

Carotid arterial stiffness and intima-media thickness: A little impact of uric acid

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Accurate assessment of cardiovascular (CV) risk is essential for clinical decision making. Serum uric acid (UA) has been proposed as a novel additional CV risk [1,2]. UA is the normal end product of purine metabolism arising from dietary and endogenous nucleic acid [3]. In the early '80s it was considered a powerful antioxidant, protecting against the effects of aging and cancer, due to a beneficial evolutionary loss of uricase activity in hominoids [4]. More recently, laboratory and epidemiological investigations have suggested elevated UA to be associated with atherosclerosis and CV events [5-9]. However, this relationship remains controversial [10] and serum UA is not listed as CV risk factor in the guidelines on CV disease prevention [11,12].

Possible underlying pathophysiological mechanisms behind the relationship between UA and subsequent coronary and cerebrovascular events include endothelial dysfunction, vascular smooth muscle proliferation and activation of inflammatory cells, all of which are affected by UA and involved in the development of atherosclerosis [13-16]. They reduce the elastic properties of the arterial wall, induce smooth muscle hypertrophy and intimal thickening, thus leading to increased arterial stiffness, carotid intima-media thickening, arterial plaque formation and coronary calcification [17-20]. These changes may occur even in the absence of clinical manifestations of disease and can be assessed at early stages by non-invasive techniques.

In the present issue of the Monaldi Archives of Chest Disease, Francesco Antonini-Canterin *et al.* [21] report a study investigating the carotid ultrasound assessment of UA effect on carotid beta stiffness index (BSI) and intima-media thickness (CIMT). In a

large sample of patients with high CV risk but no history of coronary artery disease, heart failure or cardiomyopathies, with normal or elevated UA levels, the authors found a significant correlation between UA levels and BSI and CIMT. However, the correlation coefficients were small with large dispersion of data as evidenced in the scatterplots. Moreover, when traditional CV risk factors for atherosclerosis, such as age, glycemia, blood pressure, LDL-cholesterol, were adjusted for in a multivariate regression analysis, the single risk factor with the largest statistical significance was age, whereas UA had only marginal significance.

The results of this study highlight some inconsistencies in the relationship between UA and CV risk prediction. Age is associated with arterial stiffness, similar to that observed in atherosclerosis [22,23]. In addition, age is associated with higher serum UA levels [10] and with most CV risk factors. The multivariate regression analysis in the present paper shows that BSI and CIMT are significantly related to age, but not to the other established risk factors and only marginally to UA levels. This indicates that age is a confounder and the relationship of BSI and CIMT with the traditional risk factors and UA is not significant or negligible because they have been adjusted for.

This reasoning is in line with previous studies in showing that when the traditional CV risk factors were adjusted for in the multivariate analysis, the relationship between serum UA levels and CIMT or arterial stiffness became weak or lost significance [24-26]. In general, the statistical association between UA and CV risk is inversely proportional to the number of covariates included in the regression model [27]. Accordingly, since UA is associated with the risk factors for atherosclerosis, it seems that the relationship between high serum UA and early measures of atherosclerosis may be due to its relationship with risk factors, particularly with age.

Furthermore, two large meta-analyses showed no significant trend in the dose-response relationship between serum UA levels and CV risk, and in the relationship between UA levels reduction from baseline to the end of follow-up and CV clinical events [28,29].

Thus, despite several reports of positive correlation of serum UA and subsequent CV events, the above observations suggest that serum UA does not fulfill some of the criteria to be considered a novel CV risk with an incremental value in providing predictive information above those provided by the well established risk factors in guiding treatment [30].

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