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Letter to the Editor

Cardiovascular risk in patients with acute gout: is there any association and need for treatment?

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Dear Editor,

Cardiovascular diseases continue to be the leading cause of death globally, with a very high prevalence, causing a major burden of disease, especially in low- and middle-income countries where there are difficulties in timely and specialized access to health care [1]. This has reinforced the need to place all efforts in primary care in order to prevent the rapid progression of cardiovascular risk at an early age. Gout is an inflammatory arthritis caused by the deposition of urate crystals in tissues which can trigger an abrupt episode of intense pain and edema in the joints, mainly in the lower limbs [2]. It has been described that the prevalence of gout varies among populations, reaching up to approximately 7% (three cases per thousand inhabitants per year) of the population [2]. According to the global epidemiological study by Dehlin *et al.* [2], Latin America and Caribbean (LAC) countries does not have reliable data on the prevalence and outcomes of this condition. However, obesity and other cardiometabolic comorbidities are strongly associated with gout, so the prevalence is probably high [3]. Thus, this is a negative vicious circle on cardiovascular risk and disease, since hyperuricemia and gout crisis generate uric acid-induced vasoactive hypertension, at the expense of microvascular and interstitial lesions of the renal and arterial parenchyma [3,4]. Thus, the question arises, is there evidence to support the causal association and need for treatment of gout crisis and cardiovascular risk?

Recently, Cipolletta *et al.* [3] conducted a case-control study evaluating the association between gout crisis and subsequent cardiovascular events in 62,574 patients with gout and 10,475 patients with gout and cardiovascular events. The authors found that those patients with cardiovascular events are more likely to have a gout crisis up to 60 days (Odds Ratio [OR] 1.93; 95% confidence interval [CI]: 1.57 – 2.38) and 120 days (OR 1.57; 95% CI: 1.26 – 1.96) prior to the event.

When calculating the ratio of cardiovascular events per 1000 persons per day in a self-controlled case series of 1,421 patients with gout and cardiovascular events, they found that the highest ratio occurred between 0 and 60 days prior to the event (2.49; 95% CI: 2.16 – 2.82). When comparing events 150 days before or 180 - 540 days after the gout crisis, a difference in incidence ratio of 1.17 (95% CI: 0.83 - 1.52) per 1000 persons per day, and an incidence ratio of 1.89 (95% CI: 1.54 - 2.30) were found [3]. Thus, the authors concluded that those patients with gout crisis have a higher probability of presenting cardiovascular events in subsequent days. So, if there is an association, should it be treated and how?

Saag *et al.* [4] performed a randomized controlled trial with the objective to find any relationship between serum urate levels, gout manifestations and cardiovascular death in patients who received febuxostat or allopurinol, where 6,190 patients were followed (febuxostat, n=3,098 vs. allopurinol, n=3,092) for 32 months. It was found that mean serum urate levels were lower in those who received febuxostat and that there was no association between these levels and cardiovascular death in this group. Also, the number of treatments required was comparable after one year of treatment in the febuxostat group *vs.* the allopurinol group (mean incidence of gout crisis per year of 0.35 vs. 0.34). Finally, resolution of tophi was > 50% in both groups [4]. Wang *et al.* [5] conducted a systematic review and meta-analysis in which they evaluated the incidence of major cardiovascular events in patients with asymptomatic gout or hyperuricemia who received allopurinol or febuxostat. A total of 18 studies with more than 270,000 patients were included, showing that there were no significant differences between the two agents in the incidence of cardiovascular events, but there were significant differences in serum uric acid levels (mean difference [MD] -0.83; 95% CI: -1.22 to -0.44; p <0.0001) and dermatologic adverse events (OR 0.55; 95% CI: 0.42 – 0.73; p <0.0001), in favor of febuxostat. However, the authors suggested the need for new studies of higher quality with the same outcome assessment due to the heterogeneity of the studies

[5]. Apparently, there is no difference in the outcome of major cardiovascular event with the use of these agents. But, what about other cardiovascular comorbidities?

Roth *et al*. [6] evaluated the usefulness of colchicine for gout crisis and its relationship with clinical outcomes in decompensated heart failure; they showed that out of 1,047 patients (of whom 237 received colchicine), there was a significant reduction in in-hospital mortality in the colchicine group (2.1% *vs.* 6.5%; p=0.009), with no differences in 30-day readmission (21.5% *vs.* 19.5%; p=0.495) [6]. This allowed the authors to conclude that colchicine could have an impact on in-hospital mortality in those with gout crisis and decompensated heart failure.

Thus, there is a trend of acute treatment of gout crisis on outcomes and cardiovascular death [7]. The evidence is heterogeneous and most of studies have been conducted in high-income countries. According to Lozada-Martinez *et al*. [8] it is necessary to design and conduct studies in LAC countries that consider the genetic and epigenetic ecology of the diseases, in order to be more precise in their approach and to be able to guarantee primary and secondary prevention results. Currently, with the integration and development of biomedical models of translational research [8,9], it would be possible to investigate in depth what other factors affect gout crisis and cardiovascular outcomes, to determine whether similar results can be achieved in the LAC population. However, to date, it is necessary to dramatically treat gout crisis, conduct epidemiological studies on the relationship between gout and cardiovascular disease, and evaluate which interventions are reproducible and more favorable for our population.

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