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COMMENTARY

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Uric acid: an old actor for a new role

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The study by Montalcini et al. reported recently in this issue of the journal *Internal and Emergency Medicine* contributes to originate new concepts about an old topic, that is uric acid and its role in vascular disease [1]. They report that in postmenopausal women serum uric acid levels are directly associated with carotid intima-media thickness independently of other cardiovascular risk factors (including the metabolic syndrome). The importance of this finding is due to the fact that an increased carotid intima-media thickness is a marker of early atherosclerosis and may predict cardiovascular events [2].

Several epidemiological studies have reported a positive association between serum uric acid concentrations and cardiovascular diseases [3]. In a recent report it has been concluded that uric acid is a strong risk factor for both myocardial infarction and stroke [4]. Elevated urate concentration is significantly and independently associated with increased risk of future vascular events in diabetic stroke patients [5].

Therefore, it could be useful for physicians to check for serum uric acid levels for risk stratification.

However, the role of uric acid as an independent risk factor for cardiovascular events is still debated [6, 7]. In fact, other confounding factors such as glucose intolerance, obesity, dyslipidaemia, hypertension, use of diuretics and insulin resistance may play a role in determining the increased vascular risk associated to elevated uric acid concentrations. These factors (including high uric acid) have been mentioned in one or more definitions of the metabolic syndrome [7]. Recently, much attention has been paid to the metabolic syndrome due to its possible role as a risk factor for the development of type 2 diabetes and cardiovascular disease. The worldwide increase in the prevalence of obesity and diabetes is a reason not only for the increasing prevalence of the metabolic syndrome but also of hyperuricaemia.

Hyperinsulinaemia and insulin resistance lead to elevated serum uric acid levels through both direct and indirect mechanisms, which include increased urate production as well as decreased renal urate excretion (probably due to the stimulating effect of insulin on urate reabsorption in the renal proximal tubule). Hypertension, use of some drugs (in particular diuretics) and renal disease are also associated to increased uric acid concentrations.

The link between uric acid and the progression of vascular disease has been examined not only in epidemiological studies but also with experimental investigations [8]. The possible mechanisms involved in this causal relationship are:

- uric acid may induce a thickening of the glomerular afferent arteriole, activation of the renin-angiotensin system, and hence hypertension;
- uric acid may contribute to endothelial dysfunction by inducing anti-proliferative effects on endothelium and impairing nitric oxide production;
- uric acid stimulates human vascular smooth muscle cell proliferation and synthesis of C-reactive protein;
- uric acid may increase platelet adhesiveness and platelet lysis (a platelet dysfunction may be linked to endothelial dysfunction);
- hyperuricaemia could promote thrombus formation;
- uric acid may have a role in oxidative stress and in the formation of free radicals;
- uric acid may enhance oxygenation of low-density lipoprotein cholesterol and lipid peroxidation.

An independent link between uric acid and endothelial function has been reported in patients with uncomplicated,

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untreated essential hypertension, independent of traditional cardiovascular risk factors [9].

Renal excretion of urate is regulated by a member of the organic anion transporter superfamily (URAT1). A specific expression of URAT1 on human aortic vascular smooth muscle cells has been reported and this could be a mechanism by which uric acid enters the human vascular smooth muscle cell, eventually leading to cardiovascular disease [10].

In patients with congestive heart failure an increased production of uric acid is mediated by activation of xanthine oxidase, a producer of uric acid from xanthine and hypoxanthine. Xanthine oxidase is also a source of free radicals and may contribute to oxidative damage in the myocardium. It has also been reported that a high serum level of uric acid is an independent predictor of mortality in patients with congestive heart failure [11]. Therefore, xanthine oxidase inhibition could be a therapeutic strategy for heart failure and it may be important to measure serum uric acid as a marker of oxidative stress in patients with congestive heart failure.

Similarly to homocysteine (an amino acid that has been linked to increased risk of premature coronary artery disease and stroke), uric acid may have a toxic effect on the vasculature by inducing clotting abnormalities and oxidative stress. However, lowering of uric acid in patients with increased vascular risk has not always been accompanied by prevention of cardiovascular events [12].

In conclusion, a better understanding of the role of uric acid in health and in disease states may help physicians to improve their performance in preventing and treating cardiovascular disease.

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