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Letter to the Editor

Hyperuricemia and tissue monourate deposits: prospective therapeutic considerations

Dear Editor,

Uric acid is the final oxidation product of purine metabolism in humans[1]. Originally considered as an inert catabolic product, it has been subsequently demonstrated to have a physiological role (i.e. a selective antioxidant activity) both by *in vitro* models and in humans[2]. Purines are components of nucleosides, the building elements of DNA and RNA. Adenosine and Guanine (purine nucleosides) are also directly involved in the synthesis of important factors, such as adenosine triphosphate (ATP), S-adenosylmethionine, and nicotine adenine dinucleotide (NADH)[3]. Due to the primary role of purine-containing molecules, vertebrates have developed effective systems for purine nucleosides synthesis starting from easily available substrates (i.e. glucose, glycine, glutamine). Physiologically, nucleosides are removed from the body by liver metabolism and the kidneys are the main excretion route. For most mammals, the purines are previously converted into uric acid, which is then catabolized into allantoin via the activity of the hepatic enzyme uricase[4]. Allantoin is a highly hydrophilic molecule, easily transported through the bloodstream, and easily excreted by kidneys due to its high filtration rate, under physiological conditions. As a result of an evolutionary advantage, humans and other primates constitutionally lack a functional uricase, and can only break purines down into uric acid[5]. When monosodium urate (MSU) concentration exceeds the chemical threshold for deposition, uric acid is prone to crystallization with subsequent deposition in a variety of human tissues. This event represents the *primus movens* for the development of gout. According to epidemiological and clinical studies, the serum uric acid (SUA) level that prevents uric acid deposition is lower than 6 mg/dl[6]. This threshold is one of the key recommendations for chronic treatment of gout, in international guidelines[7,8]. Furthermore, a threshold value < 6 mg/dl seems to optimally identify true healthy subjects and should be reasonably considered for all subjects[9]. The lowering of sUA levels below 6 mg/dl favors MSU crystals dissolution with consequent improvement of gout signs and symptoms[10].

Although patients with asymptomatic hyperuricemia might never experience the symptoms of a gout flare, ultrasound studies have revealed that up to one-third of them may have urate deposits and evidence of inflammation in joints and surrounding soft tissues[11-15]. The reliability of ultrasound based imaging in revealing the musculoskeletal involvement in patients with gout has been widely demonstrated[16-19]. Sonographic findings related to MSU deposition include the presence of tophi, bone erosion, hyperechoic enhancement of the superficial margin of the hyaline cartilage (double contour sign) and hyperechoic spots.

The double contour sign has been reported in gouty patients and it is likely to reflect the tendency of MSU to crystallize on the cartilage surface[12]. In a series of outpatients with hyperuricemia (defined as SUA levels ≥ 7 mg/dl in two measurements in the two past years) the double contour sign was observed in 25% of first metatarsal-phalangeal joints and in 17% of knee joints. In negative controls (normouricemic subjects), no double contour sign was reported in any joint tested with ultrasound[13]. Furthermore, concomitant observations led up to the conclusion that morphological changes in musculoskeletal structures of patients with hyperuricemia can involve both the intra and extra-articular tissues. Notably, tophi formation was observed in 6% of patients (0% in the normouricemic group, $p < 0.0001$), a result confirming

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previous similar findings (tendon and synovium tophi formation in 34% of subjects with asymptomatic hyperuricemia)[12]. These proportions could even be underestimated due to the relative low degree of sensitivity of ultrasound based techniques in detecting small MSU deposits. All the anatomical alterations occurring in asymptomatic hyperuricemia represent the basis for the proposal of a the new nosographic entity, namely "hyperuricemia with MSU deposits", that now appears clearly identifiable as a phase preceding the intermittent flare stage[11].

The tendency of uric acid to tissue deposition and subsequent damage or interaction with physiological processes could explain the detrimental effects of hyperuricemia on systems and organs different from those of primary rheumatologic interest. Accordingly, several experimental studies provided evidence of the potential pathogenetic role of uric acid in a variety of cardiovascular (CV) conditions and renal diseseas[20]. Large population prospective studies revealed the predictive role of chronically elevated SUA in the progression of endothelial dysfunction, coronary artery disease and renal failure, and supported the evidence of tissue damage induced by persistent elevation of SUA levels[21-23]. However, while clinical evidence supports the common association of hyperuricemia and obesity, a recent meta-analysis revealed that high SUA levels are an independent risk factor for the development of type 2 diabetes mellitus. Notably, both insulin resistance and iperinsulinemia, key features of metabolic syndrome, are related with reduced renal uric acid excretion and increased uricaemia[24]. The increase of 1 mg/dl in SUA is associated with an increased risk of CV conditions as incident hypertension, coronary artery disease, stroke, diabetes and renal failure[25,26]. Greater sustained decreases in SUA levels were associated with less renal function decline ($p < 0.001$) by statistical modeling. The study data predicted that for every 1 mg/dL of chronic reduction of SUA level in subjects with gout, there would be a preservation of 1.15 mL/min of eGFR[27].

Asymptomatic hyperuricemia, as well as gout, have been recognized as independent risk factors for CV disease: even if currently there is no consensus in treating it, Japanese national guidelines recommend the urate lowering treatment also in patients with asymptomatic hyperuricemia and absence of any CV risk factor[7,8,28]. Increased CV risk in patients with gout has been associated with subclinical inflammation due to MSU crystal deposition. This hypothesis seems adequately supported by the observation of a fourfold increase of leukocyte counts in synovial fluids with crystals deposition compared with fluids without crystals when obtained from asymptomatic joints. Further techniques as Gadolinium-enhanced MRI and Doppler ultrasonography have shown the low grade inflammation detectable around asymptomatic tophi[29]. Asymptomatic hyperuricemia has also been related to increased levels of proinflammatory markers, including white cell count, CRP, IL-6, IL-1, IL-18 and TNF. MSU crystals activate NLRP3 inflammasone, the same induced by cholesterol crystals and, thus, induce increased levels of IL-1beta and IL-8. In clinical studies, treatment with XO inhibitors improved endothelial dysfunction and oxidative stress in patients with stable coronary artery disease, exercise capacity in patients with chronic stable angina and reduced morbidity and mortality in patients with congestive heart failure and a history of gout. The improvement of endothelial function via inhibition of XO appears likely related to the reduction of oxidative stress rather than lowering SUA levels[24].

SUA levels reduction can be obtained through different pharmacological approaches, mainly including drugs that inhibit uric acid production (such as xanthine oxidase (XO) inhibitors allopurinol and febuxostat), and uricosuric agents (i.e probenecid, benzbromarone). Based on previous assumptions, lowering sUA levels should translate into CV and renal benefits. In blood vessels, uric acid leads up to overproduction of reactive oxygen species (ROS) and vascular inflammation, while in the kidney uric acid promotes renin release and decreased NO production, interstitial inflammation, microvascular rarefaction and interstitial fibrosis.

Data from clinical studies indirectly support the multidimensional impact of high SUA levels in different study populations. In hypertensive patients with SUA above 8 mg/dl, the XO inhibitor febuxostat provided an antihypertensive effect at 6 months that was not observed with allopurinol[24]. This was probably due to the major reduction of oxidative stress and uricaemia observed with febuxostat when compared with allopurinol.

Furthermore, urate lowering therapy exerts renoprotective effects in patients with chronic kidney disease and hyperuricaemia. In two clinical trials, patients with mild to moderate chron-

ic kidney disease treated with allopurinol underwent a lower decrease of GFR after 12 and 24 months compared to subjects receiving only usual care[24]. Losartan, an angiotensin receptor blocker with uricosuric properties, has shown renoprotective effects in a post-hoc analysis of an open label trial on 1342 patients with type 2 diabetes mellitus and nephropathy[30]. Furthermore, a recent post-hoc analysis of an open-label clinical trial with febuxostat showed an improvement of GFR by 1.15 ml/min for each 1 mg/dl SUA decrease[27].

On the basis of the evidence provided by ultrasound, epidemiological and clinical trials, we strongly support the important need to recognize hyperuricemia with MSU deposits as a specific stage among the pathogenetic events occurring in gout, that both in subclinical and asymptomatic cases, has to be defined as the presence of monosodium urate crystals in tissue progression, as recently proposed by other researchers[11,31]. From a therapeutic perspective, since "hyperuricemia with MSU deposits" represents the stage at which an objective ongoing pathological process can be clinically observed, it could be proposed as the "threshold for intervention". Since high SUA levels and gout appear as independent risk factors for cardiovascular and kidney disease, an early approach to the treatment of gout and associated comorbidities is advisable. New imaging techniques may help both in the evaluation of burden of crystal deposition in asymptomatic subjects and to better deal with the strategic objective of gout treatment, namely the resolution of urate crystal deposition[10].

The recognition and characterization of this apparently new nosographic entity implies further efforts by preclinical and clinical researches in order to better characterize the pathogenetic events occurring in the progression of gout, as well as the optimization of the diagnostic and therapeutic algorithm[31].

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Conflict of Interest

The Authors declare that they have no conflict of interests.

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