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Review

Chronic kidney disease: Which role for xanthine oxidoreductase activity and products?

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ABSTRACT

The present review explores the role of xanthine oxidoreductase (XOR) in the development and progression of chronic kidney disease (CKD). Human XOR is a multi-level regulated enzyme, which has many physiological functions, but that is also implicated in several pathological processes. The main XOR activities are the purine catabolism, which generates uric acid, and the regulation of cell redox state and cell signaling, through the production of reactive oxygen species. XOR dysregulation may lead to hyperuricemia and oxidative stress, which could have a pathogenic role in the initial phases of CKD, by promoting cell injury, hypertension, chronic inflammation and metabolic derangements. Hypertension is common in CKD patients and many mechanisms inducing it (upregulation of renin-angiotensin-aldosterone system, endothelial dysfunction and atherosclerosis) may be influenced by XOR products. High XOR activity and hyperuricemia are also risk factors for obesity, insulin resistance, type 2 diabetes and metabolic syndrome that are frequent CKD causes. Moreover, CKD is common in patients with gout, which is characterized by hyperuricemia, and in patients with cardiovascular diseases, which are associated with hypertension, endothelial dysfunction and atherosclerosis. Although hyperuricemia is undoubtedly related to CKD, controversial findings have been hitherto reported in patients treated with urate-lowering therapies.

1. Introduction

Chronic kidney disease (CKD) is characterized by a high urinary albumin/creatinine ratio and a low estimated glomerular filtration rate (eGFR) based on measurement of serum creatinine. These parameters allow to graduate the seriousness of the disease, distinguishing five stages. However, most patients are unaware of their condition until the disease reaches its higher stages. CKD has a higher diffusion in low- and middle-income than in high-income countries. Also, genetic factors may contribute to CKD risk [1].

Although a higher prevalence of CKD in the lower stages was found in females, males show higher mortality, suggesting that renal disease progress in males more rapidly to end-stage, when only dialysis and kidney transplantation can guarantee survival. About 10% of the population worldwide is affected by CKD that resulted the 12th leading cause of death in the last Global Burden of Disease Study report. The

Abbreviations: CKD, chronic kidney disease; COX-2, cyclooxygenase 2; CVD, cardiovascular disease; eGFR, estimated glomerular filtration rate; eNOS, endothelial NO synthase; FAD, flavin adenine dinucleotide; MAPK, mitogen-activated protein kinases; Moco, molybdopterin cofactor; NADH, reduced nicotinamide adenine dinucleotide; NADPH, reduced nicotinamide adenine dinucleotide phosphate; NLRP3, Nod-like receptor protein 3; NO, nitric oxide; Nrf2, nuclear factor erythroid 2-related factor 2; PDGF, platelet-derived growth factor; RAA, renin-angiotensin-aldosterone; RNS, reactive nitrogen species; ROS, reactive oxygen species; UA, uric acid; ULT, urate-lowering therapy; XDH, xanthine dehydrogenase; XO, xanthine oxidase; XOR, xanthine oxidoreductase.

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main risk factors for CKD are high blood pressure and high fasting plasma glucose, together accounting for more than three quarters of all cases. In addition, the risk of CKD from cardiovascular disease (CVD) and gout must be considered. On the other hand, almost 7% of the total CVD burden can be attributed to impaired kidney function [2].

The activity of the xanthine oxidoreductase (XOR) produces uric acid and can generate reactive oxygen (ROS) and nitrogen (RNS) species. Hyperuricemia and oxidative stress are implicated in the development of hypertension, insulin resistance, dyslipidemia and endothelial dysfunction, which are risk factors for cardiometabolic and renal disorders.

The present review explores the role of XOR activity and products in the development and progression of CKD.

2. Xanthine oxidoreductase: activities, products and functions

Human XOR is a multi-level regulated enzyme, which has acquired many physiological functions following a complicated evolutionary process. The main activity of XOR is to catalyze the transition from hypoxanthine to xanthine and then to uric acid, thus assuming a rate-limiting function in purine metabolism, being the last two irreversible products in higher mammals. This role is carried out both by the xanthine dehydrogenase (XDH, EC 1.17.1.4) and xanthine oxidase (XO, EC 1.17.3.2) activities, which produce reduced nicotinamide adenine dinucleotide (NADH) and ROS, respectively. XOR gene codes for the dehydrogenase form, which is prevalent inside the cell, in particular in liver, gut and lactating mammary gland. XO derives from the oxidation of specific cysteine residues or from their loss, due to partial proteolysis of XDH; XO can be found in plasma and in milk. During the reversible transition from XDH to XO an intermediate form is generated, which is able to react with both NAD^+ and O_2 [3,4]. The conversion from XDH to XO occurs when the enzyme is released in blood from hepatocytes or in the intestinal lumen from enterocytes, during the physiological turnover of these cells, as well as in milk from the mammary cells, during lactation.

In particular conditions, such as hypoxia and low pH, XOR has NADH oxidase activity, which produces ROS, as well as nitrite reductase activity, which generates nitric oxide (NO) [5–7]. Physiological amount of endothelial XOR-derived NO can modulate vasodilation concurring to blood pressure regulation or can generate cytotoxic RNS by reacting with ROS, thus contributing to inflammatory reaction of leukocytes. In pathological conditions, such as hypoxia and re-oxygenation or ischemia/reperfusion, the aforementioned cytotoxic reactions can contribute to the tissue damage. In fact, XOR-generated ROS contribute to the physiological cell redox signaling, but may cause oxidative stress and induce oxidative stress or endothelial dysfunction, as well as mutagenesis or cytotoxicity [8,10–12,14,17–21].

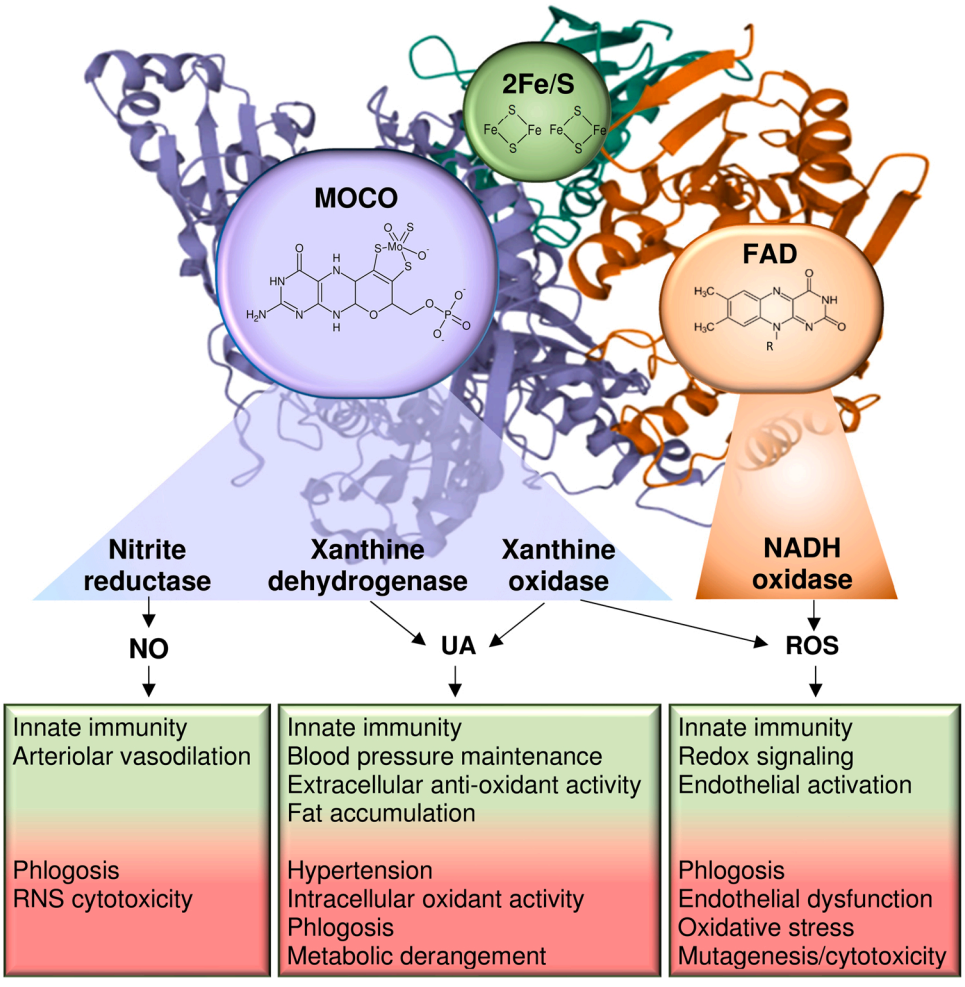

Fig. 1. Xanthine oxidoreductase (XOR) structure and pathophysiologic effects induced by products of its enzymatic activities. XOR is a 300 kDa enzyme formed by two identical subunits, each composed of three domains, characterized by different cofactors: two non-identical iron-sulfur clusters (2Fe/S) for the 20-kDa N-terminal domain (green), a flavin adenine dinucleotide (FAD) cofactor for the 40-kDa intermediate domain (orange) and a molybdopterin cofactor containing a molybdenum atom (Moco) for the 85-kDa C-terminal domain (violet). The C-terminal domain is responsible for (i) xanthine dehydrogenase activity, which produces uric acid (UA) and reduced nicotinamide adenine dinucleotide (NADH); (ii) xanthine oxidase activity, which produces UA, superoxide ion and hydrogen peroxide (reactive oxygen species, ROS); and (iii) nitrate/nitrite reductase activities that generate nitric oxide (NO). The intermediate domain possesses NADH oxidase activity, which produces ROS. XOR products have physiological roles (reported in the green portion of the box) at low levels, but they exert pathological effects (reported in the red portion of the box) at high levels [15,16]. NO promote local arterial vasodilation and contribute to innate immunity by generating reactive nitrogen species (RNS) and by activating endothelium. High levels of NO can induce phlogosis and tissue damage by producing cytotoxic RNS. UA stimulates innate immunity, supports blood pressure by activating the renin-angiotensin-aldosterone system, has a fundamental antioxidant activity in biological fluids and contributes to fat accumulation. However, hyperuricemia promotes hypertension, chronic inflammation and lipidic and glycidic metabolism derangements. In addition, intracellular UA accumulation, as well as UA oxidant products contribute to oxidative stress. ROS have a redox signaling function that is essential for innate immunity, because it is implicated in cell activation, proliferation and migration. On the other hand, exceeding amounts of ROS can

induce cell injury, when produced in excessive quantities [8]. Moreover, even if knock-in mice, expressing high XO activity showed growth and survival levels similar to wild type mice, the knock-in mice had increased tumor incidence, as a consequence of the higher ROS production and the deriving immune response by macrophages [9]. Uric acid plays different physiological roles: it has a fundamental antioxidant function in plasma and other body fluids, supports blood pressure by acting on kidney, is a proinflammatory agent and influences hepatic metabolism by favoring gluconeogenesis and fat accumulation. On the other hand, hyperuricemia promotes hypertension, dangerous chronic inflammation, metabolic derangements and has a pro-oxidant intracellular activity (Fig. 1) [10–14].

3. Gout and chronic kidney disease

Hyperuricemia is defined as an increased serum urate concentration > 6.0 mg/dL (>360 mol/L) for females and > 7.0 mg/dL (>420 mol/L) for males. It may have genetic causes, can be determined by increased hepatic biosynthesis, or by reduced renal or intestinal excretion of urate, may have dietetic origins, deriving from an excessive intake of food rich in purine or fructose, as well as from alcohol abuse, or may depend on high cell turnover, as during tumor lysis syndrome [22,23]. Although, not all patients with hyperuricemia necessarily develop gout, the limited solubility of urate may lead to its deposition as crystals, mostly in the joints, inducing both inflammatory symptoms and structural damage, and giving rise to chronic gouty arthritis and sometimes to nephrolithiasis [24]. The chronic deposition of urate precipitates in the distal tubules and in the medullary interstitium causes a form of CKD called gout nephropathy [25]. Hyperuricemia and gout are on the rise in developed countries; their association with cardiovascular outcomes has been reported and could be justified by the correlation between hyperuricemia and major risk factors for CVD, such as hypertension, type 2 diabetes, metabolic syndrome and kidney disease [26].

In a rat model of hyperuricemia, the Nod-like receptor protein 3 (NLRP3) inflammasome-mediated inflammation and autophagy contributed to the development of renal damage including tubular injury and kidney fibrosis [27]. The NLRP3 inflammasome signaling pathway is activated in gouty nephropathy patients and can induce the inflammatory response, which contributes to the renal damage (Fig. 2) [28].

Hyperuricemia was associated with an increased risk of acute kidney injury in a meta-analysis based on eleven observational studies including 70,264 hospitalized patients. In fact, 70% of uric acid is excreted by the kidneys after glomerular filtration and absorption by proximal tubules, allowing a crystal-induced direct tubular toxicity [29].

Another mechanism of kidney damage mediated by uric acid is related to the chronic activation of the renin-angiotensin-aldosterone (RAA) system with the consequent arteriolopathy and glomerulosclerosis (see the following chapter and Fig. 2) [30].

An observational retrospective study including gouty patients with CKD at stage 3, which were treated with XOR inhibitors for one year, showed that the reduction of uricemia at an optimal level could help to conserve and improve renal function [31].

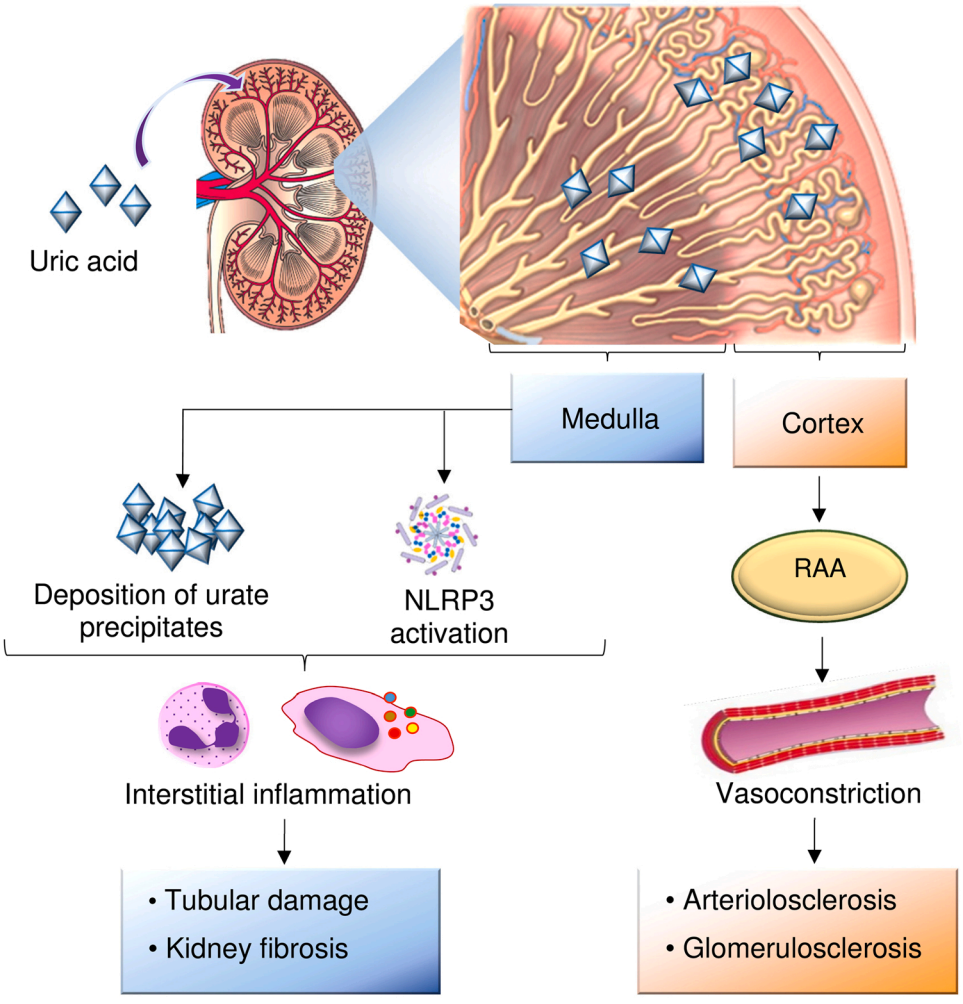

Fig. 2. Mechanisms of kidney damage mediated by hyperuricemia. Hyperuricemia may affect both the medulla and the cortex of kidney. In the medulla, high uric acid concentration causes the deposition of urate precipitates and activates the Nod-like receptor protein 3 (NLRP3) inflammasome, thus inducing chronic interstitial inflammation and tubular damage, which lead to kidney fibrosis [28]. In the cortex, hyperuricemia increases the activity of renin-angiotensin-aldosterone (RAA) system that stimulates persistent vasoconstriction of the afferent arterioles with consequent glomerular damage leading to glomerulosclerosis [30].

Hyperuricemia and gout are often associated to CKD and their prevalence is directly proportional to the severity of kidney pathology in the Uric Acid Right for heArt Health (URRAH) Project study, a multicenter, retrospective, observational cohort study, which involved 26,971 individuals. Among the subgroup of patients treated with the XOR inhibitor allopurinol, those who received treatment in the early stages of the disease, but not those who received treatment in more advanced phases, experienced effective protection. A possible reason for this discrepancy could be that XOR inhibition also decreases the production of ROS that contributes to the development of renal damage. Hyperuricemia seems to have a pathogenic role in the initial phases of CKD, but in the advanced stages of CKD, when renal excretion declines, hyperuricemia represents also a consequence of the disease [32].

4. Hyperuricemia and hypertension

The vast majority of CKD patients is suffering from hypertension that is both a cause and an effect of CKD. Some of the mechanisms inducing an increased blood pressure include upregulation of the RAA system, endothelial dysfunction or atherosclerosis, which may be influenced by XOR activity and products [33,34].

Uric acid can induce hypertension through various mechanisms. Hyperuricemia is associated to the activation of both plasma renin and intra-kidney angiotensin activities, which produce renal vasoconstriction and may generate ischemia, and oxidative stress in the kidney. The consequent activation of the immune system triggers persistent kidney vasoconstriction and salt-sensitive hypertension. In addition, uric acid oxidative products decrease endothelial NO availability, thus impairing vasodilation. Independently from uricemia level, increased intracellular uric acid, either produced by XOR activation or by uptake via specific urate transporters, causes activation of both mitogen-activated protein kinases and reduced nicotinamide adenine dinucleotide phosphate (NADPH) oxidase, with the consequent induction of oxidative stress and inflammation (Fig. 3) [35,36].

After a 5-year follow-up, a cohort study comprising 3584 prehypertensive Japanese patients evaluated the cumulative incidence of hypertension. After adjustments for confounding risk factors, the blood pressure resulted significantly higher in subjects with hyperuricemia compared to those without hyperuricemia, suggesting a causal role of hyperuricemia in the initial phase of hypertension development [37].

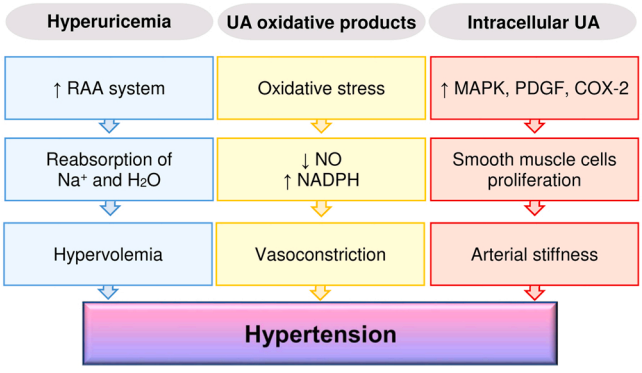

Fig. 3. Uric acid (UA) and hypertension. An exceeding amount of UA can lead to hypertension through different mechanisms. Hyperuricemia stimulates the renin-angiotensin-aldosterone (RAA) system that causes the reabsorption of sodium (Na^+) and consequently water (H_2O), thus inducing hypervolemia. Uric acid oxidative products can cause oxidative stress and induce vasoconstriction by lowering the availability of endothelial nitric oxide (NO) while increasing the activity of reduced nicotinamide adenine dinucleotide phosphate (NADPH) oxidase. Intracellular accumulation of UA induces the proliferation of smooth muscle cells that leads to arterial stiffness by increasing the activity of mitogen-activated protein kinases (MAPK), platelet-derived growth factor (PDGF) and cyclooxygenase 2 (COX-2) [36].

Hyperuricemia is associated with vascular stiffness, because of the increase in oxidative stress on the vascular endothelium and of the production of vasoconstrictors and activation of vascular smooth muscle cells, which changes the structural properties of artery wall by increasing the recruitment of collagen fibers and inducing a progressive elastic fiber degeneration. In the kidney, the consequent alterations of the flow can damage microcirculation and cause vascular injury, which, together with the relative chronic inflammation and to the activation of the RAA system, can lead to hypertension and CKD [38,39]. Uricemia levels and arterial stiffness were significantly higher in hypertensive than normotensive patients [40]. A study population enrolling 1114 newly diagnosed, never-treated hypertensive patients reported the association between the level of arterial stiffness and uricemia and insulin resistance, evaluated by the homeostatic model assessment index [41].

A meta-analysis was conducted by selecting 15 studies reporting only randomized controlled studies to determine the correlation between the level of uricemia and blood pressure. The treatment with allopurinol resulted in a significant decrease of systolic blood pressure in hyperuricemic patients even without the use of antihypertensive drugs [42].

5. Reactive oxygen species and endothelial dysfunction

ROS and RNS are continuously generated in living beings and play a physiological role in signal transduction. However, an excessive production of oxidants can cause oxidative stress with consequent alteration of biological molecules, such as lipids, proteins, glycides and DNA, with pathological consequences for cells and tissues [17,43]. A high level of oxidative stress, as measured by the plasma cystine/glutathione ratio, was significantly associated with mortality in patients with coronary artery disease [44]. Due to its metabolic functions, the kidney is vulnerable to oxidative stress, which can accelerate the progression of CKD and its complications. The main sources of ROS include the mitochondrial respiratory complex, NADPH oxidases, endothelial NO synthase (eNOS), myeloperoxidase and XOR [45].

A cohort of 1591 subjects from Norway aged between 50 and 62 years, without diabetes mellitus or cardiovascular and renal disease, was followed for 6 years. After a multivariable statistical analysis, a high urinary excretion of the oxidatively damaged RNA marker 8-oxoGuo independently predicted an increased risk of low-grade albuminuria (Fig. 4) [46].

Oxidative stress promotes inflammation and both are CKD hallmarks, as well as endothelial dysfunction, which contributes to the process of arteriosclerosis. Oxidative stress is implicated in glomerular injury with albuminuria and subsequent glomerulosclerosis. Vascular alterations lead to arterial stiffness and hypertension and this process already begins in children and is present in patients with CKD initial phases [45,47,48].

ROS may cause endothelial dysfunction with impairment of eNOS and consequent local vasoconstriction ultimately leading to glomerular ischemia. In addition, the microvascular alterations promote the leukocytes recruitment that increases the production of ROS and RNS, which in turn contribute to apoptosis of podocytes and renal tubular epithelial cells (Fig. 4) [49,50].

ROS overproduction has been reported at the beginning of CKD progression together with the activation of the nuclear factor erythroid 2-related factor 2 (Nrf2) transcription factor, which regulates the expression of several antioxidant proteins, thus blocking inflammatory pathways. Although, it is not definitely clear if Nrf2 activation can help prevent or slow CKD progression, solid evidence suggests that ROS-antioxidant altered systems play a crucial role in CKD [51,52].

In addition to the contribution of XOR activity in ROS production, oxidative stress can be induced by hyperuricemia, which also promotes inflammation and endothelial dysfunction [36]. In vitro experiments suggest a possible mechanism of endothelial dysfunction and consequent kidney disease due to the phenotypic transition of vascular endothelium induced by uric acid through oxidative stress and

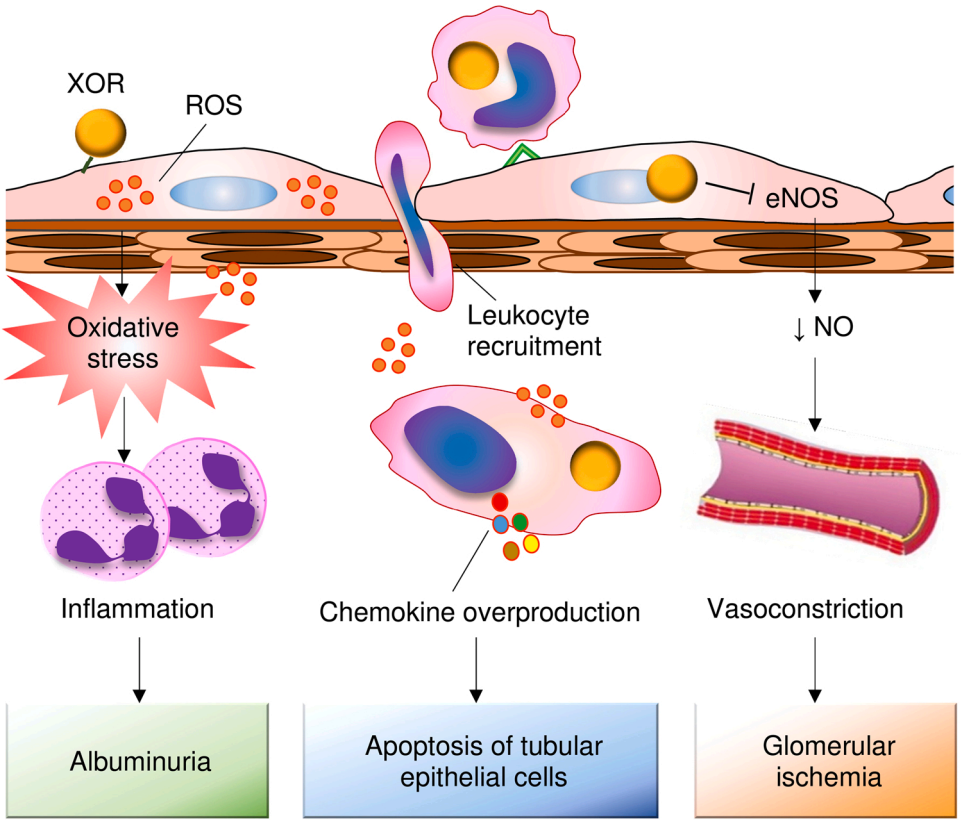

Fig. 4. Kidney damage induced by excessive reactive oxygen species (ROS) production. Exceeding amounts of ROS induce oxidative stress and phlogosis that can cause albuminuria, as well as leukocytes recruitment that contribute to apoptosis of podocytes and renal tubular epithelial cells. ROS may also cause the impairment of nitric oxide (NO) synthase (eNOS) and consequent local vasoconstriction ultimately leading to glomerular ischemia [46,50].

glycocalyx shedding [53].

6. Chronic kidney disease in diabetes and metabolic syndrome

Diabetes is the most frequent cause of CKD because hyperglycemia damages blood vessel and nephrons, thus triggering the development of hypertension. Over time, lipid metabolism alterations can be added, leading to metabolic syndrome and/or CVD. High XOR activity and hyperuricemia are risk factors not only for gout, CKD and CVD [16], but also for obesity, insulin resistance, type 2 diabetes and metabolic syndrome [20,54,55] (Fig. 5).

Hemodialysis patients with or without type 2 diabetes were analyzed for plasma XOR activity, uricemia and glycemia. Diabetic patients showed a higher XOR level, which has been significantly associated with glucose plasma level, while in non-diabetic patients XOR plasma activity has been significantly associated with the level of uricemia [56]. Pre-dialysis CKD patients with or without diabetes were tested for plasmatic XOR. XOR activity was significantly higher in diabetic CKD patients than in those without diabetes, after adjusting for several confounders [57].

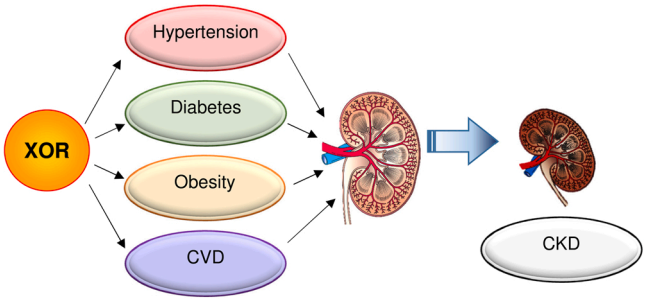

Fig. 5. Xanthine oxidoreductase (XOR) activity and chronic kidney disease CKD). The increase in XOR activity not only promotes the development and progression of CKD through the production of uric acid and reactive oxygen species, it also promotes the main pathological conditions leading to CKD: hypertension, diabetes mellitus, obesity and cardiovascular diseases (CVD) [16].

A retrospective 5-year cohort study was conducted including 9721 Japanese healthy subjects to evaluate if obesity predicts the insurgence of metabolic syndrome. Overweight subjects had increased cumulative incidences of hypertension and diabetes, even in individuals with normal fasting blood glucose. Baseline hyperuricemia was a risk factor for hypertension in lean subject and for hypertension and diabetes in obese subjects [58].

A retrospective observational study included 155 Japanese hyperuricemic patients with or without diabetes, which were treated for 6 months with XOR inhibitor febuxostat. The resulting control of the uricemia was similar in the two groups, but only non-diabetic patients experienced a significant increase in eGFR values, while the renoprotective effect was attenuated in diabetic patients [59].

In a pilot study, 65 diabetic patients with hyperuricemia and nephropathy were treated for 28 weeks with placebo or with the XOR inhibitor topiroxostat, which not only controlled the serum uric acid level but also prevented decline of eGFR [60].

In a cohort of 3808 Chinese women, the chances of having metabolic syndrome were statistically higher for hyperuricemic women than for their counterparts without hyperuricemia and the association was stronger in the premenopausal women than in postmenopausal ones [61].

7. The association of chronic kidney disease with cardiovascular disease

In a 5-year Japanese cohort study including 4915 subjects, asymptomatic hyperuricemia predicts a higher risk of developing cardiometabolic diseases, such as hypertension, obesity and CKD [62].

In a cross-sectional study were enrolled 26,768 Chinese participants, which were divided for sex and serum uric acid quartiles. Hyperuricemia was significantly associated with both risk factors for CVD and renal diseases, namely obesity, hypertension, diabetes mellitus, dyslipidemia, CKD and nephrolithiasis, especially in women [63].

A significant correlation was observed between the level of uricemia and inflammatory markers of coronary microvascular endothelial dysfunction in postmenopausal women, suggesting an early coronary atherosclerosis [64].

Hyperuricemia indicates advanced arterial stiffness and was an independent predictor of all-cause mortality in heart failure patients with preserved [65] as well as reduced ejection fraction [66].

8. Urate-lowering therapy

XOR inhibition suppressed the expressions of genes responsible for hypercholesterolemia-associated inflammation and fibrosis in ApoE knockout mice with CKD, possibly exerting renoprotective effects against hypercholesterolemia-associated kidney injury [67]. In experimental kidney diseases, treatment with allopurinol was able to prevent renal NLRP3 inflammasome activation, thus showing renoprotective effects [68,69].

Eighty Japanese hyperuricemic patients with diabetic nephropathy were treated for 24 weeks with the XOR inhibitor topiroxostat at 40, 160 mg per day or placebo, to delay the deterioration of renal function. Treatment with the highest dose was significantly effective by reducing albuminuria [70]. However, in a randomized, controlled trial, including 363 patients with stage 3 or 4 CKD, but without gout, no significant differences were observed in the eGFR values between those receiving treatment for 2 years with allopurinol and the placebo group [71]. Similarly, the urate-lowering therapy (ULT) with topiroxostat or febuxostat did not significantly decrease the urinary protein/creatinine ratio in CKD stage 3 and 4 patients with hyperuricemia after a 24-weeks treatment, despite the effectiveness in serum urate lowering [72].

The administration of allopurinol for 12 weeks effectively and safely normalized the asymptomatic hyperuricemia in patients with stage 3 CKD, compared to placebo controls, without improving their endothelial function, as measured by brachial artery flow-mediated dilation [73].

Treatments with ULT conferred a significant renoprotection in trials reporting a progressive deterioration of kidney function, but were ineffective when such progression was not observed. Thus, ULT was recommended in CKD patients with hyperuricemia and evidence of deteriorating renal function [74]. In addition, ten randomized controlled trials with a total of 1480 CKD patients found that ULT with topiroxostat had a significant renoprotective effect compared to placebo, by improving eGFR and reducing the urinary albumin/creatinine ratio [75].

Treatment with XOR inhibitors decreased all-cause mortality in 2429 Japanese patients in dialysis due to end-stage renal disease, regardless of the level of serum uric acid [76].

Systematic reviews of randomized controlled trials were performed in CKD patients to verify the efficacy of XOR inhibitors in improving renal outcomes. The obtained findings suggest that the treatment can improve disease course in young subjects or in patients at early CKD stages [77]. Moreover, significant improvement in eGFR values after ULT were reported only in long-term studies [78–80].

9. Conclusions and future perspectives

The data so far available seem to indicate that an increase in the XOR activity, and the relative production of uric acid and ROS, promotes the initial phases of the CKD, due to both the effect on microcirculation and the tissue damage, as well as on arterioles and promotion of hypertension, which are consequent. However, since purine metabolism differs considerably from species to species, it must be considered that the results derived from animal experiments need to be confirmed by those in human studies. Once the renal or vascular damages attributable to the uric acid are settled, they cannot regress; this can explain the lack of success with ULT at advanced stages of CKD. It must be underlined that it has not been ascertained which is the optimal level of uricemia; however, its containment within the parameters considered physiological, could reduce the risk of developing hypertension and CKD, in particular in the presence of overweight and hyperglycemia.

By inhibiting XOR activity, XOR-derived NO cannot be produced and this can aggravate the hypoxic renal conditions that inhibit the eNOS activity. Moreover, XOR inhibition is not without risks, such as the rare but dangerous allopurinol hypersensitivity or the increased risk of cardiovascular death with febuxostat [81]. On the other hand, the use of XOR inhibitors results not only in the control of the uricemia but also in lowering the production of ROS and RNS with a globally antioxidant effect and a reduction in the expression of proinflammatory molecules, which can also provide protection against CKD. In addition, XOR inhibition, by abolishing its rate-limiting function in purine metabolism, increases the availability of adenosine, which may downregulate the release of proinflammatory mediators [82,83].

On the other hand, it cannot be excluded that the protection given by XOR inhibitors in renal damage could depend by mechanisms other than the lowering of ROS production. This at least considering non-competitive inhibitors; indeed, while the allopurinol inhibits not only XOR activity, but also the purine salvage pathway, the non-competitive XOR inhibitors can enhance the purine salvage pathway, favoring the final availability of ATP [84,85].

The activities of XOR and its products form a complex balance. For this reason, it is not surprising that the use of ULT gives rise to so different results, depending on many parameters, such as the age and the sex of the patient, the type of comorbidities, the stage of the pathology and so on.

Retrospective studies are desirable to ascertain whether the uricemia control with XOR inhibitors at the first occurrence of the CKD, as well as in obese and/or diabetic patients, manages to slow down the advancing of the atherosclerosis, the appearance of cardiovascular pathologies and the progress of renal diseases.

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CRediT authorship contribution statement

Letizia Polito, Massimo Bortolotti, Maria Giulia Battelli, Andrea Bolognesi: Conception and design of study. **Letizia Polito, Massimo Bortolotti, Maria Giulia Battelli, Andrea Bolognesi**: Acquisition of data. **Letizia Polito, Massimo Bortolotti, Maria Giulia Battelli, Andrea Bolognesi**: Analysis and/or interpretation of data. **Letizia Polito, Massimo Bortolotti, Maria Giulia Battelli, Andrea Bolognesi**: Drafting the manuscript. **Letizia Polito, Massimo Bortolotti, Maria Giulia Battelli, Andrea Bolognesi**: Revising the manuscript critically for important intellectual content. Approval of the version of the manuscript to be published.

Declaration of Competing Interest

The authors declare that they have no conflict of interest.

Data availability

No data was used for the research described in the article.

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