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METABOLISM (R PASQUALI, SECTION EDITOR)

Increased Serum Uric Acid as a Risk Factor for Cardiovascular Diseases

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Abstract Uric acid, the final product of purine catabolism, tends to accumulate in humans due to the lack of the enzyme uricase. Serum uric acid (SUA) higher than 7 mg/dL is defined as hyperuricemia, the main established risk factor for the development of gout. Nonetheless, since the nineteenth century evidence has increased about the involvement of SUA in the development of cardiovascular diseases. This review will analyze the evidence supporting the existence of a causal relationship between hyperuricemia and the most common cardiovascular disorders such as hypertension, coronary artery disease, heart failure and stroke. We will also review the strength of the relationship as well as the role of hyperuricemia as a new risk factor for cardiovascular diseases. Finally we will discuss if treating hyperuricemia could have a role in terms of cardiovascular prevention.

Keywords Serum uric acid · Hyperuricemia · Gout · Cardiovascular disease · Cardiovascular risk factor · Hypertension · Acute coronary syndrome · Heart failure · Stroke · Xanthine oxidase · Allopurinol

Introduction

Nearly two centuries ago hyperuricemia was first recognized as the primary cause of gout [1]. Nowadays, even if we are certain about the relationship between the crystalline form of uric acid (UA) and the rheumatologic disease, we do not have the same clear-cut evidence about the effective pathophysiological implications of soluble UA. This article we will be mainly focused on the state of the relationship between UA and cardiovascular diseases.

Uric acid is the final product of both endogenous and exogenous purine degradation [2]. It is primarily produced in liver and intestine in a metabolic process which starts from xanthines and hypoxanthines and which involves the enzyme xanthine oxidase. Unlike many other mammals whose urate levels are less than 1 mg/dL because of the conversion of UA to the more soluble allantoin, human beings tend to accumulate urate in serum due to the lack of the uricase enzyme. In humans the upper limits of normality for serum UA are about 5.5 mg/dL in men and about 1 mg/dl lower in women until menopause, when the two levels become comparable. Hyperuricemia is currently defined in presence of serum uric acid (SUA) levels higher than 7 mg/dL. Several mechanisms can be responsible for an increase in the levels of SUA ranging from an enhanced production as a consequence of either altered cellular turnover (e.g., cancer, leukemia) or increased purine ingestion, to a variable degree of impaired excretion [3]. In fact, since more than 70 % of urate clearance depends on the kidney, any impairment in renal function usually yields urate retention. A condition of reduced urate excretion can also be hypothesized in presence of a normal filtrating function as a consequence of a defective activity of some recently identified urate transporters that are located in the proximal tubule [4]. In addition, hyperuricemia can be associated with the use of some medications as loop and thiazide diuretics, theophylline and sodium valproate as well as with the presence of gastro-enteric diseases since the small bowel is responsible for the 15 % remnant uric acid clearance. The role of fructose intake is an open question since it has been demonstrated to be associated with uric acid increase in some studies [5], but not confirmed in others at isocaloric feeding conditions [6•].

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Pathophysiological Aspects of SUA: How and why Hyperuricemia Produces Vascular Damage

Despite that UA has been considered as an inert metabolic substance for a long period of time, nowadays we have the evidence that nothing could be more far from this assumption. At normal serum levels UA exerts some anti-oxidant properties acting as a strong peroxynitrite scavenger. On the contrary, high UA levels are considered as a promoter of oxidative stress. The biochemical process leading to hyperuricemia increases the generation of free oxygen radicals in the proportion of one molecule of superoxide for each single molecule of UA produced [7•] with a negative impact on the microcirculation and the development of arteriolar disease particularly at renal level. Experimental evidence suggests that hyperuricemia can impair endothelial function by promoting an increased oxidative state, which in turn down-regulates endothelial nitric oxide (NO) production, in a condition where NO has a central role in the modulation of vascular flow and blood pressure [8]. Hyperuricemia also inhibits endothelial cell proliferation and migration [9] and stimulates the release of inflammatory C-reactive protein, growth factors and free oxygen radicals [5]. In addition, the negative effects of UA also involve the smooth muscle cells where it is capable of stimulating cellular proliferation via the mitogen-activated protein kinase (MAPk) pathway and to induce the synthesis of pro-inflammatory substances as chemokine, monocytes chemoattractant protein-1 (MCP-1) and C-reactive protein. Finally, UA is also proven to strongly activate the renin-angiotensin system, promoting both angiotensin 1 (AT1) and angiotensin 2 (AT2) receptor and AT2 expression, with demonstration of AT2's ability to inhibit cell proliferation and to promote endothelial senescence and apoptosis [10].

Uric Acid: A Cardiovascular Risk Factor?

In recent years an interesting debate has developed around the potential role of serum UA as a cardiovascular risk factor and the importance of the issue is still increasing as the prevalence of hyperuricemia is growing with an actual prevalence that involves over 20 % of the adult US population [11•]. However a definite answer to the question has not been provided so far and the main potential bias is that elevated levels of serum UA have been described as a confounding factors in patients with additional cardiovascular risk factors such as metabolic syndrome [12•] and diabetes [12•, 13].

Hyperuricemia and Hypertension

Hypertension is the most common risk factor for cardiovascular disease in the general population. The first hypothesis of an association between hypertension and UA dates back to the 1870 s, owing to the observation that hypertension was a common finding in the gouty patients, whilst a large fraction of hypertensive population was affected by hyperuricemia. This can be explained by considering that the kidney is involved both in the control of blood pressure and in urate metabolism. However it was only in 2001 that the first experimental demonstration of the underlying mechanisms relating hyperuricemia and hypertension was achieved. Johnson et al. [14] demonstrated a blood pressure elevation within 3 weeks from the beginning of a hyperuricemic diet in rats and observed an association between increased UA levels and the development of tubule-interstitial injuries. These renal abnormalities can be explained as the consequence of a urate induced NO deficiency combined with a strong activation of the renin-angiotensin system and can be prevented with the use of angiotensin II receptor blockers. Interestingly, both renal lesions and blood pressure abnormalities can be prevented only by reducing early hyperuricemia while no benefit has been observed in animals with chronic urate disorders when cardio-renal damage is mainly due to other mechanisms (e.g., salt-sensitivity and established arterial stiffness) [15]. In humans the first reliable demonstration of a linking between serum uric acid and the onset of high blood pressure has been published in the early 1990s [16]. These preliminary results have been confirmed more recently [17, 18] and, in particular, the study of Krishnan et al. has demonstrated that the linear relationship between blood pressure and UA is still significant after a full adjustment for several confounders and after exclusion of patients with impaired glucose tolerance, diabetes and metabolic syndrome [19].

In addition, a recent meta-analysis carried out between 1972 and 2009 and involving 18 studies reported a slight but significant increase in the relative risk for incident hypertension in subjects with elevated serum uric acid with an excess of 13 % for each 1 mg/dl UA over the recommended level [20••]. The relationship between serum UA and hypertension is more evident in younger subjects as suggested by Feig et al., who found that 90 % of adolescents with primary hypertensive disease had UA levels greater than 5.5 mg/Dl [21]. Similar findings have been reported in the National Health and Nutrition Examination Survey 1999–2006 on US adolescents, in which participants with SUA ≥5.5 mg/dL had a 2.03 times higher odds of having elevated blood pressure compared to controls with normal urate levels [22••]. A positive relationship between serum uric acid and hypertension has been reported even in children [23]. In particular the results of the Bogalusa Heart Study have reported that elevated childhood SUA levels are associated with increased blood pressure values that persist into adulthood, in males and females, whites and blacks, suggesting that early elevations in SUA levels may play a key role in the development of human hypertension [24]. Conversely, the strength of the correlation

progressively decreases with increasing age and this can explain the negative results of the only longitudinal study [25] that enrolled older people, mainly in their sixth decade of life. These data strongly support the hypothesis that elevated levels of serum UA affect the earliest steps of the hypertensive disease, while in the elderly patients other factors probably overcome the impact of UA.

Hyperuricemia and Related Cardiovascular Diseases

Several cardiovascular diseases other than hypertension have been correlated with serum urate levels. In the early 1950s Gertler et al. reported for the first time that serum UA levels were significantly higher in patients hospitalized for coronary artery disease (CAD) when compared to matched hospitalized controls without CAD [26]. Since that initial observation the number of surveys investigating the interactions between serum UA and cardiovascular diseases has progressively increased showing, however, conflicting results. Indeed, while some very positive results have been reported in the National Health and Nutrition Examination Survey I (NHANES I) [27], the Framingham Heart Study failed to confirm the relationship between serum UA and cardiovascular diseases when the results have been adjusted for the presence of concomitant risk factors including hypertension and the diuretic use [28]. More recently a large meta-analysis has been published supporting the role of elevated serum UA as risk factor for coronary heart disease [29], and this has been confirmed by the cumulative review of 26 prospective cohort studies representative of more than 400,000 patients [30•] that supports the independent association between hyperuricemia and coronary heart disease morbidity and mortality, with an overall risk of death that increased by 12 % for each 1 mg/dl increase of SUA. High levels of serum UA on admission are also recognized to predict a worse short and long-term outcome in patients with acute myocardial infarction [31••].

However, the predictive role of serum uric acid is not restricted to coronary artery disease and some studies have demonstrated its association with the development of congestive heart failure (CHF) [32, 33••] as a consequence of its involvement and progression of hypertension and left ventricular dysfunction [34]. Accordingly, UA is actually considered to be an independent marker of all-cause mortality in HF patients [7•].

Another field of recent interest is the association between hyperuricemia and stroke, a life-threatening disease involving each year about 795,000 subjects according to the 2009 report of the American Heart Association and Stroke Statistics Committee [35]. However, although the relationship between serum UA and hypertension is proven, one of the most common causes of stroke, studies investigating the direct involvement of hyperuricemia in patients with stroke have reached non univocal conclusions so far. Positive evidence has been provided by some groups of researchers [36, 37] and recently confirmed by the meta-analysis of Kim et al. who reported a slight but significant increase in the risk of both stroke incidence and mortality in adults with elevated SUA [38]. Conversely, the independent association of SUA with ischemic stroke has been denied by other studies as the First Mexican multicenter register on ischemic stroke (PREMIER study) [39••] and the results are inconsistent also when serum UA is considered as a marker of stroke outcome [40••].

So, what to do with High SUA Patients?

Beyond the well established importance of reducing serum UA level to prevent the deposit of crystals of monosodium urate typical of gout, the suggested causative role of hyperuricemia in the development of cardiovascular diseases might suggests the recommendation for a pharmacological approach in a larger proportion of subjects with high cardiovascular risk. According with the pathophysiology of serum uric acid disorders, the use of xanthine oxidase inhibitors as allopurinol and febuxostat, should be preferred over uricosuric drugs as probenecid. The former have a demonstrated capacity to decrease serum UA and to prevent the production of superoxides through the blockade of the enzymatic activity. Inhibition of xanthine oxidase per se is reported to improve endothelial function [41], left ventricular ejection fraction [42] and to reduce the cumulative oxidant state [43] beyond its effects on plasma urate concentrations. In addition, some recent data have demonstrated that an effective pharmacological reduction of serum UA is leading to an improvement in blood pressure control in adolescents with a recent diagnosis of arterial hypertension [44].

Moreover, the activation of the renin-angiotensin system that is associated with high concentrations of UA [25] indirectly supports a specific role for angiotensin II receptor blockers (ARBs) that can be reasonably preferred in the management of hypertensive disease associated with hyperuricemia. Among the ARB's, losartan has also demonstrated the unique property to reduce serum urate concentrations by a remarkable uricosuric agent that belongs to the native losartan and does not involve its active metabolite responsible for the antihypertensive effect [45]. This dual effect can largely contribute to the cardiovascular benefit observed in patients treated with losartan, both in terms of stroke prevention and blood pressure control [46].

Conclusion

The presence of hyperuricemia affects a remarkable proportion of subjects in the general population and its prevalence is

progressively rising because of some changes in the dietary habits associated with a significant increase in life-span. Despite some conflicting observations accumulating evidence suggests that hyperuricemia may be a potential cardiovascular risk factor. This suggest the possibility that a more effective control of serum uric acid in addition to the management of other conventional risk factors may play a primary role in the prevention of cardiovascular diseases and further prospective data are awaited in the near future.

Compliance with Ethics Guidelines

Conflict of Interest Claudio Borghi, Alessandra Reggi, Alessandra Pavesi, and Arrigo FG Cicero declare that they have no conflict of interest.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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