

## Correspondence

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### The increase in serum uric acid induced by diuretics could be beneficial to cardiovascular prognosis in hypertension: a hypothesis

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Hyperuricaemia has a higher prevalence in hypertensive than in normotensive subjects [1,2], and it associates with obesity, hypertriglyceridaemia, hypercholesterolaemia, low serum high-density lipoprotein-cholesterol and insulin resistance [2,3]. Multivariate analyses of the results of various epidemiological studies that included blood pressure and several metabolic-syndrome risk factors revealed positive associations between serum uric acid and the occurrence rate of certain cardiovascular outcomes [4,5]. This led some researchers to conclude that elevated serum uric acid concentration is an independent cardiovascular risk factor [5]. However, other epidemiological studies disclosed no independent associations between serum uric acid and indicators of cardiovascular prognosis [6,7].

No mechanism linking raised serum uric acid levels and cardiac and/or vascular damage in man has been positively identified, despite extensive dedicated research. In addition, no sufficiently powered study has addressed the question of whether reducing serum uric acid concentration improves cardiovascular prognosis independently of concomitant changes in other variables that may be relevant. However, appropriate studies have disclosed that antihypertensive therapy with diuretics increases serum uric acid and improves cardiovascular prognosis [8,9]; this deserves detailed consideration.

#### Generation, antioxidant action and excretion of uric acid

Uric acid, which is the final product of purine metabolism in man, is formed from xanthine through a reaction that is catalysed by xanthine dehydrogenase or by xanthine oxidase [10]. These enzymes also mediate the production of xanthine from hypoxanthine [10]. Low oxygen tension and various proinflammatory cytokines stimulate the formation of xanthine oxidase [10]. The productions of xanthine and uric acid catalysed by xanthine oxidase are accompanied by the cogeneration of the superoxide anion radical. Superoxide reacts with

nitric oxide and produces peroxynitrite [11], which generates free radicals [12]; this results in cytotoxic oxidations [13].

Uric acid is endowed with powerful antioxidant capacity. It can scavenge peroxynitrite, peroxynitrite-derived free radicals and hydroxyl radical [12,14].

In individuals with unimpaired renal function, approximately two-thirds of all uric acid produced is excreted by the kidneys. Most of the uric acid in the proximal tubule undergoes net reabsorption in this site, where secretion and reabsorption coexist [15]. The amount of uric acid that is excreted in urine, expressed with respect to the amount filtered, varies between 6 and 12% in normal circumstances [15].

Plasma volume expansion increases the renal excretion of uric acid by reducing its proximal tubular reabsorption, and vice versa [15]. Thus, increased reabsorption would account for the rise in serum uric acid that occurs when salt intake is low [16]. Serum uric acid concentration associates positively with sodium reabsorption in the proximal tubule [17]. Proximal tubular uric acid reabsorption is enhanced and the renal excretion of urate is lowered by exogenous administration of angiotensin II [18] or of noradrenaline [19].

Insulin reduces the renal excretions of sodium and uric acid, in both normotensives and hypertensives, independently of insulin sensitivity [20,21]. Therefore, the elevation in serum uric acid associated with insulin resistance [3] appears due to renal retention [21].

It has been hypothesized that a hitherto unidentified signal could trigger a reduction in the renal clearance of uric acid and an attendant increase in serum uric acid in response to oxidative stress [22].

The increase in serum uric acid that accompanies hypertension is due to lower than usual renal excretion of this substance [23,24].

#### Diuretics and uric acid

All frequently used thiazide-type diuretics [25,26], loop agents [25,26], and potassium-retaining drugs and their combinations with thiazides [25,27] diminish the renal excretion of uric acid and augment serum uric acid. This pharmacological action seems to be mainly or

totally due to increased net reabsorption of uric acid in the nephronal proximal tubule [15,25,27–29].

Diuretic-induced elevations in serum uric acid are dose-dependent [30] and become noticeable at low doses [31]. Once-daily treatments with hydrochlorothiazide 12.5 mg [32,33], chlorthalidone 12.5–25 mg [9,34–36], bendrofluazide 1.25 mg [30,37], or indapamide 1 mg [38] all increase serum uric acid. Moreover, hydrochlorothiazide 12.5 mg and bendrofluazide 1.25 mg once daily augmented serum uric acid while they had no significant effect on serum potassium concentration in several well-conducted studies [30,32,37].

Increases in serum uric acid unrelated to uric acid formation entail increases in antioxidant capacity. Thus, the exogenous administration of uric acid elevates total plasma antioxidant capacity [39]. Furthermore, the total antioxidant capacity of deproteinated plasma was found to be higher in treated hypertensives with added cardiovascular risk factors than in controls; this difference was associated with an increased use of diuretics and aspirin by treated hypertensive patients, and the authors concluded that diuretic-raised serum uric acid levels could partly explain their findings [40].

### Diuretic-induced increases in uric acid and cardiovascular prognosis in hypertension

In the Systolic Hypertension in the Elderly Program, the outcomes of cardiovascular events or strokes were better in patients treated with chlorthalidone than in those who received placebo [9]. The possibility that this could be explained by a rise in serum uric acid that occurred in the chlorthalidone-treated patients [9] is supported by a recent finding that serum uric acid concentration is associated with improved prognosis in patients suffering an acute ischaemic stroke [41].

In the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT), patients on diuretic-based antihypertensive pharmacotherapy (chlorthalidone at 12.5 or 25 mg/day) had lower risks for stroke, heart failure, hospitalized/treated angina and coronary revascularization than patients on lisinopril-based therapy, and they had a lower risk of heart failure than patients who received an amlodipine-based treatment [42]. These differences in favour of the diuretic occurred despite the fact that the incidences of hypokalaemia and diabetes and mean serum cholesterol were highest in the chlorthalidone group. Various factors might account for the differences noted between the effects of the three therapies on cardiovascular prognosis; *inter alia*, the superiority of the diuretic could partly be explained by an elevation in serum uric acid and therefore in antioxidant capacity. The ALLHAT report [42] does not refer to serum uric

acid, but chlorthalidone at the doses used increases this variable [9,34–36].

The effects of antihypertensive treatments with placebo, low-dose diuretics, beta-blockers, angiotensin-converting enzyme inhibitors, angiotensin II antagonists, calcium antagonists and alpha-1 adrenoceptor blockers on cardiovascular prognosis were evaluated in a recent network meta-analysis that comprised more than 190 000 patients. None of the other treatment strategies was better than low-dose diuretics for any of the outcomes considered (coronary heart disease, stroke, cardiovascular disease events, cardiovascular disease mortality and total mortality) [43]. Low-dose diuretics reduced the risk of cardiovascular disease events to a greater extent than four of the other five active treatments considered, and they were associated with lower risks of heart failure and stroke than angiotensin-converting enzyme inhibitors [43].

### Hypothesis

Diuretics reduce the renal excretion of uric acid and raise serum uric acid, even at the low doses currently used to treat hypertension. Uric acid is a powerful antioxidant, and elevations in its serum concentration originating in reductions in its excretion entail increases in plasma antioxidant capacity. Given that increased oxidations possibly have a bearing on the pathogenesis of the unfavourable changes in the heart and the vessels that accompany hypertension [44,45], the increase in serum uric acid caused by low-dose diuretics could add to the positive effect that high blood pressure reduction with these agents has on cardiovascular prognosis [46]. This mechanism could explain, at least in part, the fact that low-dose diuretics appear to be superior to other antihypertensive agents in terms of cardiovascular prognosis [42,43]. In any event, it may explain why diuretics are not inferior to other antihypertensive agents despite the fact that even low-dose diuretics have untoward effects on potassium turnover and on carbohydrate and lipid metabolism [42,43].

A first approach to testing the present hypothesis would require a sufficiently powered trial to discriminate between the responses of cardiovascular outcomes, serum uric acid and total plasma antioxidant capacity to antihypertensive therapy with a thiazide-type diuretic and to an agent that does not modify serum uric acid concentration. Sodium and purine intakes should be assessed to allow improved clinical deductions by comparison with what might be inferred from the available results of large studies on antihypertensive agents.

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