Author’s response to reviews

Title: Impact of comorbidities on gout and hyperuricaemia: an update on prevalence and treatment options

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Answer to reviewers

We thank the reviewers for their helpful comments and revised the manuscript according to these comments:

Reviewer #1 Mariano Andres

- Page 4, paragraph 2 (Cardiovascular and renal comorbidities in gout): To clarify the lower incidence of gout in DM, the authors explain the relationship between glycosuria and urine urate excretion. This might be a possible explanation but there can also be others. For example, metformin, a widely used and first-line antidiabetic agent, acts intracellularly through PPAR-gamma modifications, that has been also reported as preventing gouty attacks. Please revise.

The following sentence has been added to the manuscript with 2 references: “The lower incidence of gout in type 2 diabetes might also partly be explained by the frequently prescribed metformin, which might bear anti-inflammatory properties through modulation of different cellular pathways, including AMP-activated protein kinase (AMPK), protein kinase A (PKA) and PPAR gamma {Agrawal, 2014 #323;Chen, 2016 #322}”
- Page 5, paragraph 2, lane 46: Formatting, please use just one decimal throughout the manuscript (but for p-values).

The manuscript has been edited.

- Page 7, paragraph 2: as this journal is not aimed at Genetics, please provide a brief explanation of what Mendelian randomization is. I see the effort in lines 31 and 32, In my opinion needs to be explain clearer.

   We tried to make ourselves clearer by adding the sentence “Mendelian randomization allows comparing cardiovascular features in patients with or without hyperuricemic genes”, hoping that the following sentences will be more easily understood.

- Page 9, paragraph 1, lane 27: please use "two" instead of "2"

   this has been changed

- Page 16, paragraph 2: please include a mention of low-dose aspirin and its relationship with uricemia, as the majority of patients with CV and/or renal disease are treated with it.

   The following sentence has been added: “Cardio-protective aspirin increases uricemia and its onset has been associated with gout flares” with two relevant references.

- Page 17, paragraph 4, lane 56: SCARs stands for "serious cutaneous adverse reactions" (please modify).

   The correction has been made.
Reviewer #2 Michael Pillinger:

I have only two minor comments.

The first is that while the authors do a very good job distinguishing between the impacts of hyperuricemia per se and gout, their approach may give a bit of short shrift to the impact of inflammation, in the gouty setting, on comorbid risk or response. This is a bit surprising given the extensive literature on inflammation and vascular disease in general, and on inflammation in rheumatic diseases and its impact on cardiovascular and cerebrovascular disease. They may want to consider addressing this topic a bit more broadly and explicitly.

We fully agree and added the following sentences: “Hyperuricemia might partially account of the increased cardiovascular risk of gouty patients, as discussed below. However, multivariate-adjusted cardiovascular risk appears as more important and less disputable in gout than in asymptomatic hyperuricemic patients, suggesting that crystal-driven inflammation plays an important part [Richette, 2014 #5], in line with the increased risk observed in rheumatoid arthritis, psoriatic arthritis or ankylosing spondyloarthritis.”

My second comment is more picayune. Under the section "Hyperuricemia and cardiovascular and renal diseases," we find the sentences,

"Allopurinol was once claimed to protect the kidneys, which led to the hypothesis that hyperuricemia was the cause of renal dysfunction. Genetic studies have now established that the disease has a renal origin, first translating into hyperuricemia, but due to a number of genetic variants, of the uromodulin or hepatocyte-nuclear factor 1 b genes".

This language conveys the clear impression that allopurinol does not protect the kidneys, which may in this context be a reasonable statement. However, later the authors present a more mixed conclusion in the paragraph that begins, "Causality can also be addressed by studying the effect of drugs." In that paragraph, the authors mention that some studies support a renoprotective effect of urate lowering. Thus, the authors may want to make sure that these two discussions do not create any ambiguity for the general reader.
We agree with the reviewer. The idea was that genetic studies showed that the disease was primarily a renal disease which caused hyperuricemia and not the reverse.

We tried to explain this in a better way: “Early treatment with allopurinol was observed to protect some patients from the renal failure observed in the disease, which led to the hypothesis that hyperuricemia was the cause of renal dysfunction. Genetic studies have now established that the disease has a renal origin, first translating into hyperuricemia, but due to a number of genetic variants, of the uromodulin or hepatocyte-nuclear factor 1 b genes {Eckardt, 2015 #171}. The observed effect of allopurinol now appears to be a non-specific renoprotective effect, observed in various nephropathies (see below).”

Finally, in discussing cardiovascular disease, the authors may wish to consider including a report potentially linking gout with aortic stenosis. (Chang et al, Am J Med 2017).

We added this valuable information and the reference.