Perspective

Serum uric acid levels and cardiovascular disease: the Gordian knot

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Abstract: Hyperuricemia is defined as serum uric acid level of more than 7 mg/dL and blood levels of uric acid are causally associated with gout, as implicated by evidence from randomized clinical trials using urate lowering therapies. Uric acid as a cardiovascular risk factor often accompanies metabolic syndrome, hypertension, diabetes, dyslipidemia, chronic renal disease, and obesity. Despite the association of hyperuricemia with cardiovascular risk factors, it has remained controversial as to whether uric acid is an independent predictor of cardiovascular disease. To settle this issue, and in the absence of large randomized controlled trials, Mendelian randomization analysis in which the exposure is defined based on the presence or absence of a specific allele that influences a risk factor of interest have tried to shed light on this.

Keywords: Hyperuricemia; cardiovascular risk factors; coronary artery disease; mendelian randomization

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Serum concentrations of uric acid, the end product of the metabolism of purine compounds, above 7 mg/dL result in hyperuricemia, causally associated with gout as evidenced in randomized clinical trials using urate lowering therapies (1). All or nearly all urate is filtrated out at the glomerulus, and decreased efficiency of renal uric acid excretion is responsible for about 85 to 90 percent of primary or secondary hyperuricemia. Hyperuricemia may also occur, but to a lesser degree, by the overproduction of uric acid due to the intake of purine-rich food, alcohol abuse or by conditions associated with high cellular turnover (large destruction of tumor cells, psoriasis, etc.). Also, numerous drugs, used frequently in patients with heart disease, such as losartan, diuretics, beta-blockers or acetylsalicylic acid may favor an increase on serum uric acid (2). In the same way genetic variation may contribute to serum uric acid levels through regulation of uric acid synthesis, excretion, or reabsorption (3).

Hyperuricemia is associated with deleterious effects on endothelial dysfunction, oxidative metabolism, platelet adhesiveness, hemorheology, and aggregation. The atherosclerotic plaque contains a considerable amount of uric acid which may increase platelet adhesiveness and potentiate thrombus formation (4). Increased serum uric acid levels may favor microvascular diseases stimulating vascular smooth muscle cell proliferation, the production of low-grade inflammatory and pro-oxidative states and the generation of vasoconstrictive substances, ultimately leading to growth, instability, and rupture of atherosclerotic plaques and facilitation of thrombosis. It is believed that the action of serum urate is elicited through the action, among other factors, of xanthine oxidase, a powerful oxygen radical-generating system in human physiology (5,6), and by altering the equilibrium the renin-angiotensin system (7), thus influencing arterial hypertension. As a support of the causative role of uric acid in the development of hypertension, two randomized trials have shown that hypertension in adolescents is preventable by lowering uric acid with either xanthine oxidase inhibitors or uricosuric agents (8,9). Meanwhile, benefits on blood pressure in

adults are less significant (10). In this context, a meta-analysis of 18 prospective cohort studies of subjects who were normotensive at baseline (n=55,607) found that hyperuricemia was associated with an increased risk for incident hypertension being this finding most striking in younger individuals and women.

There is also increasing evidence that elevated serum uric acid levels may predict the development of type 2 diabetes. Biologically, uric acid plays an important role in worsening the insulin resistance phenotype in animal models by inhibiting the bioavailability of nitric oxide, which is essential for insulin-stimulated glucose uptake (11). On the other hand hyperinsulinemia, as a consequence of insulin resistance, causes an increase in serum uric acid concentration by both reducing renal uric acid secretion (12) and the accumulation of substrates required for uric acid production (13). In this context, Kodama *et al*. (14) found, in a meta-analysis of 11 cohort studies (42,834 participants) which included 3,305 incident cases of type 2 diabetes, that hyperuricemia was positively associated with the development of type 2 diabetes.

Despite the association of hyperuricemia with cardiovascular risk factors, it has remained controversial as to whether uric acid is an independent predictor of cardiovascular disease, with many studies in favour (15-19) and others against (20,21). One example of the latter is the study of the Framingham Heart Study cohort (20), which did not reveal a significant association between uric acid levels and the incidence of coronary heart disease or cardiovascular mortality after adjustment for cardiovascular risk factors. The authors indicated that the observed lack of association was likely because of the close association between uric acid and known risk factors such as decreased glomerular filtration rate, the use of diuretics and insulin resistance. Similarly, some meta-analyses have not reached an agreement about the utility of uric acid as a cardiovascular risk factor per se (22,23). Also, hypoxaemia, body mass index, and C-reactive protein concentrations have been demonstrated to be higher in hyperuricemic congenital heart disease patients, although no significant differences were seen in mortality between congenital heart disease patients with high and low serum uric acid concentrations (24). By contrast, other authors have found that high uric acid levels may predict the risk for stroke (25) and heart failure (26) besides being predictive of symptom status and prognosis (27). Likewise, some authors have detected an increased risk of both cardiac and total mortality with increasing serum uric acid levels (28). Nonetheless, establishing whether serum uric acid is an independent risk factor has been complicated by interactions between serum uric acid levels, cardiovascular risk factors and kidney function.

Intervention studies are needed to determine whether serum uric acid levels and cardiovascular disease are indeed associated but, up to date, there has only been a randomized, double-blind, placebo-controlled, crossover trial in patients with angina pectoris which concluded that the uric acid lowering drug allopurinol is a useful, well tolerated, and safe anti-ischaemic treatment option in patients with angina (29). The mechanism of the anti-ischaemic effect of allopurinol, a xanthine oxidase inhibitor, might be related to the improvement in the peripheral endothelial function. Nonetheless, while the results of this study showed a benefit of allopurinol, the overall effects were modest and the study population small (n=65).

Being faced by this Gordian knot and, in the absence of costly randomized controlled trials, considered the gold standard since they provide the highest level of statistical evidence, some authors have turned to Mendelian randomization analysis. This is the case of Keenan *et al*. (30), who tried to assess whether serum urate levels were causally relevant in type 2 diabetes mellitus, coronary heart disease, ischemic stroke, and heart failure. Twenty eight single nucleotide polymorphisms known to be associated with serum urate levels were examined in association with various vascular and nonvascular risk factors to assess pleiotropy. To limit genetic confounding, 14 single nucleotide polymorphisms, exclusively associated with serum urate levels, were used in a genetic risk score to detect associations with cardiometabolic diseases. Their results revealed no evidence to support a causal role of circulating serum urate levels in type 2 diabetes mellitus, coronary heart disease, ischemic stroke, or heart failure. Moreover, they state that decreasing serum urate levels may not translate into risk reductions for cardiometabolic conditions.

A lack of association between individual genetic variants associated with serum urate levels and hypertension, glucose, lipids, and coronary artery diseases has been also reported by others (3,31,32). Yang *et al*. (33) used Mendelian randomization to establish a genetic urate risk score based on the analysis of eight genetic loci (SLC22A11, GCKR, R3HDM2-INHBC region, RREB1, PDZK1, SLC2A9, ABCG2, SLC17A1) that showed genome-wide significant association with urate levels in a meta-analysis. This score explained, in average, 6.0% of serum urate variance, compared to an average of 0.8% when individual

SNPs were considered. As in the study of Keenan *et al*. (30), they did not observe an association between the genetic urate score, fasting glucose levels or coronary heart disease. Pfister *et al*. (34) established a risk score based on eight serum-uric-acid-raising common allelic variants, identified in genome-wide association studies and evaluated the association of this score with type 2 diabetes in several case-control studies including 7,504 diabetes patients and 8,560 non-diabetic controls. Their results did not support a causal relationship between uric acid and the development of type 2 diabetes, limiting the expectations that uric-acid-lowering drugs would be effective in the prevention of type 2 diabetes. Similarly, Palmer *et al*. (35) conducted a Mendelian randomization analysis and found no strong evidence for causal associations between a variant at the SLC2A9 gene (rs7442295), associated with uric acid levels, and ischaemic heart disease or blood pressure. Another large meta-analysis, including over 28,000 participants, showed no association between nine different loci associated to serum uric acid levels and the risk of coronary artery disease (36). In this context, Keenan *et al*. (30), by examining a much larger cohort of coronary heart disease cases than in previous studies (33-36) obtained a similar result.

Because the association between genes and disease is not generally subject to confounding by environmental factors or reverse causality, causal inferences between exposure and disease can be examined more specifically using Mendelian randomization (37,38). This methodology is inspired by Mendel's second law, which states that unlinked or distantly linked segregating gene pairs assort independently at meiosis. In other words, gene transfer from parent to child is a chance occurrence, similar to the random assignment into different experimental groups as in a randomized controlled trial (39). However, we may find several scenarios violating the Mendelian randomization assumptions, such as inadequate phenotype definition, time-varying exposures, the presence of gene-environment interaction, the existence of measurement error, the possibility of reverse causation, deviations in the expected allelic frequencies due to several causes (population stratification, existence of linkage disequilibrium phenomena, pleotropic activity of some genes, etc.), the existence of an appropriate instrument (simple or multiple polymorphism, or genetic risk scores) for the study of interest, the lack of compliance with the conditions that should be met by instrumental variables, or problems with sample size (39-41).

The Gordian knot, according to prophecy, was to be undone only by the person who was to rule Asia, and that was cut, rather than untied, by Alexander the Great. Only large, randomized controlled trials will be able to disentangle the role of hyperuricemia in cardiovascular disease, undoing the knot rather than cutting it.

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Footnote

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