Uric Acid, Vascular Stiffness, and Chronic Kidney Disease: Is There a Link?

Juan C. Ramirez-Sandoval^a L. Gabriela Sanchez-Lozada^b Magdalena Madero^b

^aInstituto Nacional de Ciencias Médicas y Nutrición Salvador Zubirán (National Institute of Medical Sciences and Nutrition Salvador Zubirán (INCMNSZ)), and ^bInstituto Nacional de Cardiología Ignacio Chávez (National Heart Institute), Mexico City, Mexico

Key Words

Hyperuricemia · Hypertension · Vascular calcification · Kidney failure · Urate-lowering therapy

Abstract

Controversy exists with regard to the causal role of hyperuricemia in chronic kidney disease. Vascular stiffness may be the link that explains the relation between hyperuricemia and kidney disease. Hyperuricemia is associated with a number of effects on the vascular endothelium and vascular smooth muscle cells, including an increase in oxidative stress, production of vasoconstrictors, and changes on the structural properties of the large artery wall. Observational evidence in large epidemiological cross-sectional studies suggests that there is an independent association between uric acid and arterial stiffness. The limited evidence from cohort studies or clinical trials does not support treatment of hyperuricemia to reduce vascular stiffness in order to prevent kidney disease. Nevertheless, vascular stiffness may be a valid, reproducible, and useful surrogate endpoint. At this point there seems to be sufficient evidence to warrant larger clinical trials to determine whether lowering uric acid concentrations would be useful for prevention or treatment of vascular stiffness and, subsequently, of cardiovascular and kidney diseases.

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Introduction

Hyperuricemia is a very common biochemical finding associated with aging, hypertension, chronic kidney disease (CKD), and cardiovascular disease (CVD) [1]. Nevertheless, the evidence for a causal link between hyperuricemia and these disorders is controversial, and it has not been firmly established [2]. Particularly, hyperuricemia in persons with CKD appears to be associated with an increased risk for cardiovascular and all-cause mortality, but the role of serum uric acid (SUA) in the initiation, progression, and development of kidney failure remains questionable [3].

Arterial stiffness could be one of the possible mechanisms by which hyperuricemia increases the risk of CKD and CVD through a pathway that involves changes in vascular elastic properties, hypertension and organ damage [4]. This review summarizes relevant studies concerning SUA and vascular stiffness and possible links to the pathogenesis and progression of CKD.

Vascular Stiffness as the Link between Hyperuricemia and CKD

Arterial stiffness may be an early marker of CVD, as it predicts cardiovascular events in patients with essential hypertension and CKD [5]. Because large-vessel arterial stiffness is common in CKD, it is believed to be one of the

Fig. 1. Estimation of PWV in healthy individuals and in those who have hyperuricemia-induced vascular stiffness (see text for details).

mechanisms accounting for the increased risk of CVD in CKD. Vascular stiffness, independent of mean arterial pressure, establishes end-organ damage by increasing the recruitment of collagen fibers and progressive elastic fiber degeneration [6]. The stiffening process facilitates the transmission of excessive pressure and flow pulsatility, which may damage microcirculation, especially in a high-flow organ such as the kidney, leading to potentially microvascular ischemia and tissue damage [7]. Systemic pulsatile pressure can cause vascular injury in low-resistance, high-flow end organs, such as the kidney and brain [8]. There are different mechanisms suggesting a causal role of arterial stiffness in CKD. A possible hypothesis is that the changes in hemodynamic stress on the kidney vasculature may result in endothelial inflammation, infiltration of vascular smooth muscle cells and macrophages, fibrosis, deposition of mucoid material, focal media smooth muscle cell necrosis and vascular calcification [9, 10]. Other plausible mechanisms are related to the effects of chronic inflammation and activation of the renin-angiotensin system [11].

Vascular stiffness is usually estimated using the arterial pulse wave velocity (aPWV) between 2 predefined sites of the arterial system such as carotid-femoral, carotid-radial, or carotid-ankle; the time delay of the arrival of the foot of the pulse wave at these 2 sites is obtained by gating to the R wave of the ECG. Figure 1 shows aPWV in healthy vessels and in vascular stiffness [12]. Different cut-off values have been proposed according to the type of aPWV [13]; unfortunately, a clear international nomenclature is not commonly used, and so analysis and comparison between studies cannot be carried out with ease. Other measurements such as aortic augmentation index (AI) may not be the ideal parameter of arterial stiffness as aPWV, since it is modified by left ventricular ejection fraction and heart rate [14]. Pulse pressure, which is the difference between systolic and diastolic pressures, is one of the simplest measures of vascular stiffness, but it is inaccurate, given the problems related to the normal amplification of the pressure wave and that assessment of pulse pressure in the periphery does not reflect the actual central pulse pressure [15].

Several observational studies have demonstrated the association of vascular stiffness with decline in kidney function [8, 16–18]. Since aortic stiffness is highly prevalent in CKD and predicts CVD events and SUA is associated with vascular disease, the relationship between UA and vascular disease could explain in part the association between the vascular stiffness and CKD.

SUA and Vascular Disease: Mechanisms of Disease

SUA may have a role in the initiation of vascular stiffness and, therefore, also a role in causing vascular disease, hypertension, and CKD. The occurrence of vascular disease may be explained by the following mechanisms: (i) uric acid gains entry to vascular endothelial cell and vascular smooth muscle cells through urate-anion exchangers such as URAT-1, which is expressed in endothelial cells and not only in kidney tubular cells [19]; (ii) high uric acid in the intracellular compartment induces several mechanisms of cellular damage by increasing the activity of nicotinamide adenine dinucleotide phosphate oxidase, which produces reactive oxygen-species and decreases the bioavailability of nitric oxide (NO) [20]; (iii) uric acid activates the transcription factors nuclear factor- κ B, activator protein-1, the mitogen-activated protein kinase signaling molecules ERK p44/42 and p38, and increases cyclooxygenase-2 mRNA expression in cultured vascular smooth-muscle cells [21]; (iv) oxidative stress induced by uric acid also activates the Notch-1 pathway in a dose- and time-dependent manner, which plays an important role in inflammation [22]; (v) uric acid stimulates increased production of the chemokine monocyte chemoattractant protein 1 (MCP-1) expression in a time- and dose-dependent manner dependent on posttranscriptional modification of MCP-1 mRNA [21]; (vi) urate-induced oxidative stress increases the production of potent vasoconstrictors such as endothelin-1 [23]; (vii) uric acid stimulates the local vascular renin-angiotensin system through the activation of mitogen-activated protein (MAP) kinase pathway. The activation of the renin-angiotensin system and reduction of NO synthesis promotes endothelial dysfunction [24]. All these inflammatory pathways may play a role in the process of arterial stiffening even in health; (viii) arterial stiffness relies on the structural properties of the large artery wall, including its essential protein, elastin. Polymers of elastin are the major extracellular matrix components deposited mainly by vascular smooth muscle cells in the arterial media providing ‘elasticity’ to the aorta and resilience against the hemodynamic stresses of the dis-

tending pressure [25]. Hyperuricemia may affect the natural turnover of non-cross-linked soluble elastin, a potential indicator of eventual vascular stiffness [26]. Finally, in the kidney, hyperuricemia-induced microvascular damage to afferent arterioles may lead to the occurrence of sodium-sensitive hypertension [27]. In this condition, increased hypertension would induce more vascular stiffness that would increase blood pressure, which would become a vicious circle with time.

UA and Vascular Stiffness: Observational Studies

Numerous epidemiological studies have described a link between hyperuricemia and CVD. Recently, Borghi et al. [28] conducted a comprehensive review of hyperuricemia and cardiovascular morbidity and/or mortality; however, most of these studies did not include vascular stiffness as a surrogate endpoint. To define the role of SUA in vascular stiffness, we summarized observational studies that report an association between vascular stiffness and hyperuricemia (table 1). Four large epidemiological transversal studies including more than 1,000 patients with differences in clinical characteristics showed a positive association between SUA and vascular stiffness, assessed for the most part by carotid-femoral PWV (cfPWV) [29–32]. In one study from Framingham Heart Study Gen III Cohort, each 1 mg/dl increase in SUA was associated with higher cfPWV [29]. Most of the studies that did not find an association in healthy individuals or in subjects without a history of CKD, CVD, or diabetes. The possible explanation behind these apparently discrepant findings may be that hyperuricemia is a stronger risk factor for vascular stiffness only if a second ‘hit’ has occurred. Several difficulties in determining whether SUA *per se* should be considered a causal factor for vascular stiffness since most of the studies had a cross-transversal design with potential residual confounding. To our knowledge, there are no cohort studies where the exposure (‘hyperuricemia’) could be assessed prior to the occurrence of vascular stiffness or CKD.

UA and Vascular Disease: Interventional Studies

Three parallel randomized, double-blind studies have tested the effect of allopurinol in vascular stiffness in subjects with stage 3 CKD [33], diabetes mellitus [34], and patients with ischemic heart disease (IHD) without CKD [35]. In each of these studies, 67 or 66 patients were assigned to allopurinol 600 mg/day for 9 months vs. placebo. Treat-

Table 1. Observational studies with a positive association between SUA and arterial stiffness

Author (reference), year	Population	Country	Type of study	Serum SUA, mg/dl, mean $\pm$ SD or median (IQR)	eGFR, ml/min/1.73 m ²	Vascular stiffness
<i>Studies with a positive association</i>						
Tausche et al. [36], 2014	17 (allopurinol, n = 8; febuxostat, n = 9)	Germany	Clinical trial	Baseline: 8 (not SD data), after 1 year: 5.01 $\pm$ 0.8 and 4.8 $\pm$ 1.6 for allopurinol and febuxostat respectively	No data	A significant cPWV increase was observed in the allopurinol group (14.1 $\pm$ 3.4 to 16.8 $\pm$ 4.3 m/s), but not in the febuxostat patients (13.7 $\pm$ 2.7 to 13.3 $\pm$ 2.3 m/s, p = 0.55)
Rekhray et al. [35], 2013	59 (allopurinol, n = 31; placebo, n = 29)	United Kingdom	Clinical trial	Baseline: 9.9 $\pm$ 1.5 and 9.4 $\pm$ 2.4 for allopurinol and placebo respectively	No data, but eGFR <30 ml/min/1.73 m ² were excluded	Allopurinol reduced left ventricular endsystolic volume, improved FMD and augmentation index
Mehta et al. [29], 2015 (Framingham heart study gen III participants)	1,992 men and 2,265 women	United States	Cross-sectional	5.3 $\pm$ 1.5	104 $\pm$ 21	Positive association with a multivariate adjusted means of cPWV of 6.90, 6.94, 7.06, and 7.15 m/s for uric acid quartile 1, 2, 3, and 4, respectively
Kuo et al. [30], 2010	5,074 men and 4,301 women	Taiwan	Cross-sectional	No data (14.5% had hyperuricemia defined as UA >6.8-men or >5.5-women)	No data but proteinuria was more frequent with hyperuricemia (9.3 vs. 2.8%)	Subjects with hyperuricemia had a significantly higher baPWV (1,618.8 (379.3) cm/s) than those without it (1,501.8 (334.9) cm/s). Hyperuricemia was a risk factor for abnormal baPWV (OR 1.89)
Park et al. [38], 2012	841 postmenopausal women	Korea	Cross-sectional	4.55 $\pm$ 0.95	No data but CKD were excluded	PWV increased according to tertiles of SUA; cPWV (β = 0.129, p < 0.01) were independently correlated with SUA after adjusting for risk factors
Zhang et al. [39], 2014	100 men with DM2	China	Cross-sectional	5.62	No data but CKD excluded	SUA was correlated with cPWV (r = 0.533, p = 0.001) and crPWV (r = 0.334, p = 0.001)
<i>Studies with a mixed result</i>						
Kao et al. [33], 2011	53 (allopurinol, n = 27; placebo, n = 26)	United Kingdom	Clinical trial	Baseline: 7.4 $\pm$ 1.5 and 7.1 $\pm$ 1.3 for allopurinol and placebo respectively	44 $\pm$ 11 and 46 $\pm$ 9 for allopurinol and placebo respectively	There were no changes in PWV at 9 months even significant regression of left ventricular mass and improved the augmentation index were observed in the allopurinol group
Szejewski et al. [34], 2013	59 (allopurinol, n = 29; placebo, n = 30)	United Kingdom	Clinical trial	Baseline: 9.7 $\pm$ 2.2	86.31 $\pm$ 13.75	No significant changes were seen in augmentation index but a significant regression of left ventricular mass was observed
Fang et al. [31], 2014	2,968 men and 2,182 women	Taiwan	Cross-sectional	UA was 4.6 $\pm$ 0.9 and 5.0 $\pm$ 1.2 for baPWV< and >1,400 cm/s, respectively	No data but eGFR <30 ml/min/1.73 m ² were excluded	Only women with upper tertiles of SUA had greater baPWV level. No association was found in men
Gu et al. [32], 2012	1,138 men and 1,236 women	China	Cross-sectional	5.5 $\pm$ 1.2 in men, 4.4 $\pm$ 1.1 in women	No data but CKD excluded	Only serum SUA was independently associated with cPWV in women. No independent association was found between SUA and crPWV or caPWV in both genders

Table 1. (continued)

Author (reference), year	Population	Country	Type of study	Serum SUA, mg/dl, mean $\pm$ SD or median (IQR)	eGFR, ml/min/1.73 m ²	Vascular stiffness
Tomiyaama et al. [40], 2003	4,488 men and 3,393 women,	Japan	Cross-sectional	6.0 $\pm$ 1.2 in men, 4.4 $\pm$ 0.9 in women	No data but CKD excluded	Age and blood pressure variables were potent significant variables for baPWV, and body mass index, triglycerides, SUA, and fasting blood sugar were significant but weak variables for baPWV in both genders.
Elsurer et al. [41], 2014	147 men and 192 women	Turkey	Cross-sectional	No data	No data but all with CKD (most in CKD stages 2 and 3)	SUA was associated significantly with PWV only in women
<i>Studies without association</i>						
Fu et al. [42], 2015	623 men and 917 women	China	Cross-sectional	4.8 (4.0–5.7)	87.5 (IQR 78.7–97.0)	SUA was higher in subjects with higher cfPWV but the association disappeared in multivariate analysis
Lim et al. [43], 2010	693 men and 583 women	Korea	Cross-sectional	5.2 $\pm$ 1.4 (6.0 $\pm$ 1.3 in men and 4.3 $\pm$ 0.9 in women)	No data but CKD excluded	SUA was not associated with baPWV and hfPWV
Tsioufis et al. [44], 2011	191 men and 101 women	Greece	Cross-sectional	5.2 (no data on IQR)	patients with UA <5.2 mg/dl had an eGFR = 83.1 $\pm$ 16.4, UA >5.2, eGFR = 80.2 $\pm$ 14.3	UA was correlated with cfPWV in the early stages of hypertension, but the association between UA and PWV disappeared after regression analysis
Alvim et al. [45], 2010	678 men and 783 women	Brazil	Cross-sectional	SUA according to APOE polymorphism: 5.0 $\pm$ 1.6 for APOE ϵ 4, 4.7 $\pm$ 1.6 for ϵ 2 and 4.8 $\pm$ 1.5 for ϵ 3	No data but mean serum creatinine was 0.99 $\pm$ 0.20 mg/dl and ϵ 3 (9.8 $\pm$ 2.2 m/s)	cfPWV was not different in patients with more hyperuricemia and APOE ϵ 4 (9.8 $\pm$ 2.1 m/s) compared with polymorphism ϵ 2 (10.0 $\pm$ 2.1 m/s) and ϵ 3 (9.8 $\pm$ 2.2 m/s)
Cicero et al. [46], 2014	248 men and 371 women	Italy	Cross-sectional	4.8 $\pm$ 1.5 (5.7 $\pm$ 1.4 in men, 4.2 $\pm$ 1.2 in women)	68.1 $\pm$ 6.2	A significant association between SUA and cfPWV was found in univariate analysis but when adjusting for age, the trend became nonsignificant
Li et al. [47], 2014	562 men and 681 women	China	Cross-sectional	5.6 $\pm$ 1.4 (6.1 $\pm$ 1.3 in men, 5.2 $\pm$ 1.3 in women)	No data	UA had an independent association with peripheral artery disease in men but not with cardioankle vascular index
Mulè et al. [48], 2014	133 men and 89 women	Italy	Cross-sectional	5.4 $\pm$ 1.3	103.5 $\pm$ 10	cfPWV was significantly higher in hypertensive patients belonging to the uppermost tertile of UA distribution but this in multiple regression model
Sabio et al. [49], 2010	102 women with systemic lupus erythematosus	Spain	Cross-sectional	4.3 (IQR 3.7–5.4)	No data but CKD were excluded	UA was associated with arterial stiffness, but not independently of age and homocysteine levels
Cipolli et al. [50], 2012	131 men and 207 women	Brazil	Cross-sectional	6.7 $\pm$ 0.2 in men, 5.4 $\pm$ 0.1 in women	99.0 $\pm$ 2.4 and 87.9 $\pm$ 3.0 in men and women, respectively	UA was associated with internal carotid artery resistive index only in women but not associated with other ultrasound parameters including stiffness index

IQR = Interquartile range; eGFR = estimated glomerular filtration rate; crPWV = carotid-radial PWV; baPWV = brachial ankle PWV; hfPWV = heart femoral PWV; CAVI = cardio-ankle vascular index; FMD = flow-mediated dilation; APOE = apolipoprotein E.

ment with allopurinol had a small but significant regression of left ventricular mass, but there were no changes in PWV at 9 months in CKD or IHD patients. Nevertheless, allopurinol significantly reduced AI in CKD and IHD patients, which was statistically significant at 9 months. The authors suggest that allopurinol caused a significant reduction in AI and improved endothelial function without a significant effect on BP suggesting improved arterial compliance [35]. It has been demonstrated that different medications to lower SUA have varied effects on vascular stiffness. In a 1-year prospective comparative study, patients with gout assigned to allopurinol had a significant increase in cfPWV (16.8 ± 4.3 m/s, $p = 0.001$ as compared to baseline), but febuxostat-treated patients experienced a beneficial yet opposite effect on cfPWV (13.3 ± 2.3 m/s, $p = 0.55$), although both medications inhibited xanthine oxidase and resulted in effective reduction in SUA levels [36]. One small study of 10 patients with diabetes mellitus and 10 healthy controls did not find any changes in cfPWV or AI after a rapid infusion of intravenous urate oxidase, although SUA decreased significantly [37]. The small and inconclusive evidence from these interventional trials calls for further studies.

Perspective and Conclusion

Vascular stiffness provides a better understanding of the relationship between SUA, CKD and CVD. Further research is clearly required in order to establish the effect of lowering SUA on cardiovascular and renal endpoints. In this regard, vascular stiffness assessed with PWV may be a reproducible, valid, short-term, and useful surrogate endpoint. Although there is a clear and proposed link between SUA and vascular stiffness, it does not yet support the specific treatment of hyperuricemia to reduce kidney or cardiovascular outcomes. Nevertheless, there would seem to be sufficient evidence to warrant larger clinical trials to determine whether lowering SUA concentrations would be useful in the prevention or treatment of vascular stiffness and, subsequently, of cardiovascular and renal diseases.

Disclosure Statement

The authors have no financial conflicts of interest to declare.

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