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Review article

Serum Uric Acid And Cardiovascular Disease

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ABSTRACT

A substantial body of epidemiological and experimental evidence suggests the significance of serum uric acid as an important and independent risk factor of cardiovascular and renal diseases especially in patients with diabetes mellitus, hypertension or heart failure. Elevated serum uric acid is highly predictive of mortality in patients with heart failure or coronary artery disease and of cardiovascular events in patients with diabetes. Moreover patients with hypertension and hyperuricemia have a 3- to 5-fold increased risk of experiencing coronary artery disease or cerebrovascular disease compared with patients with normal uric acid levels. Although the mechanisms by which uric acid may play pathogenetic role in cardiovascular disease is unclear. Hyperuricemia is associated with deleterious effects on endothelial dysfunction, oxidative metabolism, platelet adhesiveness, hemorheology, and aggregation. Xanthine oxidase inhibitors (e.g., allopurinol) or a variety of uricosuric agents (e.g., probenecid, sulfinpyrazone, benzbromarone, and benziodarone) can lower elevated uric acid levels but it is unknown whether these agents reversibly impact cardiovascular outcomes. Hyperuricemia will become then a meaningful target for the prevention and treatment of cardiovascular disease. Overall, serum uric acid may be a powerful tool to help stratify risk for cardiovascular disease. At the very least, it should be carefully considered when evaluating overall cardiovascular risk**.**

KEYWORDS: Hypertension; uric acid; gout; allopurinol; coronary heart disease.

INTRODUCTION

The association of gout with cardiovascular disease, first described in the 19th century was thought to be an association, rather than a cause, of cardiovascular disease. More recent evidence from cohort studies suggests a causal relationship between hyperuricaemia and risk of adverse cardiovascular events. Some studies have only been able to show this for women, while others have failed to demonstrate this association after controlling for various well known atherosclerotic risk factors. Elevated serum uric acid might merely represent an indirect marker of the metabolic syndrome. Because hyperuricemia is closely related to obesity, hypertension, and dyslipidaemia, it has been difficult to establish whether or not an independent association between uric acid and cardiovascular disease exists. To examine this question, various aspects of uric acid metabolism and function need to be understood as discussed in this review[1].

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 (Fig. 1).

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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[2]. 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[3]. Serum uric acid concentrations within the population have a Gaussian distribution, with a typical reference range (95% CI) of 120-420 mmol/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[2]. All species apart from humans 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[4]. In humans, the urate oxidase gene located on chromosome 1 is not expressed due to two non-sense mutations. Loss of uric oxidase activity appears to have developed under evolutionary pressure, suggesting that higher serum uric acid concentrations, or reduced urate oxidase may confer important advantages in humans[5]. Uric acid is the last stage in purine degradation in humans, because all primates lack the enzyme (uricase) to convert uric acid into allantoin as shown in Fig. 1.

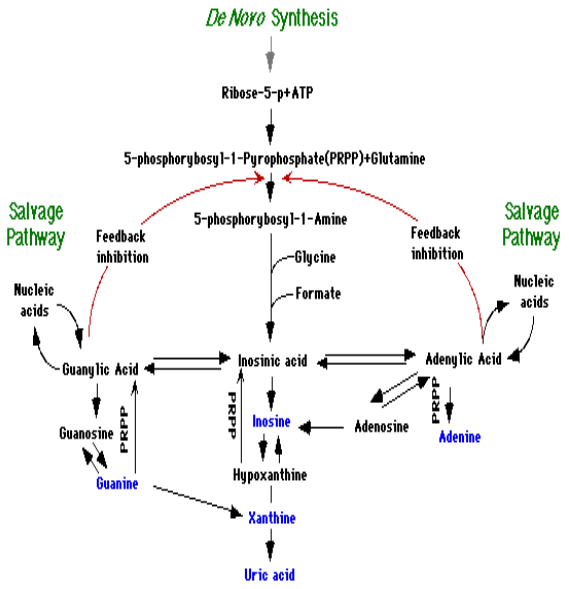

Figure 1.Uric acid synthesis.

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[6,7]. Observational studies show that serum uric acid concentrations are higher in patients with established coronary heart disease compared with healthy controls[8]. Elevated serum uric acid concentrations are also found in healthy offspring of parents with coronary artery disease, indicating a possible causal relationship. However, hyperuricemia 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. About one quarter of hypertensive patients has co-existent hyperuricemia and, interestingly, asymptomatic hyperuricemia predicts future development of hypertension, irrespective of renal function[9]. 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[10]. The proportional hazard ratio for one SD elevation of uric acid (29.2 mmol/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. 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[9]. Indeed, the US National Health and Nutrition Survey (NHANES) III showed that age adjusted rates of myocardial infarction and stroke are higher across increasing serum uric acid quartiles among male and female hypertensive patients[11]. 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[12]. Comparison of those individuals within the highest

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serum uric acid quartile (0373 mmol/l) versus those in the lowest quartile ((319 mmol/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[13]. 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 mmol/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[14]. 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[15]. 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[16].
Similar findings have been reported from the Social Insurance Institution of Finland Study[17] and Framingham Heart Study[18]. 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[19]. 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[20]. 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[9].

The association of high serum uric acid levels with cardiovascular disease may be due to the role of uric acid as an antioxidant (Ames et al., 1981; Davies et al., 1986)[21,22], because an elevated serum UA level may be a defense mechanism against atherosclerosis. Uric acid concentrations may increase in an attempt to block lipid peroxidation and other related phenomena (Nieto et al., 2000)[23]. This again suggests that elevated uric acid levels are a consequence of disease. On the other hand, increased uric acid levels may instead contribute to the development of cardiovascular disease by exerting a negative effect on the endothelium. There is some evidence that serum uric acid could possibly promote, rather than prevent, oxygenation of low-density lipoprotein cholesterol and lipid peroxidation (De Scheerder et al., 1991)[24]. This can lead to an increase in platelet adhesiveness, resulting in thrombus formation that can contribute to the development of atherosclerosis, increasing the likelihood of the development of cardiovascular disease. High uric acid levels can also stimulate the release of free radicals, which have been shown to be involved in adhesion molecule expression by inflammatory cells as well as in inflammatory cell activation and adherence to the damaged endothelium (Waring et al., 2000a)[9]. This ultimately results in endothelial injury, again increasing the risk of cardiovascular disease development. This mechanism is supported by the positive correlation found between elevated uric acid levels and chronic inflammation in chronic heart failure (Leyva et al., 1998)[25]. In addition, an elevation in plasma uric acid concentration is associated with an increased level of C-reactive protein that has been identified as an important indicator of myocardial infarction, stroke, and vascular death (Kang et al., 2005)[26].

Table 1, highlights the mechanism of hyperuricemia-induced cardiovascular rise in certain population groups.

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Table 1. Uric acid is increased in groups at cardiovascular risk. [27].

Group	Mechanism
Postmenopausal women and men	Estrogen is uricosuric
African Americans	Unknown
Renal disease	Decrease in Glomerular filtration rate increases uric acid levels
Diuretics	Volume contraction promotes urate reabsorption
Obesity/insulin resistance	Insulin increases sodium reabsorption and is tightly linked to urate reabsorption
Hypertension	Urate reabsorption increases in setting of increased renal vascular resistance; microvascular disease predisposes to tissue ischemia that leads to increased urate generation (from adenosine breakdown) and reduced excretion (due to lactate competing with urate transporter in the proximal tubule); some hyperuricemic hypertension may be due to alcohol ingestion or lead intoxication.
Alcohol use	Increases urate generation, decreases urate excretion

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. 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[28]. Under conditions of hypoxia and tissue ischaemia, vascular adenosine synthesis and release are upregulated, causing significantly increased circulating concentrations (Fig. 2)[29].

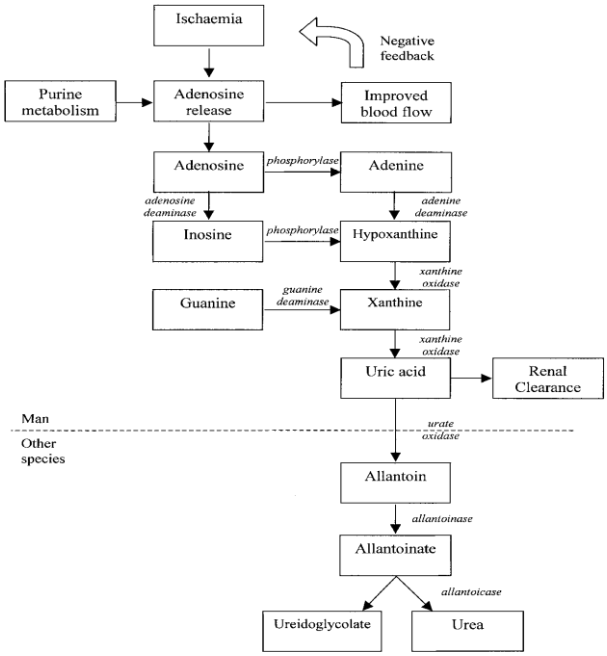

Figure 2.Uric acid synthesis in hypoxia and tissue ischaemia.

Cardiac and visceral ischaemia promote generation of adenosine, which may serve as an important regulatory mechanism for restoring blood flow and limiting the ischaemia[30]. 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[31]. Xanthine oxidase activity[32] and uric acid synthesis[33] 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[24]. 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 [34]. 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

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concentrations could predict subclinical ischaemia[35]. 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[36], through activation of several pathways including the sympathetic nervous system[37]. 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[9].

SERUM URIC ACID AND ATHEROSCLEROSIS

The pathophysiological link between the elevated serum uric acid and atherosclerosis are endothelial dysfunction and inflammation. (Reactive oxygen species) ROS production by xanthine oxidase can induce endothelial dysfunction by reducing bioavailability of nitric oxide[39]. Serum uric acid, by its antioxidant properties, could counteract Reactive oxygen species generation. There are also evidences in animal experiments that the high serum uric acid impairs endothelial dependent vasodilatation[39]. An independent association between the serum uric acid level and C-reactive protein and other inflammatory markers (blood neutrophils, interleukin, TNF-alfa) has also been described[40,41]. So far there is evidence that the increased serum uric acid level is associated with subclinical atherosclerosis. The relationship between serum uric acid and the development of coronary artery disease and cerebrovascular disease was investigated in many studies. In NHANES I, ARIC and Rotterdam studies the high serum uric acid level was associated with an increased risk of stroke[42]. In NHANES I study there was a 48% increase in the risk of ischemic stroke in women for every 1.01 mg/dl increase in serum uric acid. In ARIC study there was an independent and positive relationship between the incidence of the ischemic stroke and serum uric acid[43]. Serum uric acid as a risk factor for the developing coronary artery disease remains controversial. In MRFIT study, the hyperuricemia and gout had an independent relationship with the risk of myocardial infarction, after adjustments for other risk factors[44]. In AMORIS study a moderate increase in the serum uric acid level was associated with increased incidence of myocardial infarction, stroke and heart failure in middle-aged subjects without prior cardiovascular disease[45]. Other studies (ARIC study, Framingham study or an Austrian study) did not found an independent association between the serum uric acid levels and the increased risk of coronary artery disease. The aforementioned studies demonstrated the strong association of serum uric acid with coronary artery disease, particularly in patients at high risk for heart disease and in women. The role of serum uric acid as a causal factor for cardiovascular events in these conditions remains to be determined[42].

SERUM URIC ACID AND HYPERTENSION

Hyperuricemia predicts the development of hypertension in the general population and an independent positive correlation between uric acid levels and the occurrence of hypertension has been reported (Jossa et al., 1994)[46]. The elevated uric acid level may be caused by the decrease in renal blood flow that develops in the early stages of hypertension. A reduced renal blood flow could alter the balance between medullary and cortical circulation, possibly resulting in a decrease in urate secretion. This could ultimately lead to an overall increase in the serum uric acid level (Messerli et al., 1980)[47]. Hypertension can also lead to microvascular disease that can cause local tissue ischemia (Puig and Ruilope, 1999)[48]. Tissue ischemia can then lead to an increase in the

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synthesis of uric acid, ultimately resulting in an increased serum uric acid level (Friedl et al., 1991)[49]. These mechanisms indicate that the increase in the plasma uric acid level may be a consequence rather than a cause of hypertension.

The association between arterial hypertension and hyperuricemia is very common. It has been reported that 25-40% of patients with untreated hypertension and more than 80% of patients with malignant hypertension have high serum uric acid levels[50]. Hyperuricemia is more common in primary hypertension, especially in patients with hypertension of recent onset and in pre hypertension associated with microalbuminuria[51]. Many mechanisms are involved in high serum uric acid level in hypertension. The reabsorbtion of the urate in the proximal tubule is increased as a consequence to the reduced renal blood flow. The microvascular renal disease leads to tissue ischemia and to the up-regulation of xanthine oxidase with increased the serum uric acid production. The reduction of the serum uric acid secretion in the proximal tubule and the use of diuretics may increase the serum uric acid level. In the recent years, several experimental studies have indicated that hyperuricemia perse can induce hypertension. In rats the high serum uric acid level induced hypertension after several weeks[52]. The hypertension was reversed after the normalization of serum uric acid with allopurinol or with an uricozuric drug. Two main mechanisms are involved in the hyperuricaemia induced hypertension. In early stage the high serum uric acid level induces renal vasoconstriction by the activation of the rennin angiotension aldesterone system (RAAS) and by the endothelial dysfunction with decreased nitric oxide level at the macula densa. In this stage, hypertension is salt resistant and it is reversed by lowering the serum uric acid level. In later stage chronic hyperuricemia induces vascular muscle cell proliferation and local activation of rennin angiotension aldesterone system with the activation of the mediators of inflammation. Progressive micro vascular renal disease is associated with afferent arteriolosclerosis and with interstitial fibrosis[53,54]. The renal histopathology changes in chronic hyperuricemia are similar to those induced by hypertension. Hypertension becomes salt driven and renal dependent and it is not normalized by lowering serum uric acid. Several clinical studies demonstrated that hyperuricemia precedes and it is associated with the development of hypertension. In the Framingham Heart Study, each increase in serum uric acid by 1.3 mg/dl was associated to the development of hypertension with an odd ratio of 1.17[55]. In the Multiple Risk Factor Intervention (MRFIT) study, in normotensive men with the serum uric acid level greater than 7 mg/dl there was an 80% increased risk for the development of hypertension[56]. The association between hyperuricemia and hypertension was more common in young people. The high serum uric acid was observed in nearly 90% of adolescents with primary hypertension and the serum uric acid level correlates with both systolic and diastolic hypertension[57,58]. In a study including adolescents with hypertension of recent onset and hyperuricemia, the reduction in serum uric acid level to less than 5 mg/dl with allopurinol was associated to the reversal of hypertension in 86% of the patients[59].

SERUM URIC ACID AND HEART FAILURE

Hyperuricemia is a common condition in chronic heart failure. Its prevalence increases as the disease progresses[60]. In a cross sectional study, 51% of patients hospitalized from chronic heart failure had hyperuricemia[61]. The serum uric acid level is higher in patients with end stage chronic heart failure and in cachectic patients[62]. It is inversely associated with functional NYHA class and maximal oxygen consumption and it is significant correlated with the severity of diastolic dysfunction. Hyperuricemia is also an independent prognostic marker in chronic and in acute heart failure (AHF)[42]. In a validation study, serum uric acid was the most powerful predictor of survival for patients with severe chronic heart failure (NYHA class III or IV): in patients with high levels of serum uric acid (> 9.5 mg/dl), the relative risk of death was 7.4[63]. In a study with AHF and systolic dysfunction the high serum uric acid level was associated with higher risk of death and new heart failure readmission[64]. Hyperuricemia was also an independent predictor of all causes mortality in unselected consecutive patients admitted with acute heart failure[65]. Recently, hyperuricemia was associated to incident heart failure in community adults. In the Cardiovascular Health Study the incident heart failure occurred in 21% participants with hyperuricemia and in 18% participants without hyperuricemia. Each 1 mg/dl increase in serum uric acid was associated to 12% increase in incident heart failure. In the Framingham Offspring cohort, the incidence rates of heart failure were 6-fold higher among those at the highest quartile of serum uric acid (>6.3 mg/ dL) compared to those

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at the lowest quartile (<3.4 mg/dL)[66,67]. Hyperuricemia appears as a novel, independent risk factor for heart failure in a group of young general community dwellers. There are several mechanisms involved in hyperuricemia- induced heart failure. The increased serum uric acid production may be due to increased xanthine oxidase substrate (ATP breakdown to adenosine and hypoxanthine) and to the up-regulation and increase in xanthine oxidase activity. When released from necrotic tissue, serum uric acid can produce additional adverse effects on cardiovascular system and can mediate the immune response[68]. In heart failure hyperuricemia is a marker of xanthine oxidase activation[69].

Several studies have shown that the reduction in the serum uric acid levels may be associated with the reduction in cardiovascular morbidity and mortality. In the Losartan Intervention for Endpoint Reduction in Hypertension (LIFE) study, the attenuation of the serum uric acid levels by losartan was associated with 29% reduction in the composite outcome of cardiovascular death, fatal or nonfatal myocardial infarction a d fatal or nonfatal stroke[70]. Some of the cardiovascular benefits of atorvastatin reported in the Greek Atorvastatin and Coronary-Heart-Disease Evaluation (GREACE) study have also been attributed to the ability of statins to lower the serum uric acid levels[71]. Allopurinol and oxypurinol are xanthine oxidase inhibitors which have been used to treat hyperuricemia. The reducing serum uric acid level in hypertension with xanthine oxidase inhibitors lowers blood pressure in young with hyper tension of recent onset. Other studies outline the potential benefits of xanthine oxidase inhibition in heart failure. In chronic heart failure allopurinol improves endothelial dysfunction, peripheral vasodilatator capacity and myocardial energy by reducing markers of oxidative stress[72]. In optional pharmacological therapy chronic heart failure (OPT-CHF) Study, oxypurinol increased left ventricular ejection fraction and improved clinical outcome in chronic heart failure patients presenting with high Serum uric acid levels[73].

URIC ACID, ENDOTHELIAL DYSFUNCTION, AND IMPAIRED NITRIC OXIDE PRODUCTION

Endothelial dysfunction, local oxidant generation, elevated circulating cytokines, and a pro-inflammatory state are common in patients with cardiovascular disease[74,75]. Endothelial dysfunction is often demonstrated by showing an impaired nitric oxide release in response to acetylcholine, which results in impaired endothelium-dependent vasodilation. Oxidants may cause endothelial dysfunction by reacting with and removing the nitric oxide. The observation that xanthine oxidase generates oxidants and uric acid in settings of tissue ischemia potentially explains why uric acid is associated with endothelial dysfunction and oxidative stress in conditions such as heart failure and diabetes[27]. Hyperuricemia is also associated with the activation of circulating platelets, which also may reflect endothelial dysfunction[76]. Allopurinol, which inhibits xanthine oxidase and hence blocks both uric acid and oxidant formation, can reverse the impaired endothelial nitric oxide production in both heart failure and type 2 diabetes. Allopurinol has also been reported to reduce cardiovascular complications after coronary artery bypass[27,76-78] and in patients with dilated cardiomyopathy. Although the beneficial effects correlate with the lowering of uric acid in some of these studies, most authorities have hypothesized that the beneficial effect of allopurinol is to reduce oxidative stress[27]. Uric acid may contribute to endothelial dysfunction. Waring et al., [79] have reported that uric acid infusion in healthy humans resulted in impaired acetylcholine-induced vasodilation in the forearm, thereby documenting impaired endothelial nitric oxide release. Serum uric acid and serum nitric oxide levels also vary during the day in a reciprocal pattern, suggesting a pattern of physiological regulation[80]. Recent studies in experimental animal models have also found that mild hyperuricemia inhibits the nitric oxide system in the kidney. The mechanism by which uric acid impairs endothelial function is not known. However, whereas uric acid is considered an antioxidant, it is also pro-oxidative under certain conditions, especially when other antioxidants are at a low level[81,82].

URIC ACID AS AN ANTIOXIDANT: A PROTECTIVE FACTOR IN CARDIOVASCULAR DISEASE?

Urate (the soluble form of uric acid in the plasma) can scavenge superoxide, hydroxyl radical, and singlet oxygen and can chelate transition metals[27]. Peroxynitrite is a particularly toxic product formed by the reaction of superoxide anion with nitric oxide that can injure cells by nitrosylating the tyrosine residues (nitrotyrosine formation) of proteins. Uric acid can also block this reaction[83]. Hink et al reported that uric acid may also prevent

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the degradation of extracellular superoxide dismutase (SOD_3), an enzyme critical in maintaining endothelial and vascular function. SOD_3 is an extracellular enzyme that catalyzes the reaction of superoxide anion ($O^{2-\cdot}$) to hydrogen peroxide (H_2O_2). The removal of $O^{2-\cdot}$ by SOD_3 prevents the reaction and inactivation by $O^{2-\cdot}$ of the important endothelial vasodilator, nitric oxide (NO). Superoxide dismutase, by removing $O^{2-\cdot}$, therefore helps to maintain nitric oxide levels and maintain endothelial function. Normally, superoxide dismutase is inactivated in the presence of H_2O_2, suggesting a feedback inactivation of the enzyme. However, uric acid blocks SOD inactivation by H_2O_2 by regenerating superoxide dismutase with the production of a urate radical[84]. This latter radical, although potentially a pro-oxidant, has been found to be markedly less reactive than classic oxidants and can be rapidly regenerated back to urate in the presence of ascorbate[85]. Ames et al.,[21] hypothesized that the uricase mutation occurred during early hominoid evolution because the antioxidant action of uric acid may have provided an evolutionary advantage and that this may account for the greater longevity of humans and the great apes compared with most other primates. The increase in serum uric acid in subjects with cardiovascular disease might therefore reflect a compensatory mechanism to counter the oxidative stress that occurs in these conditions[22]. However, this does not readily explain why higher uric acid levels in patients with cardiovascular disease are generally associated with worse outcomes.

URIC ACID PARADOX

Uric acid has several biological properties which can be either beneficial or detrimental. Serum uric acid is a powerful antioxidant and it protects against free radical damage. Along with ascorbate, serum uric acid accounts for up to 60% of the serum free radical scavenging capacity. SUA reacts with a variety of oxidants and it prevents the formation of peroxynitrite and the inactivation of the nitric oxide by superoxide anions. In individuals with hyperuricemia, the plasma total antioxidant capacity is elevated, which suggests that hyperuricemia may be a compensatory mechanism to counteract the oxidative stress damage related to atherosclerosis[70]. The serum uric acid paradox lies in the fact that high serum uric acid, which has antioxidant properties, is associated with an increased cardiovascular risk. The theory of the antioxidant, pro-oxidant redox shuttle: proposes that serum uric acid, which under normal circumstances is an antioxidant, becomes pro-oxidant in the atherosclerotic medium with ROS generation[23]. The excess of serum uric acid has deleterious effects: endothelial dysfunction, proliferation of vascular smooth muscle cells, increased platelet adhesiveness, oxidation of LDL cholesterol and lipid peroxidation. All these pathological processes might contribute to the pathogenesis of atherosclerosis and cardiovascular disease[42].

ROLE OF ALLOPURINOL

It is not known whether lowering uric acid levels with allopurinol will be effective in people with more severe or longstanding hypertension as compared with those in the preliminary studies cited. Nor do we know whether the beneficial effect of allopurinol observed in completed and preliminary human studies is due to the reduction of uric acid or to a reduction in xanthine oxidase–associated oxidants. Although the experimental studies suggest that the benefit results from lowering uric acid, the improvement of endothelial function observed in patients with hyperuricemia and heart failure or diabetes occurred among patients[86]. Patients who received allopurinol but not among those receiving other drugs designed to lower uric acid levels[87,88]. One possible explanation for this result is that xanthine oxidase inhibitors are more effective than other agents in lowering intracellular levels of uric acid, and consequently had a greater influence on intracellular regulation of endothelial vascular activity[26]. Alternatively, uric acid may be more of a marker, and the benefit of allopurinol may be the result of its ability to block xanthine oxidase-associated oxidants. We need a better understanding of the biologic functions of uric acid as they may relate to cardiovascular disease. Although uric acid may have proinflammatory effects on vascular cells and adiposities, it can also function as an antioxidant. It has been suggested that the antioxidant effects of uric acid are protective in several neurologic diseases, including multiple sclerosis and Parkinson's disease. Conversely, uric acid can also function as a pro-oxidant, either by generating radicals during its degradation or by stimulating NADPH oxidase. Uric acid can also stimulate innate immunity through the effects of microcrystalline uric acid on the function of dendritic cells and T cells. Studies suggest a role for T cells in the pathogenesis of salt-sensitive hypertension. Thus, it remains possible that uric acid may have a

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variety of as yet incompletely defined actions in cardiovascular disease[86].

CONCLUSIONS AND FUTURE PERSPECTIVES

The role of serum uric acid as an independent risk factor for the cardiovascular disease is controversial, since hyperuricemia is associated to other traditional risk factors. Elevated serum uric acid level also represents a strong prognostic marker for cardiovascular events, particularly in patients at high cardiovascular risk or with established cardiovascular disease. Many factors contribute to high serum uric acid level and the mechanisms linking the urate and the cardiovascular disease are not completely understood yet. When associated with increase oxidative stress, hyperuricemia may be a marker of the increased xanthine oxidase activity. If serum uric acid has a protective role as an antioxidant or a causative and deleterious role is still debatable. More prospective randomized trials lowering serum uric acid are needed in order to clarify the role of the uric acid in the development and progression of cardiovascular disease and to establish if reducing serum uric acid level will translate into a better cardiovascular outcome. Hyperuricemia will become then a meaningful target for the prevention and treatment of cardiovascular disease.

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