

**Review**

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# Uric Acid – Key Ingredient in the Recipe for Cardiorenal Metabolic Syndrome

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**Key Words**

Uric acid · Fructose · Cardiorenal metabolic syndrome · Chronic kidney disease

**Abstract**

Elevated serum uric acid levels are a frequent finding in persons with obesity, hypertension, cardiovascular and kidney disease as well as in those with the cardiorenal metabolic syndrome (CRS). The increased consumption of a fructose-rich Western diet has contributed to the increasing incidence of the CRS, obesity and diabetes especially in industrialized populations. There is also increasing evidence that supports a causal role of high dietary fructose driving elevations in uric acid in association with the CRS. Animal and epidemiological studies support the notion that elevated serum uric acid levels play an important role in promoting insulin resistance and hypertension and suggest potential pathophysiological mechanisms that contribute to the development of the CRS and associated cardiovascular disease and chronic kidney disease. To this point, elevated serum levels of uric acid appear to contribute to impaired nitric oxide production/endothelial dysfunction, increased vascular stiffness, inappropriate activation of the renin-angiotensin-aldosterone system, enhanced oxidative stress, and maladaptive immune and inflammatory responses. These abnormalities, in turn, promote vascular, cardiac and renal fibrosis as well as associated functional abnormalities. Small clinical trials have suggested that uric acid-lowering therapies may be beneficial in such patients; however, a consensus on the treatment of asymptomatic hyperuricemia is lacking. Larger randomized controlled trials need to be performed in order to critically evaluate the beneficial effect of lowering serum uric acid in patients with the CRS and those with diabetes and/or hypertension.

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## Introduction

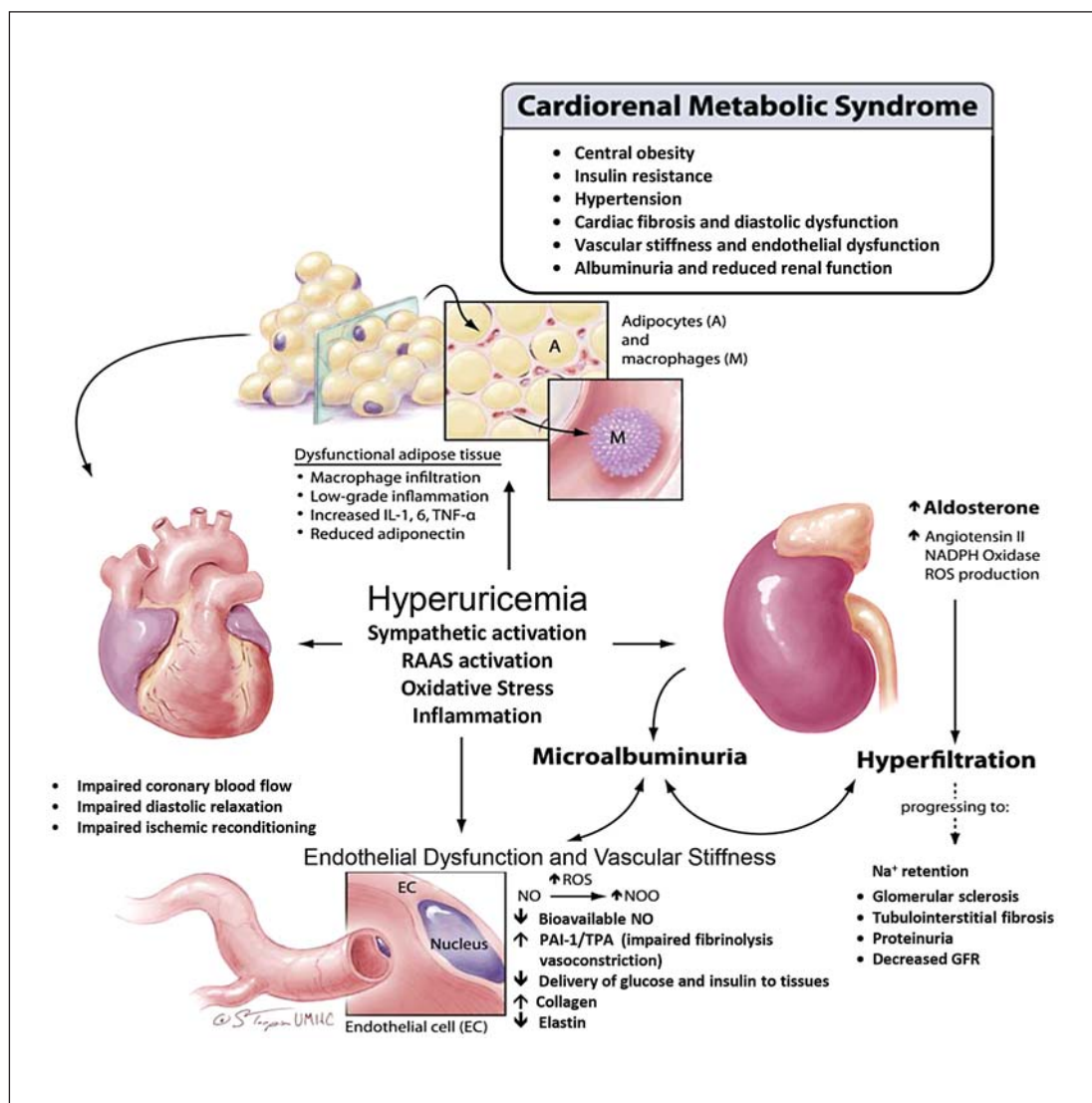
The prevalence of obesity continues to increase throughout the world, and childhood-adolescent obesity is emerging as a major public health issue [1, 2]. Currently, more than half of the adults in the United States are either overweight or obese, and more than 13 million children are obese [3–5]. Obesity is associated with an increased prevalence of the cardiorenal metabolic syndrome (CRS), a constellation of interactive cardiovascular disease (CVD) and chronic kidney disease (CKD) risk factors comprising obesity, insulin resistance, metabolic dyslipidemia, hypertension, cardiac diastolic dysfunction and renal abnormalities including proteinuria [2–6]. Increased fructose consumption has been implicated in the development of the obesity epidemic in the United States. Indeed, the consumption of high-fructose corn syrup (HFCS) has increased for the last three decades, and the increase in the intake of HFCS far exceeds the changes in the intake of any other food or food group [2, 7, 8]. The percentage of HFCS sweeteners increased from 16% in 1978 to 42% in 1998, and since then it has stabilized [9].

Accumulating evidence suggests that hyperuricemia is one of the important factors that may significantly contribute to the development and progression of the CRS. The Swedish pharmacist Carl Wilhelm Scheele discovered uric acid in 1776 in a bladder calculus [10]. Subsequent reports indicated a relationship between elevated serum uric acid levels, gout, hypertension and CKD [11–14]. Elevated levels of uric acid have been associated with inflammation, oxidative stress, insulin resistance, dysglycemia, endothelial dysfunction, vascular, renal and cardiac stiffness, cardiac diastolic dysfunction, renal hyperfiltration and proteinuria, all components of the CRS [2, 5, 6] (fig. 1). The significance of a Westernized diet, high in fructose, and hyperuricemia in the development of the CRS is underscored by the relationship between increased consumption of sugar-sweetened beverages, hyperuricemia and all components of this syndrome [2, 15, 16] (fig. 1).

## Uric Acid Metabolism and Development of Hyperuricemia with a High-Fructose Diet

Uric acid production and metabolism are complex processes involving various factors that regulate hepatic production, and renal and gut excretion of this compound. Uric acid is the end product of an exogenous pool of purines and endogenous purine metabolism. The exogenous pool varies significantly with diet, and animal proteins contribute significantly to this purine pool. The endogenous production of uric acid is mainly from the liver, intestines and other tissues like muscles, kidneys and the vascular endothelium. Uric acid formation from purine catabolism occurs by a series of enzymatic reactions that ultimately involve the xanthine oxidase enzyme. An intermediate product of this metabolism is inosine. This intermediate is converted by the purine nucleoside phosphorylase to hypoxanthine. Xanthine oxidase converts hypoxanthine to xanthine and subsequently to uric acid [2, 6, 7, 15, 16].

The production and catabolism of purines are relatively constant between 300 and 400 mg per day. The kidneys eliminate approximately two-thirds, while the gastrointestinal tract eliminates one-third of the uric acid load [6, 15]. Almost all uric acid is filtered from glomeruli, while post-glomerular reabsorption and secretion regulate the amount of uric acid excretion [17, 18]. The proximal tubule is the site of uric acid reabsorption and secretion, and approximately 90% is reabsorbed into blood. This is primarily accomplished at the proximal tubular level by transporters that exchange intracellular anions for uric acid [17, 18]. Almost all reabsorption of uric acid occurs at the S1 segment of the proximal tubule. In the S2 segment of the proximal tubule, uric acid is secreted to a greater extent than that which undergoes reab-



Color version available online

**Fig. 1.** Mechanisms by which elevated uric acid promotes components of the CRS.

sorption. Post-secretory reabsorption occurs at a more distal site of the proximal tubule, and approximately 10% of the filtered uric acid appears in the urine [17–19].

Increased serum uric acid levels as seen in obese patients and in persons with renal impairment are driven by multiple mechanisms. In obesity, especially with increased HFCS consumption, there is an increased hepatic production of uric acid [6–9]. As the glomerular filtration rate (GFR) falls, serum uric acid levels increase progressively, and approximately 50% of renal patients become hyperuricemic by the time they start dialysis [11, 20–22]. Although hyperuricemia and hyperinsulinemia are closely linked, the mechanisms behind this association remain unclear. One mechanism likely relates to the fact that hyperuricemia promotes insulin resistance and associated hyperinsulinemia [2, 3]. Renal tubular function is influenced by insulin metabolic signaling, and urinary uric acid clearance decreases with decreasing insulin-mediated glucose disposal [23]. Recent studies have shown that adipose tissue may contribute as an endogenous source of uric acid, and that

uric acid increases the inflammatory macrophage infiltration and inflammation in adipose tissue [24, 25].

Uric acid is a by-product of uncontrolled fructose metabolism, which is mediated through increased fructokinase activation. Fructokinase has no negative feedback system, and adenosine triphosphate is used as a source of phosphorylation [26, 27]. This results in intracellular phosphate depletion and the rapid generation of uric acid due to activation of adenosine monophosphate deaminase [2, 26, 28]. Serum uric acid increases rapidly after ingestion of fructose, resulting in increments as high as 2 mg/dl within 1 h [28]. The induction of the fructokinase enzyme by fructose in the liver provides a feed-forward mechanism for continued production of uric acid in the setting of high-fructose Western diet consumption [2, 26, 28].

### Uric Acid, Cardiorenal Metabolic Syndrome and Diabetes

Epidemiological studies have confirmed the association of hyperuricemia with the CRS [2, 7, 8, 23, 24, 27]. A cross-sectional analysis of 1,370 adolescents aged 12–17 years using data from the National Health and Nutrition Examination Survey (NHANES) [29] showed that the prevalence of the syndrome was <1% in the lowest quartile of uric acid serum levels, 3.7% in the second quartile, 10.3% in the third quartile and 21.1% in the highest quartile. Fructose-rich diets can raise uric acid production and induce the components of the syndrome through mechanisms independent of energy intake or weight gain [2, 30, 31], effects typically not observed with solely glucose-rich diets [2, 30, 31]. In the Finnish Diabetes Prevention Study [32], which involved lifestyle intervention in high-risk, middle-aged subjects with impaired glucose tolerance, elevated baseline uric acid and its increase over time predicted a two-fold increase in the likelihood of developing type 2 diabetes mellitus (T2DM). A meta-analysis of 11 cohort studies with 42,834 participants that reported >3,000 incident cases of T2DM with a follow-up period ranging from 2.0 to 13.5 years suggested that serum uric acid levels had a positive correlation with the development of T2DM regardless of various study characteristics [33].

#### *Uric Acid and Cardiovascular Disease*

Hyperuricemia has been associated with hypertension in multiple studies, and it has been hypothesized that elevated uric acid might play a role in the pathogenesis of primary hypertension [34–36]. In an early study, hyperuricemia was reported in 25–40% of untreated hypertensive subjects and in 75% of malignant hypertensive subjects [34]. A study of more than 3,000 Framingham Study participants showed that elevated serum uric acid levels were an independent predictor of hypertension incidence and longitudinal progression at a 4-year follow-up [35]. In a study of children referred for evaluation of hypertension, uric acid levels were directly correlated with both systolic and diastolic blood pressure in the 63 subjects with hypertension [20]. In the 1999–2006 NHANES study of 6,036 adolescents between 12–17 years of age [21], 17% were obese [body mass index (BMI)  $\geq$ 95th percentile] and 3.3% had elevated blood pressure. Further, 34% had a uric acid level  $\geq$ 5.5 mg/dl and, when compared to participants with uric acid levels <5.5 mg/dl, had a 2.03-fold higher odds of having elevated blood pressure. Elevated serum uric acid has also been independently associated with a nondipper circadian pattern. In a study of 112 persons with essential hypertension, of which 60 were nondippers, the nondippers had higher serum uric acid levels [36]. This nondipping pattern is also seen in persons with obesity, salt sensitivity, the CRS and renal disease [2, 3].

There is mounting evidence that lowering of serum uric acid levels is a strategy that may help lower elevated blood pressures. For example, in a randomized, double-blind, placebo-controlled trial involving 30 adolescents with newly diagnosed, never-treated stage 1 essential hypertension and serum uric acid levels  $\geq 6$  mg/dl, allopurinol treatment was superior to placebo in reducing mean systolic and diastolic as well as 24-hour ambulatory blood pressures [37]. In a study of pregnant women, the mean serum uric acid values for women with preeclampsia were high, and serum uric acid levels of  $\geq 5.5$  mg/dl indicated an increased likelihood of preeclampsia in hypertensive pregnant patients [38]. Moreover, in a randomized controlled trial, men who were administered 200 g fructose daily for 2 weeks displayed an increase in 24-hour ambulatory blood pressures, which was prevented with concomitant administration of allopurinol [39]. These results support the notion that consumption of high-fructose diet and consequent hyperuricemia raise blood pressure, and that lowering uric acid with allopurinol lowers blood pressure as well as the associated CVD risk. A meta-analysis of 16 studies including 238,449 adults found that hyperuricemia was associated with a higher risk of both stroke incidence and mortality [40]. This association of elevated uric acid with increased risk for stroke could be observed in both diabetic and nondiabetic populations.

Elevated serum uric acid levels have been shown to be associated with impaired endothelium-mediated relaxation, vascular stiffness and a restrictive left ventricular filling pattern/diastolic dysfunction [2, 3, 5]. Increasing serum levels of uric acid have also been significantly linked to the progression of congestive heart failure [41, 42]. In a randomized, placebo-controlled, double-blind crossover study of patients with New York Heart Association class II–III chronic heart failure comparing 300 mg allopurinol daily (1 month) versus placebo, allopurinol significantly increased the forearm blood flow in response to acetylcholine as compared to placebo [41]. Another study assessing the development of CVD in patients with hypertensive nephropathy and impaired kidney function [estimated GFR (eGFR)  $< 45$  ml/min/1.73 m<sup>2</sup>] found that the use of allopurinol decreased CVD morbidity and all-cause mortality [42]. These observations underscore the notion that elevated uric acid promotes endothelial dysfunction, vascular and cardiac stiffness as well as CVD [2, 3].

#### *Elevated Uric Acid and Chronic Kidney Disease*

It is unclear whether uric acid is a marker or an independent risk factor for the initiation and progress of CKD. However, uric acid can accelerate renal disease in experimental animals and is epidemiologically associated with progressive renal disease in humans. In animal models of CKD, hyperuricemia leads to worsening proteinuria and renal failure along with associated glomerular sclerosis and tubulointerstitial fibrosis [2, 43, 44]. In rodent models, high dietary fructose-associated hyperuricemia produces CRS with glomerular hyperfiltration, renal hypertrophy and subsequent increases in proteinuria and reductions in creatinine clearance [44]. Epidemiologic studies have shown that hyperuricemia is an independent risk factor for renal dysfunction in the normal population and in patients with hypertension, diabetes and CKD. The CRS is strongly associated with CKD (defined as GFR  $< 60$  ml/min/1.73 m<sup>2</sup>) and microalbuminuria, with the risk of CKD increasing progressively with the number of criteria that constitute the syndrome [16, 27, 29]. It has been proposed that increased HFCS consumption causes renal disease in concert with abnormalities characterizing the CRS via increases in uric acid production [2]. Recently, a relationship between sugar-sweetened soda consumption and hyperuricemia and kidney disease has been found in an analysis of data from the ARIC study [45]. As compared to the participants who drank less than one soda per day, the odds ratio for CKD significantly increased to 2.59 among participants who drank more than one soda per day and had a serum uric acid level of  $> 9.0$  mg/dl. A study of 21,475 healthy volunteers followed prospectively for a median of 7 years



found that a slightly elevated uric acid level (7.0–8.9 mg/dl) was associated with almost twice the risk for incident kidney disease (OR 1.74), and further elevations ( $\geq 9.0$  mg/dl) were associated with more than three times the risk (OR 3.12) [46]. A recently conducted Swiss population-based, cross-sectional study of >5,000 participants aged 35–75 years found that uric acid levels are an independent risk factor for CKD in both men and women [47].

There is emerging evidence that lowering of uric acid is a key strategy for reducing progression of renal disease. In a prospective randomized trial of 113 patients with an eGFR  $< 60$  ml/min/1.73 m<sup>2</sup>, subjects received treatment with allopurinol 100 mg per day versus standard therapy. In the standard therapy group, the eGFR decreased by  $3.3 \pm 1.2$  ml/min/1.73 m<sup>2</sup>, and in the allopurinol group, the eGFR increased by  $1.3 \pm 1.3$  ml/min/1.73 m<sup>2</sup> after 24 months [48]. In a randomized controlled trial of hyperuricemic CKD patients treated with either allopurinol or usual therapy for 12 months, 16% patients in the allopurinol group reached the combined end points of significant deterioration in renal function and dialysis dependence compared with 46.1% in the control group [49]. In an analysis of 838 patients with CKD stage III/IV, a 1 mg/dl greater baseline uric acid level was associated with a 17% increased risk of all-cause mortality and a 16% increased risk of CVD mortality [50]. In a study of >300 patients with IgA nephropathy, hyperuricemia independently predicted renal survival at 1, 3 and 5 years after adjustment for GFR. In the same study, a greater number of hypertensive and hyperuricemic subjects had a reduction in antihypertensive drug dosage when treated with allopurinol [51]. The results of a meta-analysis of 11 randomized controlled trials with a total of 753 participants showed that uric acid-lowering therapy was associated with a decrease in serum creatinine and an increase in eGFR, suggesting that lowering of uric acid slows the decline of kidney function [52]. A post hoc analysis of the Febuxostat Open-Label Clinical Trial of Urate-Lowering Efficacy and Safety study [53] in 116 hyperuricemic patients with gout treated with febuxostat for 5 years demonstrated an inverse correlation between serum uric acid reduction and rate of eGFR decline. Individuals with the greatest reduction in serum uric acid following febuxostat treatment experienced the slowest rate of renal function decline, and for every 1 mg/dl decrease in uric acid, the model projected an expected improvement in eGFR of 1 ml/min/1.73 m<sup>2</sup> from the untreated value [53]. Further, a post hoc analysis of data from participants (patients with type II diabetes and nephropathy) in the Reduction of Endpoints in Non-Insulin-Dependent Diabetes Mellitus with the Angiotensin II Antagonist Losartan (RENAAL) trial showed that the risk of a kidney event end point declined by 6% per 0.5 mg/dl decrement in uric acid levels [54]. After adjustments, approximately 20% of the renoprotective effect of losartan was attributed to this drug's uric acid-lowering properties.

### **Uric Acid, Endothelial Dysfunction and Vascular Stiffness**

Endothelial dysfunction and arterial stiffness play a central role in the development and progression of hypertension cardiac diastolic dysfunction as well as CVD and CKD [2, 3, 5]. Accumulating evidence suggests that increased serum uric acid levels may be associated with endothelial dysfunction and vascular stiffness, especially in the presence of the CRS [55]. A cross-sectional evaluation of the ARIC study population in the United States showed that serum uric acid levels were associated with intimal medial thickness in both sexes [56]. A cross-sectional study of 3,772 Chinese adults found that serum uric acid was associated with increased carotid femoral pulse wave velocity independent of conventional CVD risk factors [57]. A study of 366 hypertensive individuals between the ages of 34 and 75 years showed that uric acid levels positively correlated with the mean maximum pulse wave

velocity and carotid intimal medial thickness [58]. Further, in a cross-sectional data analysis of 982 Japanese individuals who underwent health screening, multivariate analysis after adjustment for classical risk factors showed an association between uric acid and high brachial-ankle pulse wave velocity in subjects with the metabolic syndrome as well as in those without [59]. Another study of 940 Chinese participants, of which 22% were hypertensive patients, serum uric acid was positively associated with carotid-femoral pulse wave velocities and central systolic blood pressure in all subjects. Patients with hyperuricemia had significantly higher central systolic blood pressures than those with normal serum uric acid [60].

### **Cellular and Molecular Mechanisms of Cardiovascular/Renal Injury**

The mechanisms by which uric acid promotes cardiovascular and renal injury are multiple, comprising cardiac, vascular, renal hepatic and adipocyte maladaptive immune and inflammatory response, inappropriate activation of the renin-angiotensin-aldosterone system (RAAS), enhanced oxidative stress and impaired nitric oxide availability.

### **Adipocyte Dysfunction, Maladaptive Immune and Inflammatory Response and Insulin Resistance**

Insulin resistance plays an important role in the development of the CRS and T2DM. Hyperuricemia was found to be an independent risk factor for progression to hyperinsulinemia in the 11-year follow-up of nondiabetic participants in the Atherosclerosis Risk in Communities Study [61]. White adipose tissue immune and inflammatory responses in obesity contribute significantly to adipose tissue and systemic insulin resistance [24, 62]. Dysregulated adipocyte function also results in increased adipose tissue lipolysis and increased secretion of cytokines, such as tumor necrosis factor alpha (TNF- $\alpha$ ), interleukin 6 (IL-6) and resistin, and decreased secretion of adiponectin [2, 24]. Recently, hyperuricemia has been shown to mediate proinflammatory response in the adipose tissue in a murine model of the CRS associated with hyperuricemia. Uric acid induced upregulation of monocyte chemoattractive protein expression and increased macrophage infiltration and proinflammatory responses in adipose tissue [24]. These effects of uric acid were contributed to the intracellular effects of uric acid [24] (fig. 1).

### **Perivascular Adipose Tissue, Endothelial Dysfunction and Vascular Stiffness**

In addition to visceral adipose tissue dysfunction, perivascular adipose tissue also contributes significantly to inflammation, insulin resistance, endothelial dysfunction and vascular stiffness [2, 63]. Although perivascular fat exerts protective vasoregulatory actions in lean mice, this protective effect of perivascular fat is lost in the setting of obesity [63]. Significant infiltration of macrophages and T cells in perivascular adipose tissue in obesity has been shown to be associated with endothelial dysfunction [63, 64]. Decreased secretion of adiponectin and increased production of cytokines from dysfunctional adipose tissue may significantly contribute to vascular inflammation, insulin resistance, vascular stiffness and impaired relaxation [63]. Elevated uric acid predisposes to all of these adipose tissue abnormalities in conjunction with the CRS [2].

### **Uric Acid, Inflammasome and Activation of Toll-Like Receptor Signaling**

In addition to immune cell polarization and dysregulation of immunity, activation of Toll-like receptor (TLR)-4 and perhaps other TLRs by uric acid may contribute to immune activation and proinflammatory response. Accumulating evidence suggests that inflammasome activation, through IL-1 $\beta$  activation, may contribute to insulin resistance and T2DM [24, 63, 64]. Insulin sensitivity improves when mice deficient in central inflammasome molecules are fed high-fat diets, and this improvement is accompanied by a suppression of immune and inflammatory responses [24, 63]. This inflammasome activation response is seen after exposure to pathogens or activation of danger-associated signals. Although activation of inflammasomes by palmitate and ceramide has been reported in obesity, uric acid-induced activation of inflammasomes suggests that uric acid is another endogenous factor that contributes to the inflammasome response in high fructose diet-induced obesity. Rodent models, in which the uricase gene has been knocked out, show extensive tubular damage due to crystal deposition, renal failure and death in a few weeks [12]. However, crystal-independent injury has also been demonstrated, and hyperuricemia has been shown to cause hypertension and an ischemic type of renal injury with collagen deposition, macrophage infiltration and tubulointerstitial fibrosis.

### **Uric Acid, RAAS Activation, Endothelial Dysfunction, Vascular Stiffness and Progression of the Cardiorenal Metabolic Syndrome**

The role of inappropriate activation of the systemic RAAS and the RAAS in adipose tissue, vasculature and kidney has been increasingly recognized as a significant factor causing cardiovascular and renal injury in obesity and diabetes [2, 3]. In addition to direct effects of angiotensin II (Ang II) and aldosterone, indirect effects of elevated uric acid occur through maladaptive macrophage and T cell polarization [2, 3, 64]. Moreover, increased production of vascular Ang II/aldosterone by perivascular fat causes vascular inflammation and impairment of vascular function. In this regard, elevated uric acid may promote RAAS activation in vascular tissues and kidney [63]. The significance of uric acid-promoting activation of renin-angiotensin is underscored by the modulation of aldosterone secretion through Ang II in the adipose tissue, production of angiotensinogen in the perivascular adipose tissue, increased plasma and adipose tissue aldosterone levels in obesity as well as aldosterone-induced endothelial dysfunction and vascular stiffness [2, 3, 63].

### **Role of Oxidative Stress and Nitric Oxide**

Enhanced production of reactive oxygen species and impaired production and bioavailability of nitric oxide play a central role in endothelial dysfunction, arterial stiffness, impaired diastolic function, hypertension and CKD [2, 3]. Production of vasoactive factors and cytokines by perivascular fat has been shown to modulate vascular function by modulating oxidative stress, vascular relaxation and vascular stiffness [2, 3, 64]. Ang II and aldosterone may also cause insulin resistance indirectly through innate and acquired immune and inflammatory mediated oxidative stress [3, 63, 64]. Thus, these are additional mechanisms by which elevated uric acid may promote the abnormalities characteristic of the CRS [2].



**Table 1.** Randomized controlled trials of lowering uric acid

Study	Patients, n	Intervention	End points	Outcome	Comments
Doehner et al. [66], 2002	14	Allopurinol vs. placebo	Peripheral blood flow, uric acid, allantoin	↓uric acid and allantoin levels; allopurinol: ↑post-ischemic blood flow	CHF patients; placebo-controlled crossover RCT
Siu et al. [49], 2006	54	Allopurinol vs. usual treatment	Serum creatinine, initiation of dialysis therapy, death	↓uric acid; there was a trend toward a lower serum creatinine level in the treatment group; 16% in the allopurinol group reached the combined end points of significant deterioration in renal function and dialysis dependence compared with 46.1% in the control group (p = 0.015)	CKD patients
Malaguarnera et al. [67], 2009	38	Rasburicase (n = 20) vs. placebo (n = 18)	Serum creatinine, serum uric acid, creatinine clearance	↓creatinine and uric acid; ↑creatinine clearance	Elderly, hyperuricemic patients
Goicoechea et al. [48], 2010	113	Allopurinol vs. usual treatment	Renal disease progression, cardiovascular events, hospitalizations of any causes	Allopurinol: ↓serum uric acid and C-reactive protein, risk of hospitalization and cardiovascular events; in the control group, eGFR $13.3 \pm 1.2$ ml/min/1.73 m <sup>2</sup> and in the allopurinol group, eGFR $11.3 \pm 1.3$ ml/min/1.73 m <sup>2</sup> after 24 months	CKD patients
Kanbay et al. [68], 2011	105	Allopurinol	FMD as a marker of endothelial dysfunction, ambulatory BP monitoring, GFR, hsCRP, serum uric acid	↓serum uric acid, systolic BP and hsCRP, ↑eGFR and FMD compared with baseline values	

BP = Blood pressure; hsCRP = high-sensitivity C-reactive protein; FMD = flow-mediated dilation; RCT = randomized control trial.

### Gender, Uric Acid, RAAS and the Cardiorenal Metabolic Syndrome

Obesity in the setting of TDM2 has been shown to have a more deleterious impact on diastolic dysfunction in women than in men [65]. Moreover, nondiabetic obese women also display an increased risk for cardiac dysfunction [65] despite the fact that nondiabetic premenopausal women exhibit less incidence of CVD compared to age-matched men. Population-based studies have documented higher ventricular and peripheral arterial stiffness in women, independent of body weight, as a potential factor contributing to the increased inci-

dence of diastolic dysfunction in obese females even before the appearance of other cardiovascular risk factors. Left ventricular mass correlates positively with glucose intolerance and insulin resistance, especially in women [63, 65]. Indeed, modulation of the RAAS by uric acid as well as high-salt and high-fructose diets in the setting of obesity may be contributing factors for the abrogation of antagonism of RAAS effects by estrogen and loss of cardiorenal protection in obese premenopausal women [3, 65].

## Conclusion

There is increasing evidence that uric acid plays a role in the pathogenesis of the CRS, T2DM, CVD and CKD. Potential mechanisms include the role for crystal-induced inflammatory response and intracellular soluble uric acid-mediated oxidative stress, activation of RAAS, impaired nitric oxide availability, maladaptive immune and inflammatory response as well as insulin resistance. Hyperuricemia may be one of the important factors contributing to abrogation of sex differences in cardiorenal protection in premenopausal women in the setting of insulin resistance and obesity. Though several small trials have shown beneficial effects of lowering serum uric acid (table 1), strong clinical data are lacking that reveal whether treating hyperuricemia in such conditions will lead to improved outcomes, and currently there is no consensus in the medical community regarding the use of serum uric acid-lowering therapy in such patients. Larger randomized controlled trials are needed to establish whether uric acid-lowering therapy is beneficial in such patients in order to be incorporated in patient management.

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