Pitfalls in the Evaluation of Uric Acid as a Risk Factor for Vascular Disease

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Abstract: The association between serum uric acid (SUA) levels and the risk for vascular disease is controversial. Several studies in the general population suggested that elevated SUA levels are independently related to increased vascular morbidity and mortality. However, in other studies this relationship was not significant when other vascular risk factors were considered. Some evidence also suggests that uric acid might be implicated in the development of hypertension, renal disease and insulin resistance. We review the epidemiological data on the relationship between SUA levels and vascular disease and summarize the potential adverse vascular effects of uric acid. We also discuss the associations of SUA levels with established vascular risk factors and the potential benefits of lowering SUA concentration. It is unclear whether uric acid is a causal risk factor for vascular disease. Until more conclusive data are available, patients with elevated SUA levels should be evaluated for the presence of more established risk factors (including type 2 diabetes mellitus, metabolic syndrome and chronic kidney disease) and treatment should be targeted against these factors.

Keywords: Uric acid, vascular risk, hypertension, chronic kidney disease, coronary heart disease.

INTRODUCTION

The association between serum uric acid (SUA) levels and the risk for vascular disease is controversial [1]. Several studies in the general population suggested that elevated SUA levels are independently related to increased vascular morbidity and mortality [2, 3]. However, in other studies this relationship was not significant when other vascular risk factors were considered [4, 5].

We review the epidemiological data on the relationship between SUA levels and vascular disease and summarize the potential adverse vascular effects of uric acid. We also discuss the associations of SUA levels with established vascular risk factors and the potential benefits of lowering SUA levels.

SEARCH METHODS

A literature search (using PubMed) was performed using the following key words: "uric acid", "coronary heart disease", "cardiovascular disease", "morbidity", "mortality", "risk", "hypertension", "chronic kidney disease", "insulin resistance" and "allopurinol" up to 10 March 2009. The authors also manually reviewed the references of retrieved articles for any pertinent material.

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EPIDEMIOLOGICAL DATA

In cross-sectional studies, patients with established coronary heart disease (CHD) had higher SUA levels [6]. However, other studies did not report an independent association between SUA levels and the presence of CHD [7]. SUA levels were also associated with the presence and extent of coronary artery calcification (a surrogate measure of coronary atherosclerosis) in patients with the metabolic syndrome (MetS) [8]. Nevertheless, this association was not observed in patients without MetS [8] or in patients with family history of hypertension [9]. In some prospective studies in the general population, elevated SUA levels were associated with higher risk for CHD morbidity and mortality [2, 3]. In contrast, SUA levels were not independent predictors of CHD events in a nested case-control study within the prospective Reykjavik study [10]. In the Framingham study, SUA levels were not independently associated with CHD events in women [4]. In men, SUA levels were inversely associated with the incidence of CHD [4]. In several studies including only men, SUA levels were not independently associated with CHD events [5, 6, 11-13]. In contrast, in a large study in 28,613 elderly women (mean age 62.3 years) followed-up for a median of 15.2 years, SUA levels were associated with increased CHD mortality [14]. In a meta-analysis of 16 prospective studies in the general population (9,458 CHD cases and 155,084 controls), elevated SUA levels were independently associated with CHD events in both genders [10]. However, this association was non-significant in the 8 studies who adjusted more completely for confounders [10].

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In the general population, SUA levels did not correlate independently with carotid atherosclerosis in some studies [15] whereas in others a correlation was observed only in men [16]. In prospective studies, elevated SUA levels were associated with higher risk for fatal and non-fatal ischemic stroke in the general population [2, 11], in elderly subjects [14, 17, 18] and in patients with type 2 diabetes mellitus (T2DM) [19]. However, an analysis of the Atherosclerosis Risk in Communities (ARIC) study confirmed this association only in patients who were not treated with diuretics [20]. In another study in 9,125 men, low and not elevated SUA levels were associated with stroke mortality [12].

In a cross-sectional study, SUA levels were higher in patients with peripheral arterial disease (PAD) [21]. However, in an analysis of the Multiple Risk Factor Intervention Trial (MRFIT), SUA levels were not independently associated with incident PAD [22].

In prospective studies in the general population, higher SUA levels were independently associated with vascular mortality in some reports [3, 13, 23] but not in all [4, 5].

In patients with established CHD, elevated SUA levels independently predicted all cause mortality in some [24] but not all studies [25]. In patients who had a stroke, elevated SUA levels also predicted a worse outcome [26-30]. However, other studies reported that SUA levels were inversely associated with neurological impairment or death in patients with stroke [31]. The potential role of uric acid in the pathogenesis of stroke was recently reviewed elsewhere [32].

Heart failure (HF) is associated with elevated SUA levels [33-35]. In addition, SUA levels directly correlate with the severity of HF [34, 36]. The excessive activation of xanthine oxidase (XO) in the failing myocardial cell might partly explain these changes [37, 38]. Decreased renal excretion of uric acid and increased XO substrate resulting from enhanced ATP breakdown might also play a role [37, 38]. Some studies suggested that elevated SUA levels are independently associated with greater risk for heart transplantation and mortality in patients with HF [39-41].

ADVERSE VASCULAR EFFECTS OF ELEVATED SUA LEVELS

In vitro studies showed that uric acid stimulates the production of the pro-inflammatory chemokine monocyte chemoattractant protein-1 (MCP-1) from rat vascular smooth muscle cells (VSMC) [42]. Uric acid also induced the production of C-reactive protein (CRP) from human VSMC and endothelial cells [43]. In animal studies, repeated administration of uric acid stimulated the synthesis of tumor necrosis factor-α (TNFα) [44]. In the general population, SUA levels correlated with high sensitivity CRP (hsCRP) levels [13, 45, 46] and with circulating levels of interleukin-6 (IL-6) and TNFα [46]. In addition, subjects with elevated SUA levels had higher risk of experiencing an increase in hsCRP and IL-6 levels [47].

In vitro studies showed that uric acid can also stimulate rat and human VSMC proliferation and migration [43, 48-50]. Interestingly, atherosclerotic plaques contain more uric acid than normal arteries [51].

In vitro studies showed that uric acid reduces the release of nitric oxide (NO) from human and bovine endothelial cells [43, 52]. In animal models, experimental hyperuricemia was associated with a fall in circulating NO levels [52]. In healthy subjects, SUA and NO levels vary during the day in a reciprocal pattern [53]. SUA levels negatively correlated with endothelium dependent vasodilation (EDV), an index of endothelial function [54, 55]. Impaired EDV was reported in patients with hyperuricemia [56, 57]. However, experimental infusion of uric acid in healthy subjects did not affect EDV [58]. In another study, infusion of uric acid improved EDV in patients with type 1 diabetes mellitus and in smokers [59].

SUA levels negatively correlated with arterial stiffness in healthy adults [55] and in stroke survivors [60]. Arterial stiffness is associated with higher vascular risk [61]. However, experimental infusion of uric acid did not affect arterial elasticity [58].

Uric acid is an important contributor to serum antioxidant activity [62, 63]. Experimental administration of uric acid increased serum antioxidant activity and attenuated the intense physical exercise-induced oxidative stress [64, 65]. However, *in vitro* studies showed that uric acid can also have pro-oxidant properties [66-68].

ASSOCIATION OF SUA LEVELS WITH VASCULAR RISK FACTORS

a. Uric Acid and Hypertension

In the general population, SUA levels correlate with blood pressure (BP) [3, 11, 13, 69, 70] and are higher in hypertensive patients [3]. Elevated SUA levels were independently associated with carotid atherosclerosis in some studies in hypertensive patients [71] but not in other [72]. SUA levels were associated with increased risk for vascular events in both hypertensive men and women [73-75]. However, in the Losartan Intervention For Endpoint reduction in hypertension (LIFE) study, SUA levels were associated with vascular events only in women [76]. In the Systolic Hypertension in Europe (Syst-Eur) trial, SUA levels did not predict vascular events in either gender [77]. In another study, the relation of SUA levels with vascular morbidity and mortality was J-shaped in both genders, with the nadir in the second quartile [78]. Uric acid was also a stronger risk factor for myocardial infarction and stroke in normotensive subjects than in hypertensive patients [2].

Preclinical and observational data suggest that uric acid might play a role in the development of hypertension [79]. In animal models, experimental hyperuricemia resulted in BP elevation [48, 49, 80-82]. Several prospective studies suggested that higher circulating uric acid levels predict an increase in BP and development of hypertension in normotensive subjects [70, 83-87]. It was reported that higher SUA levels are associated with increased proximal tubular sodium reabsorption [88]. However, a study in older men did not find a correlation between SUA levels and incident hypertension [89].

b. Uric Acid and Kidney Disease

Chronic kidney disease (CKD) is associated with increased vascular risk [90-92]. In the general population, SUA levels correlate with serum creatinine levels [3, 6, 13, 89] and are inversely associated with estimated glomerular filtration rate (eGFR) [13, 84, 89]. SUA levels correlated

with urinary albumin excretion in patients with T2DM [93, 94] and in some studies in hypertensive patients [95]. However, SUA levels did not correlate with microalbuminuria in other studies in hypertensive patients [72] or in normotensive subjects [96].

It was proposed that uric acid might be involved in the development of CKD [97]. In animal studies, experimental hyperuricemia is associated with increasing proteinuria, worsening renal function, glomerulosclerosis, renal interstitial fibrosis and preglomerular vasculopathy [48, 49, 80, 81]. Increased renal renin expression appears to be implicated in these adverse effects of uric acid on renal function [48, 81]. In humans, hyperuricemia also appears to be associated with an activated intrarenal renin-angiotensin system [98]. Some studies in the general population showed a relationship between elevated SUA levels and increased incidence of CKD [99, 100]. In the Cardiovascular Health Study, SUA levels did not predict incident CKD but were independently associated with the progression of pre-existing CKD [101].

c. Uric Acid and Insulin Resistance

In the general population, circulating uric acid levels are inversely associated with insulin sensitivity [84]. SUA levels also correlate with other markers of insulin resistance, including elevated triglyceride levels [11, 70, 89] and lower high density lipoprotein cholesterol levels [13, 69]. In addition, SUA levels correlate with markers of obesity, including body mass index (BMI) [3, 11, 13, 69, 70, 84, 89] and waist circumference [69, 70]. Insulin resistance is inversely associated with urinary uric acid clearance [102] and experimental insulin infusion decreased urinary excretion of uric acid [103-105]. Patients with MetS may have higher SUA levels [54, 106, 107] and this is also observed in children and adolescents with MetS [108]. Interestingly, diabetic patients may have lower SUA levels [6, 12, 13].

Even though elevated SUA levels appear to reflect insulin resistance, prospective studies in the general population suggested that elevated SUA levels might also be associated with increased risk for incident hyperinsulinemia [109] and T2DM [5, 69, 110]. In addition, higher SUA levels predicted an increase in BMI in non-obese subjects [111].

d. Association of SUA Levels with other Vascular Risk Factors

SUA levels are higher in men than in women [3, 4, 73]. In the general population, SUA levels do not change substantially with age in men, whereas in women they increase after the menopause [4]. SUA levels might be more predictive of vascular risk in women than in men [1].

In the general population, SUA levels also directly correlate with other vascular risk factors, including total cholesterol levels [3, 11, 13, 70, 89], increased alcohol consumption [3, 6, 13, 70] and less physical activity [6].

The relationship between SUA levels and smoking is controversial, with some studies reporting higher SUA levels in smokers [11, 13] and others lower [6, 12, 70].

SUA levels might differ among ethnic groups. Some reports suggested that black subjects have lower SUA levels than Caucasians [112] but larger studies reported the opposite [113]. Hispanics appear to have similar SUA levels with white subjects and lower than blacks [113].

INTERVENTIONAL STUDIES

Allopurinol, an inhibitor of uric acid production, improved EDV in high-risk patients with hyperuricemia [57], in hypertensive diabetic patients [114], in smokers [115] and in patients with heart failure [116-118]. A recent study also reported a reduction in BP with allopurinol in hypertensive adolescents with SUA levels $\geq$ 6 mg/dl [119]. A reduction in plasma renin activity and systemic vascular resistance was also observed [119]. In patients with hyperuricemia, allopurinol increased eGFR and reduced hsCRP levels and BP [120]. In patients with CKD, treatment with allopurinol appeared to delay the deterioration of kidney function [121, 122]. In patients undergoing coronary artery bypass graft surgery, allopurinol appears to reduce morbidity and mortality [123]. Oxypurinol, the active metabolite of allopurinol, might also improve outcome in patients with heart failure and elevated SUA levels [124]. However, allopurinol and oxypurinol not only reduce SUA levels but also inhibit the production of free radicals from XO, an important oxidative enzyme [1]. Therefore, the relative contribution of the reduction in SUA levels to the beneficial effects of allopurinol and oxypurinol is unclear [1]. In one study, the improvement in EDV with allopurinol correlated with the decrease in SUA levels [118]. However, others reported that the antioxidant action of allopurinol and not the fall in SUA levels was the main driver of the improvement in endothelial function [116]. In another study, lowering SUA levels with urate oxidase in diabetic patients did not improve endothelial dysfunction or arterial elasticity and did not reduce BP [125].

Several cardiovascular drugs can affect SUA levels [126]. Treatment with diuretics raises SUA levels, particularly when used at higher doses [3, 13, 74]. In the Systolic Hypertension in the Elderly Program (SHEP), hypertensive patients who showed an increase in SUA levels < 0.06 mmol/l during chlorthalidone treatment had lower risk for CHD events than patients with an increase $\geq$ 0.06 mmol/l [74]. This difference occurred despite the lower BP in the former patients [74]. However, there was no difference in stroke and total vascular events among patients with an increase in SUA levels < or $\geq$ 0.06 mmol/l [74]. In the LIFE study, losartan attenuated the increase in SUA levels compared with atenolol and this was associated with a reduction in vascular events [76]. Atorvastatin also decreases SUA levels [106, 127]. In patients with CHD and MetS, a statin-induced fall in serum uric acid levels was associated with reduced risk for vascular events [106]. However, when the change in renal function was considered, the change in SUA levels did not predict vascular risk [106].

CONCLUSIONS

It is unclear whether uric acid is a causal risk factor for vascular disease. Some evidence suggests that uric acid might be implicated in the development of hypertension, renal disease and insulin resistance. The complex interactions between SUA levels and established or emerging risk factors as well as treatments may explain the controversies in the literature.

Until more conclusive data are available, patients with elevated SUA levels should be evaluated for the presence of more established risk factors (including T2DM, MetS and CKD) and treatment should be targeted against these factors.

ABBREVIATIONS

ARIC	=	Atherosclerosis Risk in Communities
BMI	=	body mass index
BP	=	blood pressure
CHD	=	coronary heart disease
CKD	=	Chronic kidney disease
CRP	=	C-reactive protein
EDV	=	endothelium dependent vasodilation
eGFR	=	estimated glomerular filtration rate
HF	=	heart failure
hsCRP	=	high sensitivity CRP
IL-6	=	interleukin-6
LIFE	=	Losartan Intervention For Endpoint reduction in hypertension
MCP-1	=	monocyte chemoattractant protein-1
MetS	=	metabolic syndrome
MRFIT	=	Multiple Risk Factor Intervention Trial
NO	=	nitric oxide
PAD	=	peripheral arterial disease
SHEP	=	Systolic Hypertension in the Elderly Program
SUA	=	serum uric acid
Syst-Eur	=	Systolic Hypertension in Europe
T2DM	=	type 2 diabetes mellitus
TNFα	=	tumor necrosis factor-α
VSMC	=	vascular smooth muscle cells
XO	=	xanthine oxidase

DECLARATION OF INTEREST

This review was written independently; no company or institution supported it financially. Some of the authors have attended conferences, given lectures and participated in advisory boards or trials sponsored by various pharmaceutical companies.

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