

Does uric acid qualify as an independent risk factor for cardiovascular mortality?

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Abstract

UA (uric acid) is the final product of purine metabolism in humans and is implicated in many disease conditions. Sustained hyperuricaemia has putative adverse roles in cardiovascular diseases. Despite strong evidence emerging from large epidemiological studies supporting the hypothesis that UA independently influences cardiovascular disease outcomes and mortality, a causal role is yet to be established. Serum UA is also considered as a useful biomarker for mortality in high-risk patients with acute coronary syndromes, heart failure and hypertension and in patients with Type 2 diabetes mellitus. Post-hoc analyses of clinical trial data suggest beneficial effects of reducing serum UA. However, these findings are inconclusive and are only hypothesis-generating. In the present issue of *Clinical Science*, Ndrepepa and co-workers have investigated the prognostic role of UA in high-risk Type 2 diabetic patients with established coronary artery disease in predicting 1-year survival and cardiovascular mortality. These results support the independent role of serum UA in predicting survival in Type 2 diabetic patients. However, long-term follow-up studies are required with serial UA measurement to establish the time-dependent association of UA with mortality outcomes.

Key words: coronary artery disease (CAD), diabetes, mortality, uric acid (UA)

Despite an accurate description of ‘gout’ by Hippocrates as early as in 460 BC, historically gout has been misinterpreted as a disease of the rich and referred to as ‘king of diseases and diseases of the kings’, and ‘a physician’s name for the rheumatism of a rich patient’. Although UA (uric acid) was first isolated from kidney/gall bladder stones in late 18th century, the role of hyperuricaemia in gout was established by the middle of the 19th century. UA is the final product of purine metabolism in humans and is implicated in many disease conditions. The balance between the breakdown of purines via the action of xanthine oxidase and the rate of UA excretion controls the level of serum UA in the body. Although it has beneficial antioxidant properties at a cellular level, sustained hyperuricaemia has putative adverse roles in cardiovascular diseases. Despite strong evidence emerging from large epidemiological studies supporting the hypothesis that UA independently influences cardiovascular disease outcomes [1,2], a causal role is yet to be established. The high correlation of serum UA with conditions such as hyperinsulinaemia, hypertension and the metabolic syndrome and renal function [1] leads to several challenges in selecting the appropriate statistical models in epidemiological studies to establish an independent association. Issues related to multiple collinearity among

variables in the regression models and to consider whether a variable as a confounder or mediator in the biological pathway due to partial understanding of the disease mechanisms are some examples.

Serum UA is considered as a useful biomarker for mortality in high-risk patients with acute coronary syndromes and heart failure and in patients with hypertension [2]. In the present issue of *Clinical Science*, Ndrepepa et al. [3] have investigated the prognostic role of UA in high-risk Type 2 diabetic patients with established coronary artery disease in predicting 1-year survival and cardiovascular mortality. Although they did not find a linear association between serum UA and mortality, levels of serum UA above 7.70 mg/dl were associated with increased mortality, independently of the effect of all traditional risk factors, other co-morbid conditions and both insulin and diuretic therapy. A consistent association was observed in the analyses after excluding mortality in the first 30 days. In the subgroup analyses, this association was consistent in all subgroups. These results support the independent role of serum UA in predicting survival in Type 2 diabetic patients; however, the authors [3] have used a single time point measurement of serum UA and have not investigated the potential pathophysiological changes over time.

Abbreviations: BP, blood pressure; UA, uric acid.

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Long-term follow-up studies are required with serial UA measurements to establish the time-dependent association of UA on mortality outcomes.

Findings from animal and *in vitro* studies suggest a potential causal role of UA in cardiovascular diseases. UA increases both proliferative and pro-inflammatory actions and contributes to endothelial dysfunction [4]. Animal studies have also suggested that UA may be a true mediator in the progression of kidney diseases [5]. Consistent findings are reported in human studies in healthy individuals [6].

Despite emerging results on UA and its association with incident renal and cardiovascular outcomes, the beneficial role of reducing UA levels on cardiovascular risk, as well as on the progression of kidney diseases, is not established yet. However, there is some evidence to suggest the potential beneficial effect of reducing UA levels in humans. A reduction in CRP (C-reactive protein) and a slower progression of chronic kidney disease are observed with allopurinol treatment, which inhibits xanthine oxidase [7]. Improvements in endothelial function following allopurinol treatment have been shown in subjects with asymptomatic hyperuricaemia [8]. Post-hoc analyses of statin trial data suggest a significant reduction in vascular events with a decrease in UA levels after adjustment for multiple risk factors [9]. Similarly, a significant proportion of relative risk reduction in cardiovascular outcomes associated with losartan use in the LIFE (Losartan Intervention For Endpoint reduction) study has been attributed to its effect on serum UA [10]. In the RENAAL (Reduction of Endpoints in NIDDM with the Angiotensin II Antagonist Losartan) study among patients with Type 2 diabetes and nephropathy, reduction in serum UA levels partially mediates the renal risk reduction associated with losartan use [11]. In a subgroup analyses of the J-HEALTH (Japan Hypertension Evaluation with Angiotensin II Antagonist Losartan Therapy) study, losartan-based antihypertensive treatment increased the kidney function and reduced BP (blood pressure), proteinuria and serum UA [12]. As all of these studies are post-hoc analysis results, the findings should be treated as inconclusive and only hypothesis-generating.

Do interventions to reduce UA levels have survival benefits? In spite of promising early phase data, agents such as allopurinol have failed to generate adequate scientific interests to conduct well-designed RCTs (randomized controlled trials) in large high-risk populations. Alternative strategies such as the use of febuxostat, a novel non-purine selective inhibitor of xanthine oxidase appears exciting [13,14]. However, there are no large clinical trials evaluating their benefits in improving survival in high-risk patients with cardiovascular disease. Future clinical trials should be considered to address the effect of these agents on BP, endothelial dysfunction, left ventricular hypertrophy, cardiovascular events and mortality in high-risk populations.

There is a strong genetic predisposition to serum UA levels in humans with heritability estimates of up to 70%. Several genetic variants that are linked to urate transport proteins are associated with serum UA levels [15]. Although it is too early to speculate, some of them have the potential to be considered as new targets for pharmacological interventions. Gender differences have been observed in the ability of some of the genetic variants in con-

trolling serum UA levels. Further research in this area may help to develop genotype-based interventions to reduce serum UA and the associated morbidity and mortality.

In summary, serum UA is associated with cardiovascular mortality. Although serum UA is amenable to interventions, the long-term effect of a change in serum UA on cardiovascular events are not known. The available evidence justifies the development of well-designed randomized controlled trials to test the efficacy and effectiveness of pharmacological interventions that reduce serum UA levels. Serum UA measurement should be part of all new cardioprotective intervention studies in the future.

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