Review

Uric acid in the pathogenesis of metabolic, renal, and cardiovascular diseases: A review

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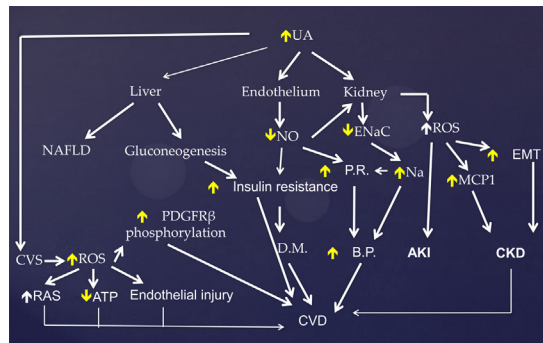
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The association between uric acid (UA) on one side and systemic hypertension (Htn), dyslipidemia, glucose intolerance, overweight, fatty liver, renal disease and cardiovascular disease (CVD) on the other side is well recognized. However, the causal relationship between UA and these different clinical problems is still debatable. The recent years have witnessed hundreds of experimental and clinical trials that favored the opinion that UA is a probable player in the pathogenesis of these disease entities. These studies disclosed the strong association between hyperuricemia and metabolic syndrome (MS), obesity, Htn, type 2 diabetes mellitus (DM), non-alcoholic fatty liver disease, hypertriglyceridemia, acute kidney injury, chronic kidney disease (CKD), coronary heart disease (CHD), heart failure and increased mortality among cardiac and CKD patients. The association between UA and nephrolithiasis or preeclampsia is a non-debatable association. Recent experimental trials have disclosed different changes in enzyme activities induced by UA. Nitric oxide (NO) synthase, adenosine monophosphate kinase (AMPK), adenosine monophosphate dehydrogenase (AMPD), and nicotinamide adenine dinucleotide phosphate (NADPH)-oxidase are affected by UA. These changes in enzymatic activities can lead to the observed biochemical and pathological changes associated with UA. The recent experimental, clinical, interventional, and epidemiologic trials favor the concept of a causative role of UA in the pathogenesis of MS, renal, and CVDs.
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Introduction

UA is a weak acid (M.W. = 168) produced in the liver, muscles, and intestines [1]. Purines are the precursors of UA. Xanthine oxidoreductase (XO) is the enzyme responsible for UA production. Exogenous sources that can increase serum UA include fatty meat, organ meat, and seafood [2]. Fructose is another source of exogenous UA. Fructose is present in fruits and added sugar. Fructokinase enzyme catalyzes the phosphorylation of fructose by consuming adenosine triphosphate (ATP). Adenosine monophosphate (AMP) thus generated finally converts to UA [3]. UA was incriminated in the pathogenesis of gout and kidney stones. However, for more than 140 years ago, high serum UA (SUA) was proposed in association with other diseases including Htn [4], CKD and DM [5]. The association between hyperuricemia and CHD was first reported in 1951 [6]. SUA bears a highly significant positive correlation with insulin resistance (IR) and insulin response to oral glucose load. Hyperuricemia encountered in case of increased IR is the sequence of decreased renal urate clearance [7]. Accumulating data point toward a possible etiologic role of increased UA in the pathogenesis of MS, CVD and renal disease [8]. Experimental and clinical trials have demonstrated the reversal or amelioration of different diseases associated with hyperuricemia after administration of hypouricemic agents. These agents are either inhibitors of the XO enzyme or stimulants of renal UA excretion. This later group supports that the therapeutic effect is a consequence of UA lowering rather than inhibition of release of free oxygen radicals on inhibition of XO enzyme. In this review, we are going to discuss the possible impact of hyperuricemia on metabolic, renal, and CVDs.

Uric acid and metabolic syndrome

MS is a group of clinical and laboratory abnormalities. Out of the five established manifestations, three or more are needed to diagnose MS. These manifestations are (1) waist circumference $\geqslant$ 90 and 80 cm in men and women respectively; (2) serum triglyceride $\geqslant$ 150 mg/dL; (3) high-density lipoprotein cholesterol (HDLc) < 40 and 50 mg/dL in men and women respectively; (4) blood pressure (BP) $\geqslant$ 130/85 mmHg; and (5) fasting blood sugar $\geqslant$ 100 mg/dL [9]. The different manifestations of MS are considered as consequences of excess fat deposition in the adipose tissue [10]. Excess intake of sugars beside purine rich foods can lead to increased incidence of hyperuricemia, obesity and DM [11]. In adults with normal body mass index, MS is 10 times higher in those having SUA $\geqslant$ 10 mg/dL compared to those with SUA < 6 mg/dL [12]. The hazard ratio of incident MS shows a steady increase when normal adults were allocated into four quartiles according to SUA. These results were still observed after considering the body composition [13]. When children (10–15 years at baseline) were followed for 10 years, high SUA was a significant predictor of incident MS in male subjects [14]. On the other hand, when elderly hyperuricemic subjects above sixty-five years were followed for more than 4 years, only female subjects showed increased incidence of MS [15]. Another prospective study assessed 1511 men and women 55–80 years old, who were not affected initially by any of the components of MS. Follow-up has demonstrated a significantly higher incidence of many components of MS, namely, hypertriglyceridemia, low HDL, and Htn in subjects with highest sex-adjusted quartile of UA [16]. A meta-analysis of eleven studies of more than fifty-four thousand participants showed that elevated SUA is associated with increased risk of MS and non-alcoholic fatty liver disease (NAFLD) [17]. By inhibiting endothelial NO synthase, decreased NO might underlie insulin resistance [18]. Hyperuricemia is significantly associated with insulin resistance in normal subjects and to lesser extent in type 1 diabetic subjects [19]. Lowering SUA by a uricosuric agent [20] or allopurinol [21] is associated with improved insulin sensitivity in human subjects (Fig. 1).

Glucose intolerance and diabetes mellitus

The link of UA to hyperglycemia was first described in the nineteenth century [22]. Elevated SUA predicted DM and insulin resistance in a fifteen-year follow-up study. Baseline SUA in this cohort of 5012 young adults was not associated with a change in serum insulin, indicating that hyperuricemia is an independent risk factor for insulin resistance and type 2 DM [23]. High normal SUA was also associated with future development of type 2 DM among lean healthy and normoglycemic women [24]. Increased hepatic glucose production is a distinguished feature of insulin resistance and type 2 DM. Intracellular UA stimulates AMPD and inhibits AMPK enzyme activity (Fig. 2). Intracellular AMPK inhibits hepatic gluconeogenesis. AMPD stimulates hepatic gluconeogenesis [25]. Decreased endothelial NO synthase (eNOS) activity in hyperuricemic patients causes increased insulin resistance [18,19]. Treatment of asymptomatic hyperuricemic personnel with allopurinol for 3 months results in significant decrease in insulin resistance and inflammation parameters [21].
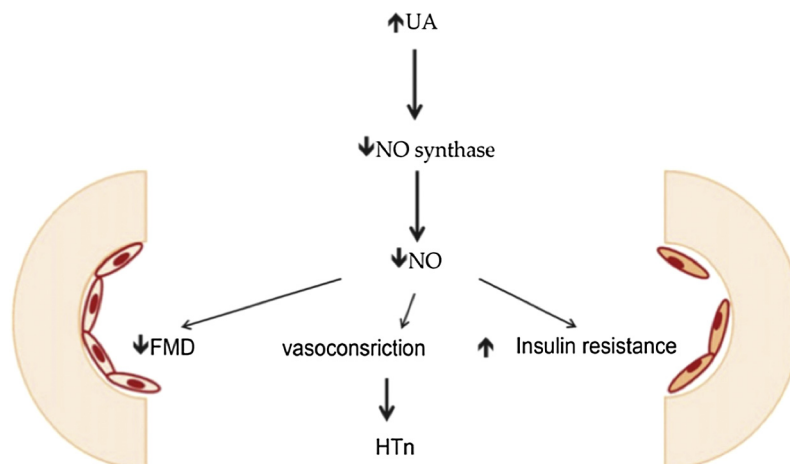
Fig. 1. Effect of intra-cellular uric acid on nitric oxide synthesis within vascular endothelium UA = uric acid; NO = nitric oxide; FMD = flow mediated dilation; Htn = systemic hypertension.
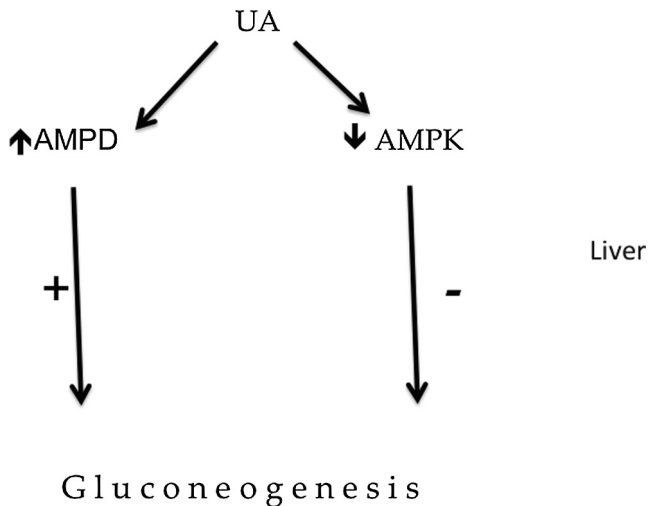
Fig. 2. Intra-cellular uric acid stimulates gluconeogenesis. UA = uric acid; AMP-D = adenosine monophosphate dehydrogenase; AMPK = adenosine monophosphate protein kinase.

Fig. 3. Uric acid as mediator of systemic hypertension. ENaC = epithelial sodium channels; Na = sodium; HTn = systemic hypertension.

However, genetic epidemiologic studies also called Mendelian randomization studies failed to prove an association between UA and type 2 DM [26,27]. Genetic polymorphisms of a well-characterized serologic variant can be utilized to study the effect of this variant on disease risk. A total of 28 genetic loci were recognized to significantly associate with SUA concentration [28]. The knowledge of genetic regulation of SUA allows the use of Mendelian randomization to examine the possible causal relation between SUA and type 2 DM risk. The genetic score in these 2 articles is mainly based on genes that control UA transport between extracellular and intracellular compartments and, hence, may dissociate the physiological serum-intracellular relationship. Intracellular UA is postulated as the cause of insulin resistance and enhanced gluconeogenesis [29]. It is not known whether the score alters the extracellular-intracellular equilibrium. The genetic score may dissociate this equilibrium and then can lead to the incorrect conception that SUA is not a risk factor for diabetes [29]. Unfortunately, we did not encounter large randomized controlled clinical studies looking for impact of SUA lowering on the development of MS and type 2 DM.

Systemic hypertension

The chance to develop Htn is greater in hyperuricemic male and female subjects; this chance augments in older age [14,30,31]. Increased SUA increases the chance of non-dipping [32]. A similar finding is encountered among CKD patients [33]. Increased SUA is significantly associated with the development of new-onset primary Htn in children [34]. In a recent meta-analysis of 25 moderate to high-quality studies selected from all the clinical trials with SUA as exposure and incident systemic Htn as outcome variables through September 2013, these 25 studies of 97,824 participants have shown that high SUA significantly predicts systemic Htn [35]. Among 118 thousand healthy subjects 40–70 years old that were screened for SUA during 2002, a quarter of them developed systemic Htn over the following 10 years. Those with SUA higher than 3 mg/dL had a greater chance to develop Htn. The higher the SUA within the normal range, the greater was the risk to develop Htn [36]. The association between high SUA and Htn is stronger in younger ages and in females [37,38]. High SUA is one of the major predictors of worse BP control [39–42]. SUA significantly correlates with sympathetic domain parameters among pre-hypertensive and hypertensive personnel [43]. The *in vivo* rise
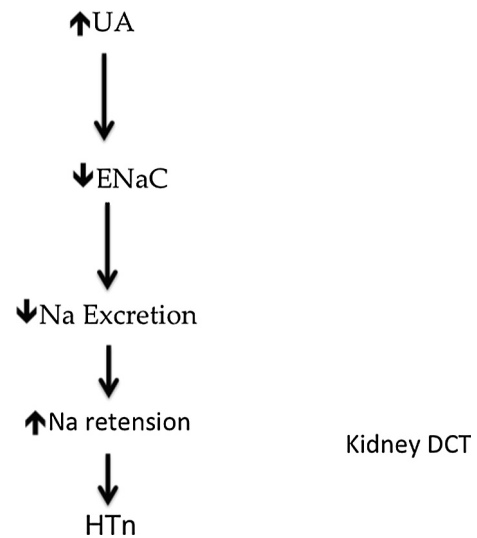
of SUA in rats induces the epithelial sodium channel (ENaC) in the distal nephron with consequent decrease in renal sodium excretion [44] (Fig. 3). One of the important determinants of SUA is the glucose transporter "GLUT9" gene [45]. GLUT9 transports UA. GLUT9 gene polymorphism confirmed a causal relationship of hyperuricemia for systemic Htn in a family study [46]. Genotype variants of GLUT9 associated with decreased SUA are associated with a significant decline of BP in different salt intake situations [47]. In adolescents with obesity and prehypertension, allopurinol or probenecid achieved marked control of ambulatory BP [48]. Allopurinol was also associated with significant decrease in office BP and body weight and increase in the percentage of dippers among overweight prehypertensive subjects [49]. Six months of febuxostat treatment resulted in a significant decrease in plasma renin activity and plasma concentration of aldosterone and a significant increase in estimated glomerular filtration rate (eGFR) in hyperuricemic hypertensive patients [50].

Adiposity

Excess fat accumulation in MS involves adipose tissue, hepatocytes and increased level of serum triglycerides [51]. NAFLD is characterized by triglyceride accumulation by variable degree within hepatocytes [52]. NAFLD is the hepatic manifestation of MS. Recent studies point toward UA as an important factor underlying excess fat storage [25,53–55]. UA up-regulates the fructokinase enzyme within human hepatocytes. This up-regulation is UA concentration dependent with stepladder increase in fructokinase activity with increasing the intracellular UA concentration from 4 to 12 mg/dL. This up-regulation is blocked on adding either probenecid or allopurinol. Stimulation of fructokinase mediates fructose-induced hepatic steatosis [56]. AMPK and AMPD within hepatocytes are incriminated in the developments of hepatic steatosis. When AMPK activity is reduced excess fat infiltration occurs, while its stimulation can prevent steatosis through increased fat oxidation and inhibition of lipogenesis. AMPD has opposing effect on fat deposition within the hepatocytes. AMPD activation increases intracellular UA synthesis [57]. Intracellular UA inhibits AMPK activity [58]. Two years ago, a novel mechanism of UA induced fatty liver was demonstrated. UA induced hepatocyte endoplasmic reticulum stress within hepatocytes. Associated with this increased stress, the sterol regulatory element-binding protein (SREBP) undergoes cleavage and nuclear translocation
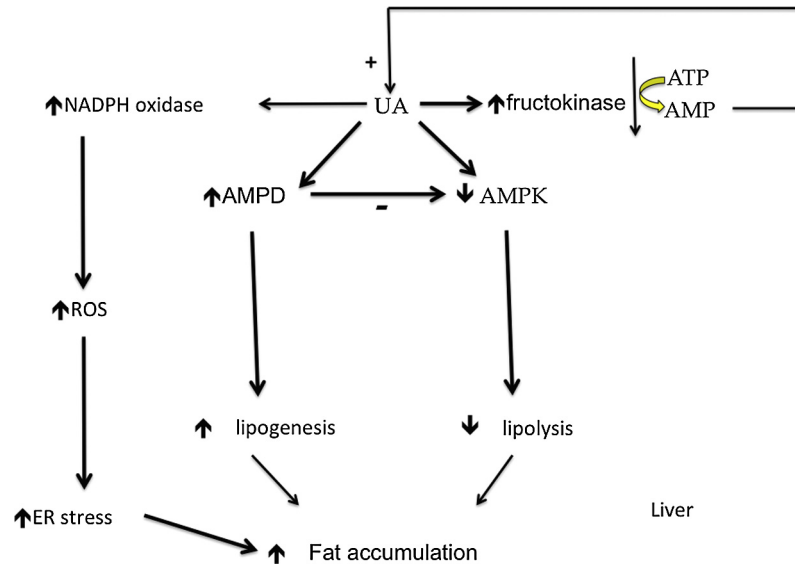
Fig. 4. Pathways of lipogenesis activated by intra-cellular uric acid. UA = uric acid; AMPD = adenosine monophosphate dehydrogenase; AMPK = adenosine monophosphate protein kinase; ROS = reactive oxygen species; ER = endoplasmic reticulum.

and stimulates triglyceride accumulation within hepatocytes [54] (Fig. 4).

Among the different components of MS, hypertriglyceridemia carries the strongest association with hyperuricemia [59,60]. The mechanism of this strong association is not yet known.

Excess fructose or sucrose intake can induce obesity beside other features of MS [11]. In contrast, if animals are fed either glucose or starch of equivalent caloric value fewer features of MS are observed [61]. These findings point to the ability of fructose to induce visceral fat accumulation compared to isocaloric glucose intake. Increased fructose intake is associated with intracellular depletion of ATP, increased AMP and increased intra-cellular production of UA. This is followed by increased SUA [62]. Increased SUA is an independent predictor of obesity [63]. URAT1 is one of the transporters of UA. URAT1 mediates intracellular shift of UA. This transporter is encountered within the adipocyte membrane [64]. Adipose tissue can also generate UA. Adipocytes have XO that can produce intracellular UA [65]. While extracellular UA acts as strong antioxidant, it acts as a pro-oxidant inside the cell where it stimulates NADPH oxidase enzyme causing increased intracellular oxidative stress, mitochondrial injury, and ATP depletion [64,66,67] (Fig. 5). XO increases fat deposition within adipocytes. XO knock-out mice get 50% reduction of their fat compared to wild mice [65]. Genetic polymorphism of URAT1 gene was associated with body mass index (BMI), waist circumference, and MS. Intracellular concentration of UA looks as an important determinant of obesity [68].

Uric acid and the kidney

The kidney is responsible for elimination of 70% of the daily UA production [69]. Renal handling of UA includes glomerular filtration, proximal tubular reabsorption, secretion and post-secretory reabsorption [70]. ABCG2 that secretes UA is restricted to the proximal straight tubule (S3 segment) [71]. URAT1 is a voltage-driven urate transporter located in the brush border of proximal convoluted tubules (PCT) and efficiently reabsorbs glomerular-filtrated UA [1,72,73]. The reabsorbed UA is then driven out of PCT cells through the basolateral membrane. The glucose transporter 9 (GLUT9) is involved in this extracellular efflux of UA [74]. ABCG2 is also expressed in the liver and intestine [75]. As UA excretion
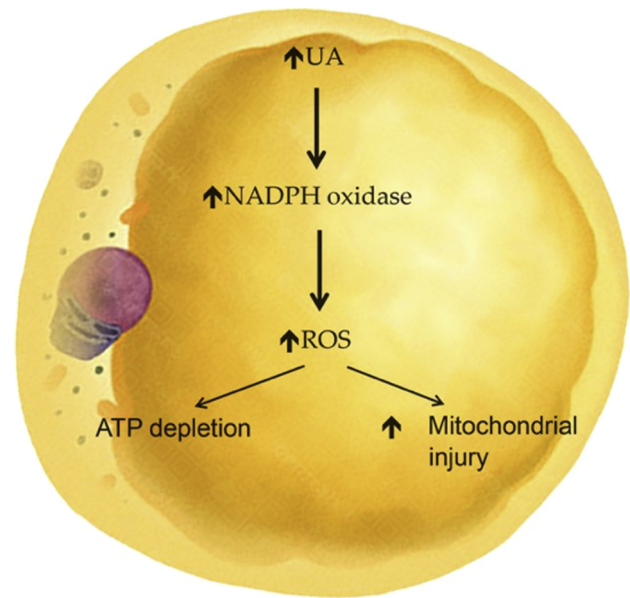
Fig. 5. Intracellular uric acid as a pro-oxidant agent. UA = uric acid; ROS = reactive oxygen species.

falls in cases of CKD, compensatory increase in intestinal secretion of UA ensues [76,77]. Whether UA is a cause or an association to renal diseases is a question that still waits for a definitive answer. We hope we can settle this controversy in the present review.

Nephrolithiasis

Increased SUA and high animal protein diet can cause hyperuricosuria. Uricosuric agents used to treat hyperuricemia can aggravate hyperuricosuria. UA within the urine (UUA) tends to crystalize when urine pH is low. Insulin resistance, obesity, high animal protein intake and gout can decrease urine pH. Hyperuricosuria in the presence of acidic urine especially in case of low urine volume can result in formation of urate stones [78]. In type 1 DM adolescents, UUA is significantly higher and urine pH is lower compared to non-diabetic controls [79]. DM patients are more prone to develop urate stones [80].

Chronic kidney disease

For the last one and half centuries, the association of gout with CKD is well recognized [81]. However, it was not known which came first. The decrease in GFR is associated with UA retention [76]. The evidence of the offending action of UA was clearly demonstrated in experimental studies. Most of the animals have low SUA thanks to the existence of the uricase enzyme that breaks down UA. To raise SUA in these animals, oxonic acid is used to inhibit the uricase enzyme. By increasing SUA, animals develop systemic Htn, glomerular Htn, glomerulosclerosis, and interstitial fibrosis [81–85]. These changes were attributed to activation of NADPH oxidase enzyme causing increased intracellular oxidative stress, mitochondrial injury, ATP depletion [66,67], endothelial injury, renin – angiotensin system (RAS) activation and increased epithelial-mesenchyme transition (EMT). Increased EMT was proved by decreased E-cadherin expression and an increased α-smooth muscle actin and vimentin. Excess interstitial infiltration by fibroblasts and progressive interstitial fibrosis eventually ensues [86] (Fig. 6). On the other hand, some early clinical studies denied UA as a risk of incident CKD [87–91]. Definition of CKD in these articles was not precise. In one of these articles, serum creatinine of 2 mg/dL was considered the cutoff point [87]. In another study the follow-up period was relatively short to detect change in serum creatinine in healthy cohort at basal assessment [88].

Before the introduction of UA lowering agents, up to a quarter of gouty patients developed proteinuria. Histologic examination of the kidneys in these patients revealed nonspecific changes, namely arteriosclerosis, glomerulosclerosis, and interstitial fibrosis. In addition, collecting ducts and the medullary interstitium in some of these patients showed focal deposition of monosodium urate crystals with secondary inflammatory response. This inflammatory response is in the form of focal granulomatous reaction with dense accumulation of macrophages and T-lymphocytes. Tubular cells within the inflammatory exudate showed a sixfold increase in macrophage migration inhibitory factor (MIF) mRNA, compared with uninvolved areas [92]. These changes were described as "gouty nephropathy" or "chronic urate or UA nephropathy" [93]. However, the focal nature of urate deposits and of the inflammatory response can't explain the diffuse pathology of CKD encountered in these cases [94]. It is worth mentioning that urate deposits could be detected in autopsies that lack evidence of CKD [95]. Irrespective of the baseline eGFR, SUA significantly predicted CKD progression over 5 years of follow-up of a cohort of IgA nephropathy patients [96]. SUA proved as a strong predictor for the development of increased urine albumin excretion rate (UAER) on follow-up of normoalbuminuric type 1 diabetic patients for 6 years. For every 1 mg/dL increase in SUA, the risk of development of albuminuria increased by 80% [97]. In a recent cohort study of 3605 normal subjects having normal kidney functions, the subjects were categorized according to the longitudinal follow-up of SUA into persistently low, fluctuating with declining or rising SUA, and persistently high SUA. Incident CKD was significantly higher in categories with rising or persistently high SUA [98]. SUA is associated with resistive indices within renal arteries estimated by Doppler study [99]. In another study in Type 1 DM there was a 2.4-fold increase in the unadjusted risk of eGFR loss in patients having SUA > 6.6 mg/dL compared to those with lower level [100]. In a study of 263 type 1 DM newly diagnosed, SUA was a significant independent predictor of macroalbuminuria after 18 years [101]. In a recent study, insulin sensitivity was significantly higher in type 1 DM who had regression of albuminuria compared to those who did not [102]. In a longitudinal study of a cohort of 20,142 type 2 DM patients having eGFR > 60 mL/min and normal UAER, De Cosmo et al., looked at the incidence of eGFR < 60 mL/min., increased UAER or both over 4 years of follow-up. They assessed the association of SUA quintiles with the onset of these CKD components using regression analysis to adjust for different confounders. 7.9% of patients developed eGFR < 60 mL/min, 14.1% developed increased UAER and 2% of patients developed both components. The higher the SUA quintile the higher is the relative risk ratio of eGFR decline. In patients who developed eGFR decline, there was a significant association of SUA with albuminuria [103]. These findings are supported by more recent results reported in Japan [104]. A cross-sectional study of more than three thousand type 2 DM patients looked for UA effect on the prevalence of diabetic kidney disease (DKD). 68% of the hyperuricemic had DKD versus 41.5% with normal UA [105]. When the data of seventy liver transplantation children were revised, a cumulative incidence of hyperuricemia of 32% over ten-year postoperative was observed. All these children underwent annual estimation of SUA, inulin and urate clearance. Decreased urate clearance was the main cause of hyperuricemia. SUA tended to predict the development of CKD [106]. A more interesting prospective observation study of a cohort of 900 healthy adult blood donors that were followed for 5 years showed that the basal SUA was a significant predictor of eGFR decline even after multivariate regression analysis [107]. The drawback of this trial is the lack of serial estimation of SUA and the limited number of females. However, this study is distinguished because the subjects were healthy normotensive subjects lacking signs of CKD on entry to the study. Another prospective study of 21,475 healthy volunteers followed for seven years looked for the association of UA level with incident CKD defined as eGFR < 60 mL/min/1.73 m^2. UA between 7 and 8.9 mg/dL was associated with almost doubling and level above 9 mg/dL was associated with tripling of incident CKD [108]. A Japanese 5-year follow-up study of more than two thousand healthy adults above the age of 40 years without CKD showed that
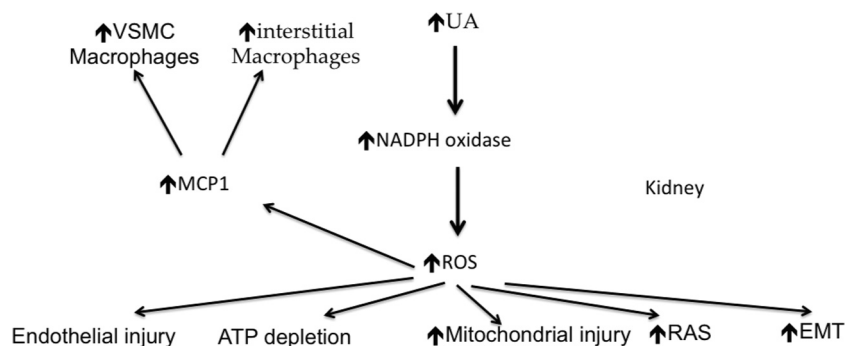
Fig. 6. Different pathogenic mechanisms of kidney injury possibly induced by uric acid. UA = uric acid; ROS = reactive oxygen species; MCPl = Macrophage chemo-attractant protein-1; RAS = renin angiotensin system; EMT = epithelium mesenchyme transition; VSMC = vascular smooth muscle cells.

SUA > 5.9 mg/dL is a significant risk factor for CKD and proteinuria [104]. A recent meta-analysis and review of 13 studies containing more than one hundred and ninety thousand participants tried to find out whether UA is an independent risk factor of incident CKD. This study confirmed that UA is an independent risk factor for the development of CKD in non-CKD healthy persons with no discrimination between male and female sex. The longer the follow-up the stronger is this association [109]. Glucose concentration in the glomerular ultrafiltrate is similar to serum concentration. This glucose is reabsorbed by the PCT. Sodium-glucose co-transporter 2 (SGLT2) present in the apical membrane is responsible for absorption of 90% of this glucose [110]. In case of hyperglycemia, SGLT2 is over expressed to increase glucose absorption [111]. Intracellular glucose increases leading to increased activity of polyol pathway leading to increased fructose synthesis. Intracellular fructose metabolism leads to increased UA synthesis [112,113]. Fructokinase knockout mice are protected against the renal degenerative changes associated with aging and increased salt intake [114]. In a recent study of 422 type 2 DM for more than fifteen years that were followed for up to 77 months, patients with SUA > 7 mg/dL in males and >6 mg/dL in females had a significantly higher rate of DKD progression, and overall mortality [115]. In a meta-analysis of 24 studies with twenty-five plus patients with CKD, elevated SUA is significantly associated with risk of mortality in these patients [116]. GLUT9 polymorphism is strongly associated with SUA in healthy subjects in the general population that have normal kidney function. In a cohort of 755 CKD patients, GLUT9 polymorphism predicted progression [117]. A causal relation of UA to CKD progression could be realized based on this study. In a retrospective cohort study of 803 CKD patients, propensity score analysis using three different methods showed a consistent impact of high UA on progression to end-stage renal disease (ESRD) [118]. XO inhibitors possibly delay the progression of CKD in adult hyperuricemic and hypertensive patients [119]. The target SUA should be <6.5 mg/dL to delay progression [77,118].

Acute kidney injury (AKI)

In 37 patients who underwent cardiac surgery, SUA was assessed 1 hour postoperative. A significant positive correlation between SUA, on one hand, and urine neutrophil gelatinase-associated lipocalin (NGAL) estimated 1 h, 6 h and 24 h postoperative, and serum creatinine measured 1 day, 2 days and 3 days postoperative respectively on the other hand. There was also a significant negative correlation between SUA and the kinetic eGFR measured 1, 2, 3 and 4 days postoperative respectively. These findings illustrated that the rise of UA one-hour postoperative precedes and significantly predicts subsequent development of AKI [120]. In another trial in patients undergoing open-heart surgery, SUA in blood samples collected 2 h postoperative had a stronger predictive value for AKI and the need for renal replacement therapy (RRT) in comparison with serum and urine NGAL [121]. Preoperative UA level was also a strong predictor of postoperative AKI. In patients undergoing radical cystectomy, preoperative SUA was an independent predictor of postoperative AKI [122]. In a retrospective study of more than two thousand patients who underwent coronary bypass surgery, preoperative SUA was a strong predictor for the development of postoperative AKI [123]. UA was not only a predictor of postoperative AKI but also predicted AKI in patients having burns [124] or those with sepsis [125]. In a retrospective analysis of all patients admitted to a tertiary hospital over 2 years, and after consideration of logistic regression analysis, patients having SUA > 9.4 mg/dL on hospital admission had significantly the highest risk to develop AKI during their hospital stay. On the other hand, those having UA < 4.5 mg/dL were at lowest risk [126]. The strength of this study is based on many points: 1st is wide spectrum of the patients' primary disease, including infectious, cardiovascular, gastrointestinal, hematology/oncology, and respiratory disorders. The 2nd point is the graded association of UA with the development of AKI. A similar retrospective study in another hospital has shown similar results [127]. When more than eleven thousands of participants were followed for about twelve years, 823 of them were admitted to the hospital because of AKI. SUA > 5 mg/dL was independently associated with these admissions. The risk of AKI was 16% higher with each 1 mg increase in SUA [128]. SUA level is a significant predictor of contrast-induced nephropathy (CIN) [129,130]. UA lowering with allopurinol in addition to saline hydration was associated with significantly lower incidence of CIN compared to saline hydration alone or saline hydration plus N-acetyl cysteine [130]. UA potentially mediates AKI through vascular, pro-oxidative and inflammatory mechanisms [131]. UA inhibits endothelial NO synthesis, and thus promotes vasospasm in afferent and, to less extent, in the efferent arterioles [82,132]. UA inhibits capillary endothelial cells' proliferation and migration [133]. It can also induce endothelial apoptosis [132]. UA also correlates with pre-glomerular arteriolopathy in human beings, an obstacle to renal autoregulation in condition of renal hypoperfusion [134]. As mentioned above, UA stimulates NADPH oxidase with consequent increase in oxidant stress. The increased oxidant stress stimulates production of macrophage chemo-attractant factor (MCP1) within vascular smooth muscle cells (VSMCs) [135]. Hyperuricemic rats show increased macrophage infiltration of their kidneys [83]. Administration of an NADPH oxidase inhibitor inhibited MCP1 production within VSMCs [135] (Fig. 6).

Preeclampsia (PE)

PE complicates 5–10% of pregnancies worldwide [136]. Affected women usually have profound long-term consequences [137]. PE is characterized by Htn, proteinuria, and edema that develop after 20 weeks of pregnancy [138]. Decreased placental perfusion due to impaired remodeling of spiral arteries might result in hypoxia [139]. UA level showed high correlation with BP in cases of PE [140]. In pregnant ladies suffering PE, serum tumor necrosis factor α (TNFα) and ICAM1 were significantly higher than control or hypertensive pregnant ladies. Subcutaneous blood vessels showed intense staining with these 2 agents. SUA showed positive correlation with TNF α and ICAM1 in PE patients [141].
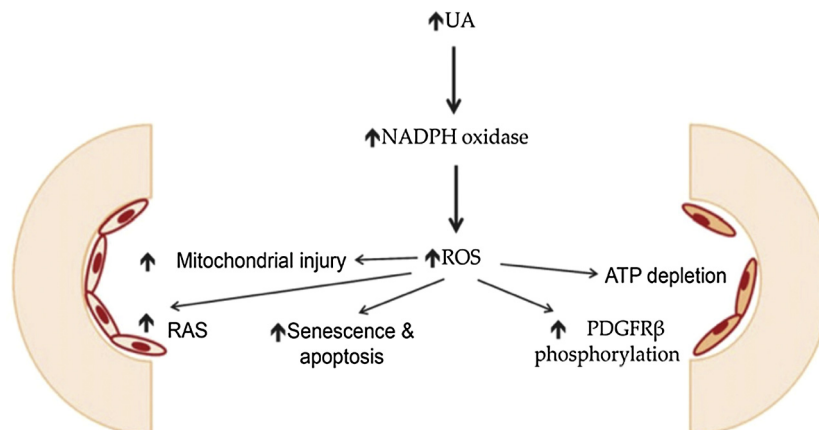
Uric acid and cardiovascular system (CVS)

Whether SUA is merely a risk marker or a risk factor for CV disease, or whether hypouricemic agents affect outcomes is still a matter of debate [142]. The association between SUA and different CVD might be confounded by different factors frequently encountered in cardiac patients. These factors include Htn, dyslipidemia, DM, alcohol consumption, hypothyroidism and diuretic use [143]. Independent of any CV risk factor, increased SUA level, even within the normal range, is a risk factor for impaired flow-mediated dilation (FMD) of brachial artery (Fig. 1), increased carotid intima-media thickness (IMTc), and increased stiffness of the aorta in healthy subjects [144–149]. In non-diabetic CKD patients (stage 3–5) who lack evidence of CVD and were not treated with either RAS blockers or statins, FMD inversely correlated with SUA [150]. Treatment of hyperuricemic type 2 DM patients with allopurinol for 3 years succeeded to reduce carotid IMT [151]. UA stimulates platelet-derived growth factor receptor β (PDGFRβ) phosphorylation in the rat aorta [152]. This discovery would explain the VSMC proliferation and CVD in hyperuricemic patients. When isolated human umbilical vein endothelial cells (HUVECs)

were exposed to 6 mg and 9 mg/dL UA, significant increase in intracellular free oxygen species was followed by senescence and apoptosis of these cells. Senescence and apoptosis of HUVECs were ameliorated on addition of either probenecid or an antioxidant like N-acetyl cysteine or tempol. In addition, UA increased expression of the different elements of RAS within HUVECs [153]. When human aortic endothelial cells (HAECs) are exposed to high UA concentration for 48 h, a significant decline in eNOS activity was observed. There was also 50% reduction in mitochondrial DNA level, a decrease in mitochondrial mass and a significant reduction in basal concentration of ATP. The higher the concentration of UA within the culture medium the greater was the reduction in intracellular ATP concentration [66] (Fig. 7).

On the other hand, some studies failed to demonstrate UA as independent CVD risk factor [154]. Analysis of data obtained from 6763 participants in the Framingham heart study failed to demonstrate a significant association between SUA and CHD and CV mortality [155]. However, many of the epidemiologic data collected in recent years favor the association between SUA and the risk of CVD. A recent study showed SUA as independent predictor of CHD [156]. In a prospective study of more than fifty thousand male subjects with history of gout in the Health Professionals Follow-Up Study, the relation between history of gout and the development of CVD was examined. After follow-up for twelve years, patients with history of gout were found at greater risk of CV mortality, mainly due to CHD [157]. Increased SUA is associated with the unstable coronary lipid-rich plaques [158]. SUA predicts HF in patients with stable CHD. This predictability is muffled, but not abolished, by different confounders [159]. SUA was measured in 705 cases of both sexes that underwent coronary angiography. 41% of cases had normal angiography and were considered the control group. A significant positive correlation between SUA and the severity of CHD score was encountered [160]. After measurement of SUA of over 400.000 in checkup centers in Stockholm, these candidates were followed for 7–17 years. The higher the basal SUA in this middle-aged population the higher is the chance to develop acute myocardial infarction (AMI), heart failure (HF), and stroke [161]. SUA is a significant predictor of poor outcomes in AMI patients complicated with reduced LV function, HF, or both [162]. The Pooled data from eleven studies that evaluated the prognostic importance of SUA demonstrated that hyperuricemia can significantly predict all-cause mortality in HF patients [163]. These data are also observed in HF patients with preserved ejection fraction [164] and in patients hospitalized with severely decompensated acute HF [165,166]. The relation of SUA with acute HF outcome is weakened with deterioration of kidney function [167]. The association

between SUA and ischemic stroke is debatable. While some accuse SUA as predictor of magnitude of infarct [168], most found SUA to play a favorable role [169–171]. Allopurinol succeeded to improve mortality rate in HF patients with history of gout [172]. However, in a more recent trial, allopurinol failed to improve left ventricular ejection fraction, or exercise capacity after 6 months in patients with HF and hyperuricemia [173]. In a cohort of 557 healthy subjects, 415 of whom were women, aged 60 years and older, men with higher SUA (>5.5 mg/dL) had significantly higher left ventricular mass compared to men with lower level [174]. The association between SUA and left ventricular hypertrophy (LVH) is more likely in women than in men when they have CKD [175]. In patients with LVH and preserved ejection fraction, SUA is associated with diastolic dysfunction in women only [176]. 37% of kidney transplant recipients that had normal graft function developed persistent hyperuricemia within the 1st post-transplant year. Hyperuricemia in these patients was significantly associated with Htn, increased pulse wave velocity, and LVH [177]. Treatment with allopurinol improved left ventricular function and coronary flow reserve in patients with dilated cardiomyopathy and concomitantly elevated SUA [178]. The association between SUA and the major cardiovascular adverse events following acute coronary syndrome is stronger in women compared to men [179]. It seems that this association in patients with normal kidney function is observed in older aged women. SUA was found as independent predictor of LVH in postmenopausal but not in premenopausal women [180]. In type 2 DM hyperuricemia was significantly associated with atrial fibrillation independent of other risk factors and all potential confounders [181]. In 200 hypertensive patients that have normal treadmill exercise test, patients with erectile dysfunction have significantly higher SUA [182]. In persons with elevated level of HDLc, SUA is associated with an increased risk of idiopathic venous thromboembolism [183]. In patients with hypertrophic cardiomyopathy, SUA is a significant predictor of adverse outcome [184]. Increased SUA was appointed as independent risk factor for overall mortality and CV mortality [185,186]. The relationship between SUA and CV mortality is higher in the lowest and highest quintiles in both men and women [187]. A prospective analysis of 329 patients with ST-elevation myocardial infarction (STEMI) and eGFR < 60 mL/min/1.73 m^2 treated with percutaneous coronary intervention (PCI) disclosed a strong correlation of SUA with 1-year mortality [188]. A recent meta-analysis of six studies, including more than 200.000 patients showed that hyperuricemia independently increases the risk of mortality from CVD and CHD [189]. The knowledge of genetic regulation of SUA allows the use of Mendelian randomization to examine the possible causal rela-

Fig. 7. Different vascular injury mechanisms possibly mediated by uric acid. UA – uric acid; ROS = reactive oxygen species l; RAS = renin angiotensin system; PDGFR – platelet derived growth factor receptor.

tion between SUA and cardiovascular risk. Genotype precedes life events and is not affected by lifestyle [190]. This analysis disclosed a causal relation between SUA on one hand and CHD, cardiovascular mortality and sudden cardiac death on the other hand [191]. These results criticize the hypothesis that the effect observed with high SUA is not due to the molecule itself but due to the induction of the XO and the effect of XO inhibitors is secondary to inhibition of the enzyme rather than the consequent control of SUA. XO activation results in increased production of free oxygen radicals with consequent increased oxidative stress and triggered inflammation. XO inhibitors can abolish this oxidative stress and burns out the consequent inflammation [192].

Conclusions

According to the recent experimental and clinical trials and to the therapeutic interventions and the Mendelian randomization studies it seems that UA is a real risk factor for the development of metabolic, renal and CVDs. The intracellular UA seems to be more pathogenic. The cell membrane urate transporters are responsible for the intra-extracellular UA shift, and hence, they are important determinants of the offending role of UA. These studies have also demonstrated that low SUA levels might carry high risk similar to the high levels. Based on these facts, more interventional studies are needed to optimize the therapeutic management of this evolving risk factor. These studies should highlight when to treat, the target SUA level and the long-term safety of the different hypouricemic agents.

Conflict of interest

The authors have declared no conflict of interest.

Compliance with ethics requirements

This article does not contain any studies with human or animal subjects.

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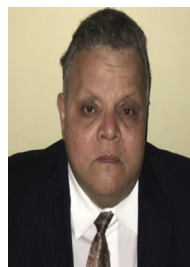
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