ischemic renal injuries and proteinuria. Novel, selective, nonsteroidal MR antagonists (finerenone, esaxerenone) have demonstrated therapeutic efficacy not only in hypertensive patients but also in diabetic patients with microalbuminuria leading these drugs to be the choice of medical therapy in CKD patients compared to steroid MR antagonists<sup>[23-25]</sup>. Moreover, it has been shown that aldosterone blockade with renin-angiotensin-aldosterone system inhibitors, such as ARBs, is renoprotective reducing albuminuria independently on control of hypertension<sup>[26]</sup>. Another new class of medication, aldosterone synthase inhibitors, which reduces aldosterone production by inhibiting aldosterone synthase shows promise on slowing of renal injury progression<sup>[27]</sup>.



Metabolomics has been demonstrated to be potential for identifying the mechanisms of underlying disease, facilitating clinical diagnosis and developing pharmaceutical treatments for CKD. It was revealed by recent research in metabolomics that CKD was significantly associated with the disorder of many metabolites, such as amino acids, lipids, nucleotides and glycoses. These might be important biomarkers inducing new targets for CKD treatment and renoprotection<sup>[28]</sup>.

During renal injury the generation of reactive oxygen species (ROS) and reactive nitrogen species (RNS) is elevated and an imbalance of ROS and RNS generation and excretion leads to inflammation, cell death, tissue injury and kidney disease progression<sup>[29]</sup>. In combination with chronic inflammation, the increased oxidative stress and malnutrition are associated with CKD and increased cardiovascular risk. Hypertriglyceridemia and low levels of high-density lipoprotein cholesterol (HDL-C), which are the main lipidemic disorders in CKD, are major risk factors for CVD<sup>[30]</sup>. It has been shown that dyslipidemia and lipid deposition in the kidneys over time worsen kidney function by causing damage to endothelial cells, mesangial cells, and glomerular podocytes, due to the activation of inflammatory cascade. Studies indicate that dietary polyunsaturated fatty acids might delay the onset of CKD and attenuate CVD and kidney disease progression<sup>[31]</sup>. It has been shown that treatment with statin can decrease CV events in patients with pre-end-stage CKD and in renal transplant patients, but not in those with end stage of renal disease<sup>[32]</sup>. Peroxisome proliferator-activated receptor-alpha (PPAR $\alpha$ ) levels are significantly lower in patients with CKD. Fibrates, which are PPAR $\alpha$  agonists, are therapeutic agents against hypertriglyceridemia and these could also protect renal function. However, conventional fibrates are decreased by renal metabolism, reducing their use in patients with impaired renal function. Recently, using mice in CKD it has been shown the renoprotective effects of pemafibrate, a novel selective PPAR $\alpha$  modulator which is mainly excreted into the bile<sup>[33]</sup>.

Moreover, previous study indicated that melatonin administration for 12 wk in diabetic nephropathy patients had beneficial effects on glycemic control, HDL-C, total antioxidant capacity and glutathione levels, and gene expression of peroxisome

proliferator-activated receptor gamma (PPAR- $\gamma$ )<sup>[34]</sup>. Recent study investigated if melatonin-stimulated mesenchymal stem cells (Exocue) secret exosomes with therapeutic effects on the improvement of kidney function in a CKD mouse model and it was indicated that Exocue could regulate inflammation and fibrosis and it could be a novel therapeutic agent for treating CKD<sup>[35]</sup>.

An additional renoprotective approach in CKD would be the regulation of metabolic acidosis and hyperkalemia, common characteristics in these patients. Previously, we have demonstrated that patients with low bicarbonate level should be treated properly even though they are receiving dialysis therapy due to metabolic acidosis results in detrimental effects<sup>[36]</sup>. It has already been reported the role of metabolic acidosis on vascular calcification and renal progression, due mainly to promotion of inflammation in arterial wall, releasing cytokines<sup>[37]</sup>. Increased intake of proteins leads to the production of increased load of acids due to degradation of proteins resulting in rapid decline of kidney function. Therefore, low protein diet, particularly from plant sources, may have beneficial effects on kidney function due to metabolic acidosis attenuation in CKD<sup>[38]</sup>, despite it has been also reported that higher intake of total protein was associated with a lower risk of cardiovascular morbidity<sup>[39]</sup>. In patients with CKD hyperphosphatemia is a potential risk factor for cardiovascular disease and bone disorders. Because of 1 gr of protein contains about 13 mg phosphorus, protein-rich foods are the main natural source of phosphorus intake. Such a result low protein diet could be effective for the management of hyperphosphatemia and renal and cardiovascular protection. The low serum phosphorus is associated with reductions in serum levels of parathyroid hormone and fibroblast growth factor 23 leading to a slow progression of vascular calcification, delayed worsening of renal function and improving cardiovascular outcomes<sup>[40]</sup>.

## CONCLUSION

We could conclude that renoprotection presents a wide field of approaches, including a strict control of blood pressure, diabetes mellitus management and a balanced nutritional therapy. In the modern era, new diagnostic measures using even isolated cells and novel

therapeutic strategies are developed in terms the renoprotection and reducing of kidney disease progression resulting in a decreased cardiovascular risk for morbidity and/or mortality in CKD patients.



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