Review

Uric acid as a risk factor for cardiovascular disease

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Introduction

Over recent years there has been renewed debate about the nature of the association between raised serum uric acid concentration and cardiovascular disease.\(^1\) Several large studies have identified the value, in populations, of serum uric acid concentration in predicting the risk of cardiovascular events, such as myocardial infarction. This has directed research towards the potential mechanisms by which uric acid might have direct or indirect effects on the cardiovascular system. It has been difficult to identify the specific role of elevated serum uric acid because of its association with established cardiovascular risk factors such as hypertension, diabetes mellitus, hyperlipidaemia and obesity.\(^2,3\) Indeed, it is not even clear at this stage whether uric acid has a damaging or protective effect in these circumstances. Increased understanding of the mechanisms underlying these associations may allow a clearer interpretation of the importance of elevated serum uric acid concentrations, and the potential value of specific urate-lowering treatment on cardiovascular disease.

Uric acid synthesis

Purines arise from metabolism of dietary and endogenous nucleic acids, and are degraded ultimately to uric acid in man, through the action of the enzyme xanthine oxidase (Figure 1). Uric acid is a weak acid (pKa 5.8), distributed throughout the extracellular fluid compartment as sodium urate, and cleared from the plasma by glomerular filtration.\(^4\) Around 90% of filtered uric acid is reabsorbed from the proximal renal tubule, while active secretion into the distal tubule by an ATPase-dependent mechanism contributes to overall clearance.\(^5\) Serum uric acid concentration within the population has a Gaussian distribution, with a typical reference range (95% CI) of 120–420 μmol/l. For an individual, urate concentration is determined by a combination of the rate of purine metabolism (both endogenous and exogenous) and the efficiency of renal clearance. Purine metabolism is influenced by dietary, as well as genetic factors regulating cell turnover. Uric acid is sparingly soluble in aqueous media, and persistent exposure to high serum levels predisposes to urate crystal deposition within soft tissues.\(^4\) All species apart from man and higher apes express urate oxidase, an enzyme responsible for further metabolism of uric acid to allantoin (a more soluble waste product) prior to excretion.\(^6\) In man, the urate oxidase gene located on chromosome 1 is not expressed due to two non-sense mutations.\(^7\) Loss of uric oxidase activity appears to have developed under evolutionary pressure,\(^7\) suggesting that higher serum uric acid concentrations, or reduced urate oxidase may confer important advantages in man.

Uric acid as a risk factor for cardiovascular disease

An epidemiological link between elevated serum uric acid and an increased cardiovascular risk has
been recognized for many years.\textsuperscript{8,9} Observational studies show that serum uric acid concentrations are higher in patients with established coronary heart disease compared with healthy controls.\textsuperscript{10} Elevated serum uric acid concentrations are also found in healthy offspring of parents with coronary artery disease, indicating a possible causal relationship.\textsuperscript{5} However, hyperuricaemia is also associated with possible confounding factors including elevated serum triglyceride and cholesterol concentrations, blood glucose, fasting and post-carbohydrate plasma insulin concentrations, waist-hip ratio and body mass index.\textsuperscript{3,8,11,12} About one quarter of hypertensive patients have co-existent hyperuricaemia\textsuperscript{13} and, interestingly, asymptomatic hyperuricaemia predicts future development of hypertension, irrespective of renal function.\textsuperscript{14}

Among patients with established hypertension, elevated serum uric acid concentration has been associated with a significantly increased cardiovascular risk during a mean 6.6-year follow-up period.\textsuperscript{15} The proportional hazard ratio for one SD elevation of uric acid (29.2 μmol/l) was 1.22 (95% CI 1.11–1.35), which was higher than for one S.D. elevation of blood glucose (1.10, 95% CI 1.02–1.19), cholesterol (1.18, 95% CI 1.09–1.29) or systolic blood pressure (1.09, 95% CI 1.00–1.19). Thiazide diuretics confer unequivocal benefits in treatment of hypertensive patients, and cause a significant reduction in cardiovascular and all-cause mortality.\textsuperscript{16} Persistence of the relationship between elevated serum uric acid concentration and increased cardiovascular risk among thiazide-treated patients has prompted speculation that uric acid elevation may attenuate some of their potential benefits.\textsuperscript{17} Indeed, the US National Health and Nutrition Survey (NHANES) III showed that age-adjusted rates of myocardial infarction and stroke

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**Figure 1.** Adenosine release is increased during hypoxia, and its local vasodilating action may preserve blood flow and prevent tissue ischaemia. Uric acid is the end-product of purine metabolism in man, whereas other species express uric oxidase, responsible for conversion of uric acid to more soluble excretory products.
are higher across increasing serum uric acid quartiles among male and female hypertensive patients.\textsuperscript{18}

Some studies have suggested that the importance of uric acid may be independent of confounding risk factors. Multivariate analysis of data from the MONICA cohort of 1044 males showed a significant association between raised serum uric acid and cardiovascular mortality, independent of body mass index, serum cholesterol concentration, hypertension, diuretic use, alcohol intake and smoking habits.\textsuperscript{19} Comparison of those individuals within the highest serum uric acid quartile (≥373 μmol/l) versus those in the lowest quartile (≤319 μmol/l) gave an adjusted risk of myocardial infarction of 1.7 (95%CI 0.8–3.3) and cardiovascular death of 2.2 (95%CI 1.0–4.8). The Gothenburg prospective study of 1462 women aged 38 to 60 years also found a significant relationship between serum uric acid concentration and total mortality during 12-year follow-up, which was independent of body mass index, serum lipid concentrations, smoking habit, blood pressure and age.\textsuperscript{20} Uric acid also has a predictive role in high-risk patient groups. For instance, diabetes mellitus is a very powerful risk factor for cardiovascular disease, and a prospective study of 1017 non-insulin-dependent patients showed that serum uric acid concentration >295 μmol/l conferred a hazard ratio of 1.91 (95%CI 1.24–2.94) of fatal or non-fatal stroke during 7-year follow-up.\textsuperscript{21}

In contrast to these findings, several studies have suggested that the relationship between elevated serum uric acid and cardiovascular risk does not persist after correcting for other risk factors. The British Regional Heart Study of 7688 men aged 40 to 59 years showed a significant association between elevated serum uric acid and fatal and non-fatal coronary disease over a mean 16.8 years.\textsuperscript{22} However, this relationship disappeared after correcting for other risk factors, particularly serum cholesterol concentration. The Coronary Drug Project Research Group studied 2789 men, aged 30 to 64 years, and found that the association between increased cardiovascular risk and elevated serum uric acid concentration was not significant after consideration of other risk factors, and when thiazide diuretic use was considered.\textsuperscript{23} Similar findings have been reported from the Social Insurance Institution of Finland Study\textsuperscript{24} and Framingham Heart Study.\textsuperscript{25}

The Atherosclerosis Risk in Communities study of 11488 healthy men and women showed an apparent association between serum uric acid concentration and early carotid artery atherosclerosis, which was dependent of other coronary risk factors.\textsuperscript{26} Similarly, the Honolulu Heart Program found that elevated serum uric acid was not an independent risk factor for the presence at autopsy of aortic or coronary atherosclerosis in Japanese men.\textsuperscript{27}

In summary, although there is overwhelming evidence that elevated serum uric acid concentrations are strongly associated with increased cardiovascular risk and poor outcome, prospective population studies are often confounded by co-existent risk factors. It remains unclear whether uric acid is an independent predictor of poor cardiovascular outcome. To unravel this association, it is important to understand the mechanisms by which hyperuricaemia relates to other risk factors, vascular dysfunction and cardiovascular disease. We shall now consider these relationships in more detail.

**Uric acid as a marker of subclinical ischaemia**

Adenosine is synthesized and released by cardiac and vascular myocytes. Binding to specific adenosine receptors causes relaxation of vascular smooth muscle and arteriolar vasodilatation.\textsuperscript{28} Adenosine makes a small contribution to normal resting vascular tone, since competitive antagonism at the adenosine receptor by methylxanthines, such as theophylline, reduce blood flow response to ischaemia in the forearm vascular bed.\textsuperscript{29} Under conditions of hypoxia and tissue ischaemia, vascular adenosine synthesis and release are upregulated, causing significantly increased circulating concentrations.\textsuperscript{30} Cardiac and visceral ischaemia promote generation of adenosine, which may serve as an important regulatory mechanism for restoring blood flow and limiting the ischaemia\textsuperscript{31} (Figure 1). Adenosine synthesized locally by vascular smooth muscle in cardiac tissue is rapidly degraded by the endothelium to uric acid, which undergoes rapid efflux to the vascular lumen due to low intracellular pH and negative membrane potential.\textsuperscript{32} Xanthine oxidase activity\textsuperscript{33} and uric acid synthesis\textsuperscript{34} are increased in vivo under ischaemic conditions, and therefore elevated serum uric acid may act as a marker of underlying tissue ischaemia. In the human coronary circulation, hypoxia, caused by transient coronary artery occlusion, leads to an increase in the local circulating concentration of uric acid.\textsuperscript{35} Study of tourniquet-induced lower limb exsanguination in patients undergoing surgery shows a five-fold increase in systemic vascular xanthine oxidase activity during reperfusion, and a significant elevation of serum uric acid, which persists for at least 2 h.\textsuperscript{36} These findings are also consistent with the inverse relation between baseline serum uric acid concentration and maximal
lower limb blood flow in patients with cardiac failure, where higher concentrations could predict subclinical ischaemia. In conclusion therefore, elevated serum uric acid may be a marker of local or systemic tissue ischaemia and provides one possible explanation for a non-causal associative link between hyperuricaemia and cardiovascular disease.

Uric acid as a marker of insulin resistance

Insulin resistance syndromes result in attenuation of insulin-mediated glucose utilization and confer a substantial increase in cardiovascular risk, through activation of several pathways including the sympathetic nervous system. Elevated serum uric acid is a consistent feature of the insulin resistance syndromes, which are also characterized by elevated plasma insulin level (fasting and post-carbohydrate), blood glucose concentration, and serum triglyceride concentration, and raised body mass index and waist-hip ratio. Insulin has a physiological action on renal tubules, causing reduced sodium and uric acid clearance. Despite blunting of the action of insulin on glucose metabolism, sensitivity to the renal effects persists. Because plasma insulin concentration is characteristically elevated, hyperuricaemia may arise as a consequence of enhanced renal insulin activity. Elevated serum uric acid concentrations predict subsequent development of diabetes mellitus and hypertension, even in the presence of normal creatinine clearance and plasma glucose concentrations, and therefore may be a subtle, early marker of peripheral insulin resistance syndromes. Thus a link between elevated serum uric acid concentration and cardiovascular disease may arise through its non-causal relationship with insulin resistance syndromes, where cardiovascular risk is mediated by other factors.

Direct impact of uric acid on vascular function

The endothelium plays a central role in maintaining vascular tone through synthesis and release of nitric oxide, a potent vasodilator. Reduction of nitric oxide bioavailability is an important early step in the development of atherosclerosis. So-called endothelial dysfunction, associated with impaired endothelium-dependent vasodilatation may arise from excessive free radical activity, which disrupts synthesis and accelerates degradation of nitric oxide. Thus increased oxidative stress appears to have an important role in development and progression of atherosclerosis and is a characteristic finding associated with its major risk factors, such as diabetes mellitus, hypertension, hypercholesterolaemia and smoking. Serum uric acid possesses antioxidant properties, and contributes about 60% of free radical scavenging activity in human serum. Uric acid interacts with peroxynitrite to form a stable nitric oxide donor, thus promoting vasodilatation and reducing the potential for peroxynitrite-induced oxidative damage. Thus, uric acid could be expected to protect against oxidative stresses.

However, uric acid has been found to promote low-density lipoprotein (LDL) oxidation in vitro, a key step in the progression of atherosclerosis, and these effects are inhibited by vitamin C indicating an important interaction between aqueous anti-oxidants. Uric acid can also stimulate granulocyte adherence to the endothelium, and peroxide and superoxide free radical liberation. Therefore uric acid may have a deleterious effect on the endothelium through leukocyte activation and, interestingly, a consistent relationship has been noted between elevated serum uric acid concentration and circulating inflammatory markers.

Uric acid traverses dysfunctional endothelial cells and accumulates as crystal within atherosclerotic plaques. These crystals may contribute to local inflammation and plaque progression, and we speculate that crystal accumulation may be greater in patients with elevated serum uric acid concentration.

Thus, while uric acid appears to make a significant contribution to serum anti-oxidant capacity, it could also lead directly or indirectly to vascular injury. It is interesting to note that treatment of chronic cardiac failure patients with allopurinol (a xanthine oxidase inhibitor) restored endothelial function. This effect may have been due to an increase in recorded serum antioxidant capacity, although the effect of uric acid was not considered. Study of the direct effects of uric acid on vascular function has been hampered by its poor solubility, although this has been overcome recently. Direct study of the actions of uric acid on endothelial function, platelet aggregation, vessel wall elasticity and autonomic cardiovascular regulation is required so that its effects on the cardiovascular system and in cardiovascular disease can be determined.

Conclusions

Raised serum uric acid concentrations are a powerful predictor of cardiovascular risk and poor
outcome, although the underlying mechanisms remain unclear. Several potential explanations have been put forward to explain the apparent association between hyperuricaemia and cardiovascular risk. Studies have demonstrated mechanisms by which uric acid could be directly injurious to the endothelium and to cardiovascular function. Paradoxically, uric acid elevation could be expected to confer protective anti-oxidant effects in the cardiovascular system, but these potential benefits may be obscured by detrimental effects elsewhere. The effects of raising or lowering serum uric acid on endothelial function, autonomic regulation and progression of atherosclerosis require direct investigation, in order to understand a possible dual action in the cardiovascular system. Identifying the mechanisms by which uric acid interacts with cardiovascular regulation will give us greater understanding of the role of hyperuricaemia for individual patients and allow a more rational approach to treatments that modify serum uric acid concentration.

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References


