Review paper

Oxidative stress mechanisms as potential therapeutic targets in chronic kidney disease

Mechanizmy stresu oksydacyjnego jako potencjalne cele terapeutyczne w przewlekłej chorobie nerek

Łukasz Dobrek

Department of Clinical Pharmacology, Wroclaw Medical University, Wroclaw, Poland
Head of the Department: Prof. Anna Wiela-Hojeńska

Medical Studies/Studia Medyczne 2022; 38 (2): 163–170
DOI: https://doi.org/10.5114/ms.2022.117714

Key words: chronic kidney disease, oxidative stress, pharmacotherapy.

Słowa kluczowe: przewlekła choroba nerek, stres oksydacyjny, farmakoterapia.

Abstract

Chronic kidney disease (CKD) is a gradual loss of kidney function over time, leading to the development of kidney failure. CKD is a consequence of common civilization diseases, such as arterial hypertension and diabetes, as well as primary kidney and urinary tract diseases of various aetiologies. The pathogenesis of CKD is complex, and the ongoing inflammation and increased oxidative stress (OS) in kidney tissues also play a significant role in the CKD pathophysiological description. Hence, attempts are being made to pharmacologically modify these important pathophysiological pathways. This article presents a brief overview of the aetiopathogenesis of OS in the course of CKD and briefly lists the research on the novel compounds with expected OS-alleviating activity in CKD based on their interference with selected pathophysiological pathways (xanthine oxidase inhibitors, nicotinamide adenine dinucleotide phosphate oxidase inhibitors, protein kinase C inhibitors, transforming growth factor β inhibitors, or activators of nuclear factor erythroid 2-related factor 2).

Streszczenie

Przewlekła choroba nerek (PChN) to postępująca utrata funkcji nerek, prowadząca do rozwoju niewydolności nerek. Przewlekła choroba nerek stanowi obecnie narastający globalny problem zdrowotny, ponieważ jest następstwem powszechnie występujących chorób cywilizacyjnych, takich jak nadciśnienie tętnicze i cukrzyca, a także pierwotnych chorób nerek i dróg moczowych o różnej etiologii. Patogeneza PChN jest złożona, a wzajemnie podtrzymujące się lokalny stan zapalny i zwiększony stres oksydacyjny w tkankach nerek również odgrywają istotną rolę w opisie patofizjologicznym PChN. W związku z tym podejmowane są próby modulacji farmakologicznej tych ważnych szlaków patofizjologicznych. W artykule przedstawiono zarys etiopatogenezy stresu oksydacyjnego w przebiegu PChN oraz pokrótce wymieniono badania nad nowymi związkami o spodziewanym działaniu łagodzącym wspomniane zaburzenie w wyniku ich ingerencji w patomechanizmy stresu oksydacyjnego (inhibitory oksydazy ksantynowej, inhibitory oksydazy fosforanu dinukleotydu nikotynamidoadeninowego, inhibitory kinazy białkowej C, inhibitory transformującego czynnika wzrostu β lub aktywatory szlaków zależnych od czynnika transkrypcyjnego Nrf2).

Introduction

Chronic kidney disease (CKD) is a leading health problem worldwide, especially in developed countries. According to the data published by the Centres for Disease Control and Prevention in 2021, more than 1 in 7, i.e. 15% of US adults (about 37 million people), are estimated to have CKD [1]. According to official data, there were 4,335,349 cases of CKD in Poland in 2017 and there were 649.2–752.1 million people with CKD in the world. Thus, the global prevalence of CKD was estimated as 9.1% of the world's population [2].

CKD is diagnosed on the basis of commonly accepted guidelines of the National Kidney Foundation (NKF) Kidney Disease Outcome Quality Initiative (KDOQI) Group. According to the former KDOQI guidelines released in 2002, CKD was defined as kidney damage for ≥ 3 months, as defined by structural or functional abnormalities of the kidney, with or without decreased GFR, manifested by either pathological abnormalities or markers of kidney damage, including abnormalities in the composition of the blood or urine, or abnormalities in imaging tests. In the abovementioned guidelines, another diagnostic criterion for

the diagnosis of CKD was GFR < 60 ml/min/1.73 m^2 for ≥ 3 months, with or without kidney damage [3]. In line with KDOQI 2012 guidelines, which are still in force, CKD is defined as abnormalities of kidney structure or function, present for > 3 months, with implications for health. The detailed criteria for CKD involve the GFR decrease < 60 ml/min/1.73 m^2 with/or the presence of one or more markers of kidney damage (albuminuria, urine sediment abnormalities, electrolyte and other abnormalities due to tubular disorders, abnormalities detected by histology, structural abnormalities detected by imaging, history of kidney transplantation) present for > 3 months [4]. The KDIGO Consensus Conference recently convened in June 2019, held on as the unchained the criteria for CKD (markers of kidney damage or GFR < 60 ml/min per 1.73 m^2 for > 3 months). The updated guidelines recommend that ascertainment of CKD, its severity, and prognosis should be based on the cause of disease, level of GFR (6 categories), and level of albuminuria (3 categories), collectively known as the CGA classification, rather than on GFR alone. Moreover, the albuminuria and GFR categories have been grouped into 4 risk categories (usually portrayed as a "heat map") according to their associations with risks for various outcomes (all-cause and cardiovascular mortality, kidney failure requiring replacement therapy, AKI and CKD progression) [5].

The clinical presentation of CKD in the stage of kidney failure is very rich and involves systemic symptoms and developing complications originating from the following: skin (e.g. pallor, itching), cardiovascular (hypertension, pericarditis, heart failure), respiratory (pulmonary congestion and oedema), digestive (gastroduodenitis, peptic ulcer disease), nervous (impaired intellectual and emotional functions, sleep disorders, polyneuropathy), and endocrine disorders (fertility disorders, secondary hyperparathyroidism, hyperphosphataemia, osteodystrophy) and general symptoms (hypothermia, electrolyte disturbances, immune disorders). The main aetiological factors of CKD are hypertensive nephropathy and diabetic nephropathy as well as diseases primarily affecting the kidneys and urinary tract, such as: chronic glomerulonephritis, tubulointerstitial nephritis, polycystic kidney disease, ischaemic nephropathy, and obstructive uropathy. The rare causes involve systemic connective tissue disease, sarcoidosis, or amyloidosis. The pathophysiology of CKD is complex, related to inflammatory, immune, and metabolic disturbances. Briefly, CKD pathogenesis involves gradual, irreversible structural loss of the nephrons, with hyperfiltration, and pressure overload of the remaining nephrons. These dysfunctions, along with the ongoing inflammation, finally lead to glomerular hypertrophy and sclerosis, and progressive fibrosis of the kidney interstitial tissue [6, 7].

Oxidative stress and low-grade inflammation in chronic kidney disease

One of the hallmarks of the pathogenesis of CKD resulting in its development, progression, and complications is low-grade ongoing inflammation that is inseparably linked to oxidative stress (OS), because reactive oxygen species (ROS) and reactive nitrogen species (RNS) are regarded as inflammatory mediators and there is a crosstalk between pathways of inflammation and OS. The ongoing inflammatory reaction is due to the presence of resident immune cells, including dendritic cells, macrophages, regulatory T lymphocytes, lymphocytes CD8, and NK, which are in close relationship with the renal parenchymal cells. Once activated by the events related to the baseline disease affecting the kidneys, these cells start the secretion of the inflammatory mediators initiating kidney response. In the course of CKD, the inflammatory-trigering factors involve metabolic acidosis development, intestinal dysbiosis and gut microbiota translocation into systemic circulation with subsequent triggering kidney inflammatory response, impaired kidney elimination of endogenous toxins (indoxyl sulphate, paracresyl sulphate, asymmetric dimethylarginine), external noxious stimuli, and dialysis-related factors that still sustain the response [8].

Thus, under a low-grade inflammation of the kidney, a chronic and persistent activation of the immune cells occurs, which results in consequent ROS/RNS production. Besides chronic inflammation, with subsequent activation of the myeloperoxidase of neutrophils and macrophages, there are also other mechanisms co-responsible for the increased oxidative stress in CKD. They involve mitochondrial sources of ROS: oxidative phosphorylation, uncoupling of the respiratory chain (misutilization of the electrons for heat and ROS production instead of ATP production), and cytosolic ones: deficiency of glucose-6-phosphate dehydrogenase, overactivity of NADPH oxidase, myeloperoxidase and xanthine oxidase, eNOS uncoupling due to restricted L-arginine availability, or the absence of cofactors (flavinmononucleotide, bihydrobiopterin, calmodulin, flavin adenine dinucleotide), along with the impairment and deficit of the antioxidant systems. The increased mitochondrial ROS/RNS generation is reported in CKD patients, especially in diabetic nephropathy [9]. Similarly, RAA system overactivation and angiotensin II action are factors enhancing oxidative stress because angiotensin II contributes to ROS production through NAPDH oxidase [10]. The next important issue is the endothelial nitric oxidase (eNOS) uncoupling in the kidney, induced by uremic toxins (e.g. asymmetric dimethylarginine). It leads to peroxynitrite overproduction, which, in turn, further inhibits eNOS activity. The reduced nitric oxide synthesis results in the tendency of vasoconstriction and consequent GFR reduction [11]. The other

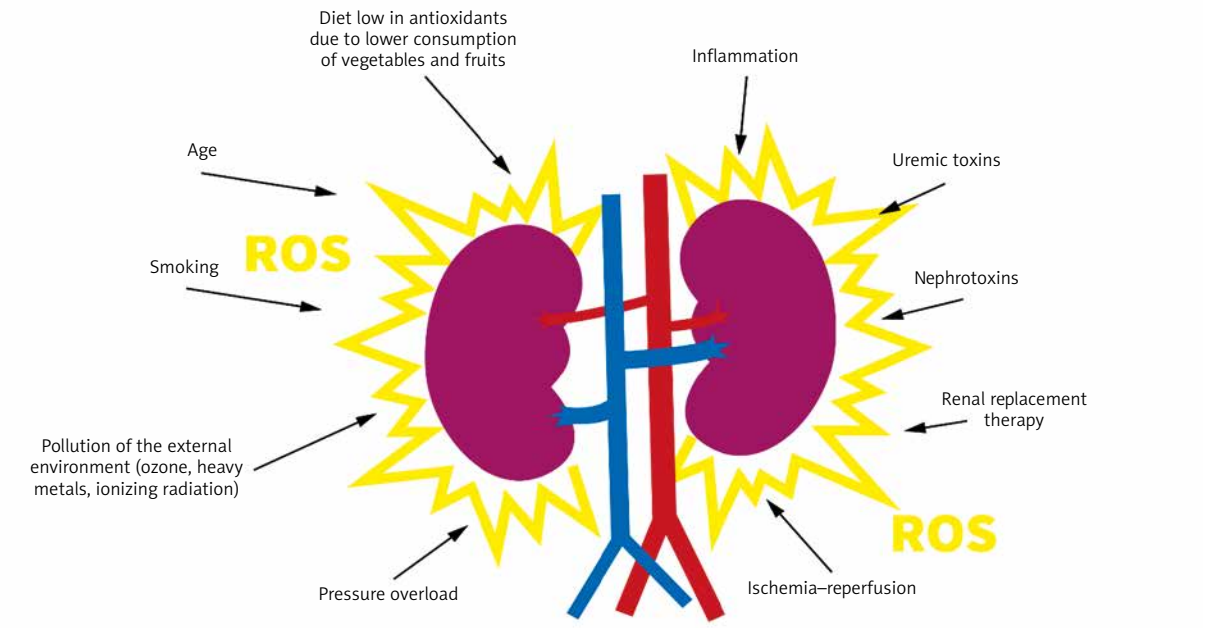

Figure 1. The aetiology of oxidative stress in chronic kidney disease

well-described mechanism favouring increased stress in the kidney is increased xanthine oxidase or myeloperoxidase activity [12].

The abovementioned mechanisms are accompanied by the decreased activity of kidney antioxidants. It was reported that the expression of kidney superoxide dismutase – a key enzyme responsible for the detoxification of free radicals – is decreased in CKD. Moreover, it was demonstrated along with insufficiency of the GSH antioxidant system and selenium deficiency [13]. The listed mechanisms are initiated by some of the external and internal factors, which are given in Figure 1. It is worth mentioning that renal replacement therapy with the haemodialysis process itself is an important source of OS because ROS/RNS are excreted by phagocytes settling on the surface of the dialysis membrane due to the bioincompatibility. Similarly, peritoneal dialysis session also triggers OS due to the bioincompatibility and high osmolality of dialysis solutions, low pH, and loss of water-soluble vitamins and trace elements in the filtrate. The supplementary OS-generating factor in CKD patients is dietary restrictions with reduced consumption of potassium-rich vegetables and fruits, which contributes to a reduced intake of antioxidants [9].

The action of ROS/RNS affects all of the kidney elements: renal microcirculation, glomerulus, renal tubules, and interstitial tissue. ROS, acting synergistically with inflammation mediators cause the remodeling of kidney tissues resulting in tubulointerstitial inflammation and fibrosis, tubular atrophy, glomerulosclerosis, and renal vasculopathy. It was shown that OS plays an important role in CKD progression, originating from diabetic nephropathy, glomerulonephritis, tubulointerstitial inflammation, or chronic renal allograft dysfunction. As mentioned above, oxidative stress impairs renal blood flow because it causes vasocontraction of the vascular smooth muscle cells. It is accompanied by impairment of the endothelial nitric oxide synthase activity, leading to the decrease of the vasoactive NO [13]. In kidney mesangium, the excessive ROS/RNS production activates the signalization pathway associated with protein kinase C (PKC), protein kinase B (PKB), and c-Jun-N-terminal kinase (JNK), which results in the phenotypic transformation into fibroblasts [14]. Moreover, an increased local synthesis of transforming growth factor β (TGF-β), as previously mentioned, accounts for the increased collagen and fibronectin synthesis. These phenomena finally lead to glomerular fibrosis [13]. Moreover, in the glomeruli mesangial cell expansion, contraction of the glomerular tuft occurs, which also contributes to filtration barrier damage. ROS/RNS also directly affect the glomerular filtration barrier because these molecules contribute to autophagy and apoptosis of the podocytes, and the damage of the barrier is further intensified by the release of the other inflammatory mediators by neutrophils and monocytes/macrophages. The changes exclude functionally damaged glomeruli, so the remaining ones are hyperfiltrated, resulting in global glomerulosclerosis [13]. In the renal tubules, the proximal coins are the location with the most accentuated oxidative stress, because this part of the nephron is characterized by high oxygen

consumption for ATP production, necessary for active pumps (e.g. 2Na/3K antiport) activity, but without the ability to synthetize oxido-protective glutathione. ROS/RNS can influence the expression of some of the active systems (e.g. Na/H antiport) thus causing decreased sodium reabsorption [13, 14]. In the other part of the nephron, ROS/RNS may act in the opposite manner, contributing to enhanced sodium reabsorption. In the ascending part of the Henle loop oxidative stress stimulates the 2Na/3K antiport and Na/K/2Cl co-transporter activity. In turn, at the level of distal tubules, the sodium channel sensitive to amiloride (ENaC) activity is increased [13]. Ultimately, taking all these facts together, it can be concluded that excessive oxidative stress favors sodium retention. Furthermore, similar to glomerulus, increased production of extracellular matrix, loss of the tubular transport properties, and phenotypic transformation to the fibroblasts takes place. Finally, fibrosis of the renal parenchyma occurs, which is responsible for the progression of kidney failure and acceleration of achieving the ERSD phase. Exposure of the renal tubular cells to aggravated oxidative stress leads to their senescence and apoptosis (as a result of oxidation and activation of caspase 3 and 8) or necrosis (due to the stimulation of the [ADP-rybose]-polymerase 1) [13, 14]. To sum up, the OS occurrence in CKD already starts in the early phase of CKD as a part of the inflammatory process, and leads to the acceleration of the disease and its progression to the ESRD stage. It is worth noting that early histopathological abnormalities in kidneys may occur without significant clinical presentation due to the high adaptability of the kidney, and once the adaptive threshold is reached, the symptoms of kidney injury rapidly progress. Furthermore, there are also systemic consequences of inflammatory and oxidative damage that take place in the kidneys. Many inflammatory compounds act as mediators of kidney-circulatory system cross-talk, which results in the reciprocal dysfunction and cardio-renal syndrome development. The common denominator of these diseases is OS-induced endothelial dysfunction and the increased risk of cardiovascular disease development. Thus, the process of atherosclerosis is exaggerated [15]. The other OS-related cardiovascular entity in CKD patients is the aggravation of hypertension and cardiac hypertrophy. Cardiac hypertrophy is intrinsically arrhythmogenic, it reduces the coronary flow reserve, increases cardiac oxygen consumption, and is strongly associated with diastolic dysfunction. Taking all these facts together, cardiac hypertrophy is a predictor of increased cardiovascular mortality in CKD patients [9]. CKD patients often present other comorbidities related to OS, like dyslipidaemia, diabetes mellitus, or vascular calcification. ROS are also genotoxic and therefore may contribute to the higher malignancy rate in CKD patients [15]. Lastly, OS in the course of CKD may also predispose to neurological disturbances (as a result of oxidation of myelin), anaemia (due to the decrease of the erythrocyte lifespan), and hormonal abnormalities (e.g. exacerbation of parathyroid-related bone disorders) [15].

Potential future options for pharmacological mitigation of kidney damage induced by oxidative stress

Because a growing body of evidence clearly suggests a role of oxidative stress in the pathogenesis of CKD, the obvious pharmacological possibility of influencing the mechanisms of oxidative stress and its reduction is the use of agents characterised by antioxidant activity (e.g. vitamin E – α-tocopherol, vitamin C – ascorbic acid, coenzyme Q10 or plant-derived compounds (e.g. quercetin, curcumin, resveratrol)). However, there are also approaches to adopt some agents, selectively targeting a specific molecular mechanism of inflammation and OS, such as allopurinol and other xanthine oxidase inhibitors, NADPH oxidase inhibitors, agents targeting and enhancing the activity of nuclear factor erythroid 2-related factor (Nrf2), protein kinase C inhibitors, or TGF-β inhibitors [16]. The selected studies relating to the use of the abovementioned compounds are listed in Table 1 [17–38].

Although these antioxidant therapies seem promising, their use is controversial and none of these molecules are routinely used in clinical practice for treatment of CKD patients. There are certain limitations of antioxidant therapy, which affects their importance in therapy. The results of different studies are divergent. Mostly, the results of *in vitro* studies confirm the ability of some antioxidants to detoxify harmful oxidants. However, these pre-clinical studies are not always confirmed in clinical trials. A possible explanation of this is that *in-vitro* studies are isolated and without a holistic nature. Also, the pre-clinical *in-vivo* studies, mostly performed in rodents, sometimes show discrepancies in translation into CKD patients, perhaps due to the use of different experimental CKD models, which may not fully reflect the pathophysiological conditions in each CKD patient. It seems that clinical trials evaluating the efficacy and safety of the antioxidant therapy should cover the selected CKD patients with confirmed oxidative stress, because this cohort would fulfill an ideal criteria "intention to treat" study. Because there are some methodological differences between the conducted studies, the results remain inconclusive and require further investigation to unequivocally assess the clinical usefulness of antioxidant therapy in patients with CKD. Moreover, it is likely that multi-drug therapy, i.e. joint, simultaneous administration of several antioxidants, is required to modify numerous mechanisms that develop during CKD, e.g. decrease of lipid peroxidation (by vitamin E supplementation), glutathione redox improvement

Table 1. The selected compounds targeted the specific inflammatory and oxidative stress mechanisms studied for their usefulness in CKD treatment. The brief rationale for use and examples of studies (both confirming – "for" and questioning – "against" the legitimacy of the use) evaluating the efficacy of the selected compounds are given

Variable	Short rationale for use	Efficacy evaluation studies (both confirming – "for" and questioning – "against" the legitimacy of the use)
Xanthine oxidase (XO) inhibitors:		
Allopurinol (first XO inhibitor generation) Febuxostat, topiroxostat (second XO inhibitor generation)	XO were shown to have antioxidant actions by scavenging $OH^{\bullet}$ as well as chlorine dioxide and HOCl in addition to its enzyme inhibitory activities and decrease of uric acid. It is unclear if potential reno-protective XO action is via anti-oxidant and anti-inflammatory mechanisms [17]	For: In hyperuricemic CKD patients treatment with allopurinol (150 mg/day for 8 weeks), improved both oxidative stress (measured by oxidised LDL, advanced oxidation protein products and nitrothyrosine serum levels) and endothelial dysfunction (ED), and after ceasing allopurinol treatment, ED and OS again worsened with an increase in serum uric acid levels [18]. In CKD patients treated with allopurinol (100 mg/day for 4 weeks), a decrease of serum uric acid and malondialdehyde (MDA) and total antioxidant activity were demonstrated, and these findings were associated with the improvement of endothelial function [19]. Against: in an experimental, *in vitro* study, rat serum obtained after oral administration of allopurinol (100 mg/kg; 2 doses) did not suppress linolenic acid peroxidation more than a control rat serum [20].
Nicotinamide adenine dinucleotide phosphate (NADPH) oxidase (NOX) inhibitors:		
Setanaxib (GKT137831) a dual NOX1 and NOX4 inhibitor APX-115 a pan-NOX inhibitor	NOX-1 and -4 were found in kidneys, with a high expression in renal vessels, glomeruli, and podocytes, the thick ascending limb of the loop of Henle, distal tubules, collecting ducts, and cortical interstitial fibroblasts. NOX are upregulated in CKD, thus NOX signaling pathways are an expected site of possible pharmacological modulation [21]	For: In an experimental mouse model of diabetic nephropathy setanaxib exhibited renoprotective effects by attenuating glomerular structural changes, podocyte loss, extracellular matrix accumulation, and albuminuria, and these effects were accompanied by a reduction of NOX activity [22, 23]. In an experimental model of diabetic mice nephropathy, administration of APX-115 leading to NOX inhibition in kidneys resulted in OS decrease as measured by plasma 8-isoprostane level. All lipid profiles, both in plasma and tissues improved and decreased urinary albumin excretion was also demonstrated with preserved creatinine level [24].
Activators of nuclear factor erythroid 2-related factor 2 (Nrf2) pathways:		
Bardoxolone methyl (a synthetic triterpenoid derived from oleanolic acid; activates Nfr2 by binding to specific cysteine residues on Keap1)	Nrf2 is the key regulator of the cellular antioxidant defense system. Factors inhibiting NF-κB system and upregulating Nrf2 signaling and leading to transcription of antioxidant genes are essential for protecting against oxidative stress. The Nrf2-Keap1 system also inhibits NF-κB-mediated OS, fibrosis, and interstitial inflammation [25, 26]	For: In mesangial cells treated with bardoxolone methyl, increased expression of the Nrf2 target genes encoding heme-oxygenase-1 and NADPH dehydrogenase, and thioredoxin was observed. In proximal tubular epithelial cells, glomerular endothelial cells, and podocytes, bardoxolone methyl was also shown to induce Nrf2 targets, as well as attenuate NF-kB activation [25]. In a clinical study of diabetic patients with CKD treated with bardoloxone methyl (25 mg daily for 28 days followed by 75 mg for another 28 days), a significant increase in eGFR correlated with a decrease in blood urea nitrogen level was revealed, and these effects were accompanied by reduced vascular dysfunction and systemic inflammation [27]. Against: In an experimental study, Zucker diabetic fatty rats (model of diabetic nephropathy) treated with an analogue of bardoxolone methyl demonstrated severe changes in food intake and diuresis with a decline in body weight, worsening of dyslipidaemia, and an increase in blood pressure, and did not display beneficial effects on proteinuria, glomerulosclerosis, and interstitial inflammation [28].

Table 1. Cont.

Variable	Short rationale for use	Efficacy evaluation studies (both confirming – "for" and questioning – "against" the legitimacy of the use)
Protein kinase C (PKC) inhibitors:		
Ruboxistaurin	PKC activation results in tissue damage through many mechanisms including activation of an extracellular signal-regulated kidney pathways and activation of NADPH leading to increased oxidative stress. The disturbances of PKC pathways were revealed mostly in diabetic CKD patients [29]	For: In an experimental study in animal models of diabetic nephropathy, ruboxistaurin normalized glomerular hyperfiltration, decreased urinary albumin excretion, preserved renal function, and reduced mesangial expansion, glomerulosclerosis, and tubulointerstitial fibrosis [30]. In a clinical study of patients with type 2 diabetes and persistent albuminuria treated with ruboxistaurin (32 mg/day for 1 year), administration of ruboxistaurin reduced albuminuria and maintained eGFR over 1 year [31]. Against: clinical trials evaluating the effectiveness of ruboxistaurin were divergent. One of the studies showed that the ruboxistaurin-treated patients had greater incidence of diabetic retinopathy development [32]. Another study showed that there were no differences in diabetic retinopathy in the ruboxistaurin-treated and placebo groups [33].
Transforming growth factor β (TGF-β) inhibitors:		
Pirfenidone	Pirfenidone was introduced as a TGF-β inhibitor used in idiopathic pulmonary fibrosis. The compound is undergoing experimental and clinical trials for kidney fibrosis and other disorders (e.g. primary sclerosing cholangitis, neurofibromatosis). Pirfenidone exerted anti-fibrotic, anti-inflammatory, and anti-oxidant effects because it inhibits NADPH-dependent microsomal lipid peroxidation and scavenges hydroxyl radicals [34, 35]	For: In patients with idiopathic and postadaptive focal segmental glomerulosclerosis treated with pirfenidone, an improvement of GFR with no effect on proteinuria was demonstrated [36]. In an experimental study by Dahl on salt-sensitive rats (animal model of hypertension-induced renal injury) pirfenidone treatment significantly attenuated proteinuria and improved renal fibrosis via the downregulation of TGFβ-Smad2/3 signaling, improvement of MMP9/TIMP1 balance, and suppression of fibroblast proliferation. Pirfenodine administration also increased CAT expression and total serum antioxidant activity [37]. In an experimental unilateral ureteral obstruction (UUO) rat model, tubulointerstitial fibrosis, apoptosis of renal tubular epithelial cells, tubular and the content of MDA were increased in the UUO group and were ameliorated significantly by pirfenidone treatment. Moreover, the activity of SOD was decreased in the UUO group, but it was increased by pirfenidone treatment, and these results showed that pirfenidone could ameliorate tubulointerstitial fibrosis by reducing the apoptosis and oxidative stress [38].

(by N-acetylcysteine administration), mitochondrial dysfunction (coenzyme Q10), a decrease in uremic toxin synthesis (by allopurinol), or attenuation of inflammatory mechanisms (by targeted therapy) [39]. Finally, the effectiveness of antioxidant therapy depends on the extent to which OS contributes to the pathogenesis of CKD in a given patient. Meanwhile, OS and inflammation coexist, being a cause and a consequence of each other, and are part of a comprehensive pathogenesis, including disorders not corrected by therapy aimed at reducing OS or inflammation. The above-mentioned limitation challenges the ability to apply the antioxidant strategies in routine clinical practice [40].

On a margin, it is worth mentioning that the drugs with an established pharmacotherapeutic position, which exert pleiotropic mechanisms of action and are used in the pharmacotherapy of various disorders, are also characterized by exerting an anti-inflammatory effect and the ability to reduce OS. Thus, these drugs may also play a nephroprotective role. β-blockers, angiotensin-converting enzyme inhibitors, angiotensin II AT1 receptor antagonists, direct renin inhibitors, and statins should be mentioned among these drugs.

To sum up, due to the complex nature of the oxidative stress integrally related to the inflammatory response, the antioxidant therapy and pharmacological therapy targeted to specific inflammatory and OS pathways seem to be rational and effective. However, it should be concluded that despite the involvement of antioxidant therapies, they have not become a standard therapeutic option in CKD, and none of the study molecules have yet been introduced into wide clinical, routine practice. Some reservations concerning both the pre-clinical and clinical research performed to date exist, e.g. low sample size, biodisponibility, and short follow-up. Thus, future prospective and comparative studies with long follow-up are needed.

Conflict of interest

The author declares no conflict of interest.

References

1. Centers for Disease Control and Prevention. Chronic Kidney Disease in the United States in 2021; https://www.cdc.gov/kidneydisease/publications-resources/CKD-national-facts.html (accessed 2/16/2022).
2. GBD Chronic Kidney Disease Collaboration. Global, regional, and national burden of chronic kidney disease, 1990-2017: a systematic analysis for the Global Burden of Disease Study 2017. Lancet 2020; 395: 709-733.
3. National Kidney Foundation. K/DOQI clinical practice guidelines for chronic kidney disease: evaluation, classification, and stratification. Am J Kidney Dis 2002; 39 (2 Suppl 1): S1-266.
4. KDIGO 2012 Clinical Practice Guideline for the Evaluation and Management of Chronic Kidney Disease. Kidney Int Suppl 2013; 3: 19-62.
5. Levey AS, Eckardt KU, Dorman NM, Christiansen SL, Hoorn EJ, Ingelfinger JR, Inker LA, Levin A, Mehrotra R, Palevsky PM, Perazella MA, Tong A, Allison SJ, Bockenhauer D, Briggs JP, Bromberg JS, Davenport A, Feldman HI, Fouque D, Gansevoort RT, Gill JS, Greene EL, Hemmelgarn BR, Kretzler M, Lambie M, Lane PH, Laycock J, Leventhal SE, Mittelman M, Morrissey P, Ostermann M, Rees L, Ronco P, Schaefer F, St Clair Russell J, Vinck C, Walsh SB, Weiner DE, Cheung M, Jadoul M, Winkelmayer WC. Nomenclature for kidney function and disease: report of a Kidney Disease: Improving Global Outcomes (KDIGO) Consensus Conference. Kidney Int 2020; 97: 1117-1129.
6. Kakitapalli Y, Ampolu J, Madasu SD, Sai Kumar MLS. Detailed review of chronic kidney disease. Kidney Dis 2020; 6: 85-91.
7. Chen TK, Knicely DH, Grams ME. Chronic kidney disease diagnosis and management: a review. JAMA 2019; 322: 1294-1304.
8. Mihai S, Codrici E, Popescu ID, Enciu AM, Albulescu L, Necula LG, Mambet C, Anton G, Tanase C. Inflammation-related mechanisms in chronic kidney disease prediction, progression, and outcome. J Immunol Res 2018; 2018: 2180373.
9. Gyuraszova M, Gurecka R, Babickova J, Tothova L. Oxidative stress in the pathophysiology of kidney disease: implications for noninvasive monitoring and identification of biomarkers. Oxid Med Cell Longev 2020; 2020: 5478708.
10. Ramalingam L, Menikdiwela K, LeMieux M, Dufour JM, Kaur G, Kalupahana N, Moustaid-Moussa N. The renin angiotensin system, oxidative stress and mitochondrial function in obesity and insulin resistance. Biochim Biophys Acta Mol Basis Dis 2017; 1863: 1106-1114.
11. Six I, Flissi N, Lenglet G, Louvet L, Kamel S, Gallet M, Massy ZA, Liabeuf S. Uremic toxins and vascular dysfunction. Toxins 2020; 12: 404.
12. Gondouin B, Jourde-Chiche N, Sallee M, Dou L, Cerinim C, Loundou A, Morange S, Berland Y, Burtey S, Brunet P, Guieu R, Dussol B. Plasma xanthine oxidase activity is predictive of cardiovascular disease in patients with chronic kidney disease, independently of uric acid levels. Nephron 2015; 131: 167-174.
13. Podkowińska A, Formanowicz D. Chronic kidney disease as oxidative stress- and inflammatory-mediated cardiovascular disease. Antioxidants 2020; 9: 752.
14. Ratliff BB, Abdulmahdi W, Pawar R, Wolin MS. Oxidant mechanisms in renal injury and disease. Antioxid Redox Signal 2016; 25: 119-146.
15. Krata N, Zagożdżon R, Foroncewicz B, Mucha K. Oxidative stress in kidney diseases: the cause or the consequence? Arch Immunol Ther Exp 2018; 66: 211-220.
16. Verma S, Singh P, Khurana S, Ganguly NK, Kukreti R, Saso L, Rana DS, Taneja V, Bhargava V. Implications of oxidative stress in chronic kidney disease: a review on current concepts and therapies. Kidney Res Clin Pract 2021; 40: 183-193.
17. Okafor ON, Farrington K, Gorog DA. Allopurinol as a therapeutic option in cardiovascular disease. Pharmacol Ther 2017; 172: 139-150.
18. Yelken B, Caliskan Y, Gorgulu N, Altun I, Yilmaz A, Yazici H, Oflaz H, Yildiz A. Reduction of uric acid levels with allopurinol treatment improves endothelial function in patients with chronic kidney disease. Clin Nephrol 2012; 77: 275-282.

19. Mohan PR, Sujith TR, Desai M, Kolla PK, Madhavulu B, Ramalingam K. Allopurinol improves endothelial function and oxidative stress in patients with chronic kidney disease. JMST 2013; 2: 8-12.
20. Klein AS, Joh JW, Rangan U, Wang D, Bulkley GB. Allopurinol: discrimination of antioxidant from enzyme inhibitory activities. Free Radic Biol Med 1996; 21: 713-717.
21. Gill PS, Wilcox CS. NADPH oxidases in the kidney. Antioxid. Redox Signal 2006; 8: 1597-1607.
22. Gorin Y, Cavaglieri RC, Khazim K, Lee DY, Bruno F, Thakur S, Fanti P, Szyndralewiez C, Barnes JL, Block K, Abboud HE. Targeting NADPH oxidase with a novel dual Nox1/Nox4 inhibitor attenuates renal pathology in type 1 diabetes. Am J Physiol Renal Physiol 2015; 308: F1276-F1287.
23. Jha JC, Gray SP, Barit D, Okabe J, El-Osta A, Namikoshi T, Thallas-Bonke V, Wingler K, Szyndralewiez C, Heitz F, Touyz RM, Cooper ME, Schmidt HH, Jandeleit-Dahm KA. Genetic targeting or pharmacologic inhibition of NADPH oxidase nox4 provides renoprotection in long-term diabetic nephropathy. J Am Soc Nephrol 2014; 25: 1237-1254.
24. Cha JJ, Min HS, Kim KT, Kim JE, Ghee JY, Kim HW, Lee JE, Han JY, Lee G, Ha HJ, Bae YS, Lee SR, Moon SH, Lee SC, Kim G, Kang YS, Cha DR. APX-115, a first-in-class pan-NADPH oxidase (Nox) inhibitor, protects db/db mice from renal injury. Lab Invest 2017; 97: 419-431.
25. Ruiz S, Pergola PE, Zager RA, Vaziri ND. Targeting the transcription factor Nfr2 to ameliorate oxidative stress and inflammation in chronic kidney disease. Kidney Int 2013; 83: 1029-1041.
26. Uddin MJ, Kim EH, Hannan MA, Ha HH. Pharmacotherapy against oxidative stress in chronic kidney disease: promising small molecule natural products targeting Nrf2-HO-1 signaling. Antioxidants 2021; 10: 258.
27. Pergola PE, Krauth M, Huff JW, Ferguson DA, Ruiz S, Meyer CJ, Warnock DG. Effect of bardoxolone methyl on kidney function in patients with T2D and stage 3b-4 CKD. Am J Nephrol 2011; 33: 469-476.
28. Zoja C, Corna D, Nava V, Locatelli M, Abbate M, Gaspari F, Carrara F, Sangalli F, Remuzzi G, Benigni A. Analogs of bardoxolone methyl worsen diabetic nephropathy in rats with additional adverse effects. Am J Physiol Renal Physiol 2013; 304: F808-F819.
29. Swaminathan S, Shah SV. Novel approaches targeted toward oxidative stress for the treatment of chronic kidney disease. Curr Opin Nephrol Hypertens 2008; 17: 143-148.
30. Anderson PW, McGill JB, Tuttle KR. Protein kinase C beta inhibition: the promise for treatment of diabetic nephropathy. Curr Opin Nephrol Hypertens 2007; 16: 397-402.
31. Tuttle KR, Bakris GL, Toto RD, McGill JB, Hu K, Anderson PW. The effect of ruboxistaurin on nephropathy in type 2 diabetes. Diabetes Care 2005; 28: 2686-2690.
32. PKC-DRS2 Group, Aiello LP, Davis MD, Girach A, Kles KA, Milton RC, Sheetz MJ, Vignati L, Zhi XE. Effect of ruboxistaurin on visual loss in patients with diabetic retinopathy. Ophthalmology 2006; 113: 2221-2230.
33. Tuttle KR, McGill JB, Haney DJ, Lin TE, Anderson PW, PKC-DRS, PKC-DMES and PKC-DRS 2 Study Groups. Kidney outcomes in long-term studies of ruboxistaurin for diabetic eye disease. Clin J Am Soc Nephrol 2007; 2: 631-636.
34. Shah PV, Balani P, Lopez AR, Nobleza CMN, Siddiqui M, Khan S. A review of pirfenidone as an anti-fibrotic in idiopathic pulmonary fibrosis and its probable role in other diseases. Cureus 2021; 13: e12482.
35. Cho ME, Kopp JB. Pirfenidone: an anti-fibrotic therapy for progressive kidney disease. Expert Opin Investig Drugs 2010; 19: 275-283.
36. Cho ME, Smith DC, Branton MH, Penzak SR, Kopp JB. Pirfenidone slows renal function decline in patients with focal segmental glomerulosclerosis. Clin J Am Soc Nephrol 2007; 2: 906-913.
37. Ji X, Naito Y, Weng H, Ma X, Endo K, Kito N, Yanagawa N, Yu Y, Li J, Iwai N. Renoprotective mechanisms of pirfenidone in hypertension-induced renal injury: through anti-fibrotic and anti-oxidative stress pathways. Biomed Res 2013; 34: 309-319.
38. Li D, Zeng H, Ji C. Effect of pirfenidone on renal tubulointerstitial fibrosis. Front Med China 2009; 3: 316-322.
39. Small DM, Coombes JS, Bennett N, Johnson DW, Gobe GC. Oxidative stress, antioxidant therapies and chronic kidney disease. Nephrology 2012; 17: 311-321.
40. Forman HJ, Zhang H. Targeting oxidative stress in disease: promise and limitations of antioxidant therapy. Nat Rev Drug Discov 2021; 20: 689-709.

Address for correspondence:

Łukasz Dobrek MD, PhD
Department of Clinical Pharmacology
Wroclaw Medical University
Wroclaw, Poland
Phone: +48 71 7840595
E-mail: lukasz.dobrek@umed.wroc.pl