Special Report

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Gout and the heart: beyond comorbidities

Gout patients are well known to suffer from cardiovascular (CV) diseases, such as myocardial infarction or stroke, but it had been linked to the frequent comorbidities they present (i.e., metabolic syndrome). However, recent reports have revealed that gout independently associates with an increased incidence of CV events, leading to higher mortality. This likely relates to the persistent, subclinical inflammation due to monosodium urate crystals. Optimal management of gout, which aims at crystal dissolution, should reduce this increased CV risk, though this has not been proven yet. However, a rapid clearance of crystals through a lower serum uric acid target, well below its saturation point is worth considering, at least in patients with a high CV risk. This review will focus on analyzing the association between gout and CV disease and its proper management, addressing whether gout-specific treatment may differ in this subgroup of patients.

Keywords: arteriosclerosis • cardiovascular risk • coronary heart disease • crystals • gout • monosodium urate

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Gout is the consequence of the deposition of monosodium urate (MSU) crystals in joints, tendons and ligaments. This relates to serum uric acid (SUA) levels that persist above its saturation point for a prolonged period [1]. Crystal deposition precedes the appearance of clinical manifestations of the disease [2]. This can be shown in some asymptomatic hyperuricemic individuals by the identification of crystals upon joint aspiration [3], or by the presence of characteristic imaging features [4–7]. Gout presents as recurrent episodes of acute joint inflammation, mainly in weight-bearing joints in the lower limbs. A predominant involvement of osteoarthritic joints has also been reported [8]. These acute attacks (or flares) usually subside after a fortnight without any treatment. Gout is the most common inflammatory arthritis in Western countries, affecting up to 6% of adult men [9]. In untreated patients while hyperuricemia persists crystal deposits grow and expand, attacks become more frequent and a form of persistent arthritis may develop [10].

MSU crystal deposits lead to a persistent low-grade inflammation at joints which can be clinically undetectable. Synovial fluid samples from asymptomatic knees with MSU crystals show an increased leukocyte count when compared with knees without crystals [11]. Leukocyte counts significantly decreased after the use of low-dose colchicine [12]. Also, an inflammatory cellular infiltrate surrounding tophi has been described [13]. MSU crystals are taken as danger signals by the innate immune system cells [14], and are able to produce inflammation through the NLR-P3 inflammasome pathway [15], ultimately inducing the production and secretion of IL-1β, the main proinflammatory cytokine associated with crystal-related inflammation. Rapid resolution of gout attacks after treatment with anakinra [16] – an anti-IL-1 agent – supports the key role of IL-1 in MSU-induced inflammation *in vivo*. The extension of crystal deposits probably influences the inflammatory load, likely rising as the crystal deposit does. This inflammatory load may be

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particularly increased in tophaceous forms, as seen in clinical practice [17].

The consequences of this persistent, low-grade inflammation are still being assessed, but cumulative evidence suggests that this sustained inflammation can be harmful for gout patients, beyond the joint involvement (pain and structural damage). The potential role of persistent, crystal-related inflammation in the atherosclerotic disease of gout patients will be discussed in this article.

Cardiovascular risk in gout patients

An increased incidence of cardiovascular (CV) events in gout has been recognized for decades [18]. In comparison to the general population, gout patients are at a higher risk of developing arteriosclerotic complications such as myocardial infarction, stroke or peripheral arterial disease. This increased risk was attributed to an increased prevalence of hypertensipon, diabetes, dyslipidemia or obesity in these patients [19]. Also, hyperuricemia is a common feature within the so-called metabolic syndrome [20], which also associates with the development of arteriosclerotic disease. Therefore, this high prevalence of known CV risk factors in patients with gout was thought to explain the increased incidence of CV events in these patients.

In the last decade, an increased CV risk has been revealed in patients suffering from chronic inflammatory conditions, and this association persists after adjusting by traditional CV risk factors. It has been described in patients with rheumatoid arthritis [21], psoriasis [22], inflammatory bowel disease [23], systemic lupus erythematosus [24] and many others. In the case of lupus, the increase in risk is shocking: in the subgroup of women in the third to fourth decade of life (the age and sex group predominantly affected by lupus), the mortality risk due to CV diseases is increased by 50 compared with age- and sex-matched controls [25]. Also, an independent relationship between gout and erectile dysfunction – where vascular disease is a well-established cause – has been recently communicated [26]. Several factors contribute to this accelerated arteriosclerosis, all linked to the persistent inflammation [27]: proatherogenic lipid profile, with reduced high-density lipoprotein (HDL) cholesterol and total cholesterol levels, increased triglycerides levels and quality changes in the composition of the HDL particles; insulin resistance and hyperinsulinemia; endothelial dysfunction, with an increased production of cellular adhesion molecules and haemostatic cytokines; and increased oxidative stress, which leads to the oxidation of low-density lipoprotein (LDL) particles. All of these alterations highly correlate with the development of the atheromatous plaque and its subsequent disorders.

As aforementioned, a persistent, subclinical inflammation accompanies the deposits of MSU crystals in joints and tophi. In fact, currently gout is taken as a persistent, subclinical condition with bouts of acute inflammation (flares) [28]. So, has this continuous inflammation any consequence in the CV risk profile of patients with gout, similar to what happens in other chronic inflammatory conditions? Several population-based studies suggest so.

After adjusting for traditional CV risk factors, gout is independently associated with a higher incidence of coronary heart disease [29–33], stroke [34] and peripheral artery disease [35], as well as an increased mortality due to CV events [29]. Women and young patients without traditional CV risk factors but who have gout show the highest increase in risk attributable to the disease [31,36]. These findings suggest a detrimental role of urate crystal-related persistent inflammation in the arteriosclerotic disease. As aforementioned, inflammatory load is higher in tophaceous patients; in this subgroup a higher risk of overall and CV mortality [37], Q-wave myocardial infarction [38] and both atrial and ventricular dysfunction by echocardiography [39], compared with nontophaceous gout patients has been reported. On the other hand, a recent report found MSU crystals in the coronary artery walls [40], thus a local detrimental effect in the atheroma plaque might also occur.

Besides inflammation, other factors, such as hyperuricemia or a frequent intake of nonsteroidal antiinflammatory agents, may contribute to this CV risk. Primates show higher uric acid levels in comparison to other animals, thus an evolutional advantage is presumed but to date unproven. A neuroprotective effect of hyperuricemia has been recently proposed based on population-based studies [41,42], though more research is still needed for ascertaining the exact role of uric acid in the development of neurological diseases. Uric acid is a potent antioxidant agent, likely accounting for 50% of antioxidant activity in *in vitro* studies, but this has not been proven *in vivo* [43]. In fact, increased SUA levels appear to promote the development of hypertension and an oxidative stress status [44]. However, it is still debatable whether asymptomatic hyperuricemia itself carries an increased CV risk [45]. So, in the case of gout patients, crystal-related inflammation seems the main cause of this enhanced arteriosclerotic disease. We have recently found [46] that patients with asymptomatic hyperuricemia and MSU crystal deposits more commonly show a severe coronary calcification (a marker of severe coronary arteriosclerosis [47]) than hyperuricemic patients without crystals and normouricemic patients. This finding supports the detrimental role of MSU crystal deposits in the CV risk profile of gout patients, even at the preclinical stage.

CV management in gout patients

As in other chronic inflammatory conditions [48], proper disease management may decrease the CV risk in gout patients. MSU crystal deposits are reversible and crystals dissolve when SUA levels fall below the saturation threshold [49,50]. Whether urate-lowering therapy could reduce the proatherogenic state led by crystal-induced inflammation remains to be demonstrated in gout patients. Two recent population-based studies have analyzed this issue [51,52]; both failed to demonstrate a CV benefit from urate-lowering therapy in gout patients. However, some issues may hamper the validity of these results. In both studies, data came from claims databases. However previous reports have shown that gout management is far from optimal in clinical practice [53] due to insufficient dosage of the urate-lowering agents [54–56], poor adherence to treatment [57] and others. Also, in the study by Kim *et al.* [49] the authors did not analyze the SUA levels achieved with the treatment, which is a marker of its efficacy. In our opinion, these recent reports should not discourage further studies to ascertain the potential benefit of urate-lowering therapy in the CV profile of gout patients. Data should derive from clinical trials as the routine clinical management of gout still warrants improvement. If proven, gouty patients at a high risk for atherosclerotic vascular disease or having already suffered a CV event, a lower SUA target may be advisable in order to aim at a rapid elimination of MSU crystal deposits [58,59]. This lower SUA target should not be achieved in a short period but during a period of dose titration, in order to prevent gout flares led by SUA reductions.

In pivotal trials [60,61], febuxostat use was associated with a slight increased risk of developing CV events, compared with the allopurinol group (1.3 per 100 patients-year and 0.3 per 100 patients-year, respectively). A background of coronary heart disease and heart failure was identified as a risk factor for the increased risk, but the exact mechanism behind it is to date unknown. Results from an ongoing trial (CARES trial [62]) – when available – are expected to clarify this issue.

Other strategies might help in controlling the CV risk in patients with gout. Colchicine reduces crystal-induced inflammation [14], and is a standard agent used for flare management and prevention [63–65]. Recently, a lower prevalence of myocardial infarction in gouty patients on colchicine has been reported [66]. This could be explained through its anti-inflammatory properties. If all crystals dissolve, acute gout attacks will not develop [46], and thus the need for nonsteroidal anti-inflammatory agents or steroids will ultimately decrease, which can have an added value in reducing the CV risk.

Conclusion

The clinical spectrum of gout is actually much wider than the classical picture of recurrent acute flares and tophi formation. Gout leads to an increased CV incidence and mortality probably associated with the persistent, subclinical inflammation due to MSU crystal deposits. Optimal management of gout, which leads to crystal dissolution, should reduce this increased CV risk, though this has not been proven yet. At least in patients with a high CV risk, a rapid clearance of crystals induced by a (lower) SUA target well below its saturation point merits consideration.

Future perspective

It has been established that gout is an independent risk factor for arteriosclerotic disease. Further studies in coming years should be able to confirm the detrimental role of MSU crystal deposition in the arteriosclerotic disease in subjects with silent deposits of MSU crystals. In line with this, the beneficial impact of MSU crystal clearance in the CV profile of gout patients must be established. Besides, efforts to improve the management of gout patients and their CV risk profile are warranted. Gout should be heeded as a CV risk factor and questions on gout should be incorporated into the standard assessment of the CV profile in patients both at general practice and rheumatology settings.

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Executive summary

- Besides the 'classical' clinical picture (flares and tophi), it is important to remember the impact of crystal-related sustained inflammation in the development of arteriosclerotic disease.
- A beneficial role of urate-lowering agents in the cardiovascular profile of gout patients remains to be established, but seems biologically plausible.
- It might be appropriate to tailor the treatment target (i.e., the serum uric acid target level) in patients with gout at a high cardiovascular risk.

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