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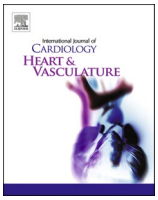

Editorial

Causal relationship between serum uric acid and cardiovascular disease: A Mendelian randomization study

Uric acid (UA) is synthesized mainly in the liver by xanthine oxidase (XO) and is the end-product of a series of reactions metabolizing purines (adenine and guanine) mostly from proteins. The interest in elevated uric acid (UA) and its cardiovascular (CV) implications has progressively increased in the last 20 years with a growing number of evidence supporting a close relationship between levels of UA, hypertension, metabolic disorders as well as major CV diseases (CAD, Stroke, HF). [1,2]. Interestingly, UA can be found plasma and in several human tissues, and biofluids, including urine, saliva, cerebrospinal fluid, and feces. UA crystals are recognized by toll-like receptors and induce inflammasome activation and this can have a significant implication in the CV response to hyperuricemia [3]. Uric acid is mainly excreted by the kidney and intestine, and most of the uric acid filtered by the renal glomeruli is reabsorbed (90 %) [4]. This complexity in the handling of serum urate along with the variable impact of many confounders and reverse causality biases, is responsible for the uncertainty in the interpretation of the mechanism(s) leading to CV disease in presence of hyperuricemia. Activation of the inflammatory response through inflammasome is the final step of vascular damage in patients with hyperuricemia, but the earlier mechanism leading to elevated serum UA is still under active scrutiny for his possible involvement in the adverse cardiovascular response. The activity of XO has been demonstrated to be indirect involved in CV damage through the increased levels of oxidative stress that is directly proportional to circulating UA [4,5]. In addition, a recent paper has reported the existence of natural mutations of XDH leading to a difference in the impact on the balance between oxygen radicals' production and nitric oxide [6]. This implies the possibility that the mechanism responsible for hyperuricemia can involve two different but integrated pathways: a urate underexcretion and/or its overproduction. The two mechanisms do not seem to have comparable cardiovascular implications since only the presence of oxidative stress is associated with endothelial dysfunction, LDL-C oxidation, raised blood pressure and instability of the atherosclerotic plaques [1,2,4,5].

Apart from these mechanistic implications, the genetic profile of patients with hyperuricemia can be very different considering that both uric acid production and urate excretion-reabsorption processes are largely under genetic control [7]. This means that any condition of disequilibrium in the variability of the different genes involved in urate handling could contribute to explain the discrepancies in the interpretation of the role of UA in CV disease as well as the heterogeneity across the population of patients with hyperuricemia.

In the present issue of IJC Heart and Vasculature, Zhang and coworkers [8] have reported the results of a two-sample Mendelian randomization (MR) approach investigating the causal link between serum UA and CVD. The use of appropriate genome-wide association study (GWAS) data for serum UA addressing its causative role on six expressions of CVD, robustly showed that a genetic predisposition to elevated serum UA levels significantly increases the risk of CVD, arterial hypertension, MI, angina and CHD. This is a giant step toward the correct interpretation of the primary role of serum urate as a causative factor of cardiovascular disease. This agrees with the results of another recent study showing a direct relationship between the circulating levels of UA and the relative risk of major CVD in patients free of any additional cardiovascular risk factor [9] with a 11 to over 20 % improvement in the predictive role of hyperuricemia when UA is added to the classical Framingham equation. Furthermore, the genetic confirmation that higher levels of UA can causatively promote CV disease, could contribute to the definition of future preventive strategies by reducing the impact residual cardiovascular risk that cannot be explained by established risk factors for CV disease. According to Zhang et al [8] the positive results of Mendelian randomization warrant early and aggressive interventions to mitigate CV risks using two different strategies aimed at reducing uric acid levels and treating more aggressively the common CV risk factors.

Once defined that genetic approach can be considered of primary importance for the identification of subjects whose serum urate levels can contribute to cardiovascular risk profile, a challenging question has to be unanswered: why the same conclusions have not been reached by several previous studies approaching the same objective? Genome wide association studies (GWAS) have been used to identify genetic polymorphisms that control SUA levels, regardless of the nature of SNP's that have been included and not considering what step of urate production/excretion was controlled by the genetic entity used to classify the population. The previous Mendelian randomization studies primarily predicted the risk for the development of gout, but failed to predict the development of hypertension, chronic kidney disease and cardiometabolic diseases [10–12].

The differences observed across the different studies could be reasonably explained by the process of selection of genes and SNP's within the initially available datasets that have considered only genetic variants involved in renal urate handling that are chiefly involved in the development of gout. Conversely, more recent studies have linked genetic polymorphisms involved in control of XOR activity showing a significant causality between uric acid production and the risk for hypertension, obesity, and chronic kidney disease [13–15]. A recent analysis based on multiple sets of genetic data showed that elevated BP mediates approximately one-third of the effect of urate on cardiovascular disease risk [16].

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So, genes appear clearly involved, but the complexity of the process of urate handling requires a careful selection of the candidate subjects to separate between the "renal/articular" and the "cardiovascular" hyperuricemia. The study of Zhang and co-workers [9] belongs to this more recent generation of studies and in conjunction with many other papers dealing with the primary role of XO activity [1,2,7] or with the predictive power of approaches based on the selection of subjects based on phenotypes (e.g. patients overproducers with high SUA/sCreat ratio) [17] should help the scientific community to clarify the close relationship between serum UA levels and the risk and progression of CV disease. The availability of biomarkers is an outstanding tool for the practice of clinical medicine, but before deciding if they are in or out the "golden circle" of well recognized predictors of major events, we should know all the possible mechanisms leading to biomarkers variability. In the case of uric acid, any attempt to explain his negative prognostic role in cardiovascular medicine has been frustrated by the lack of consideration that one size does not fit all, and in particular that for the same levels of circulating uric acid we can have remarkably different clinical implications that can primarily involve the joints, the kidney, the heart and the vessels, the metabolic profile and the genetic approach could be very helpful in the patient's selection process that means also in the more precise approach to knowledge and prevention of cardiovascular disease.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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