Author's response to reviews

Title: Factors influencing the crystallization of monosodium urate: a systematic literature review

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Author's response to reviews: see over
Referee 1

1. The first paragraph of the methods section is a bit difficult to follow. For example: “bibliographic references of individual publications were also checked”. Was this performed for the articles selected for inclusion? Is this then stating the same as the last sentence?

The bibliography search was performed on all articles that were not excluded at the title and abstract exclusion stage. This has been clarified in the methods section (page 5, line 83). The repeat statement identified by the reviewer has been removed from the manuscript.

2. Please clarify if the title and abstract revision and exclusion was performed by one or two reviewers independently.

This process was completed independently by two reviewers. This information has been added to the methods section (page 5, line 81).

3. Were congress abstracts of the last couple of years reviewed to check for recent unpublished data?

Congress abstracts were not searched for in this review. Our focus was on journal articles identified through online databases. This has been added to the methods section (page 5, line 76).

4. Please clarify what is meant by the third question of the quality assessment.

The third question of the quality assessment was, “Are the results stated consistent with the results presented?” When addressing this question during our data extraction process we assessed whether the figures or data presented in each article supported the written results section. We have clarified this question in the methods section of our manuscript (page 5, line 98).

5. In the results section, no data on the quality of the studies is presented. Some data should be presented in the results and not solely in the supplementary material.

The quality results paragraph (page 6, lines 120-124) has been edited to emphasise our findings on the quality of research articles included in our analysis.

6. The research question is “to identify the factors that contribute to MSU crystallization in gout”: I would argue that even though the literature on MSU crystal structure provides an appropriate background understanding, these studies do not fulfil the inclusion criteria. Therefore I would remove the section on MSU crystal structure from the results section and consider including some of its data in the introduction.

We thank the reviewer for this suggestion and agree that the category of “MSU crystal structure” did not fulfil the inclusion criteria for our research question. We have reorganized the manuscript so that the MSU crystal structure paragraph (originally included in the results section) has been edited and moved to the introduction section to provide background on MSU crystal structure at the molecular level (page 3, line 45). The abstract (page 2, line 9) and methods (page 5, line 88) have had minor edits to accommodate this change. Table 1 and Supplementary Table 1 have also had the crystal structure sections removed.

7. Discretionary revision - Supplementary Table 1 is a very nice summary of some of the main characteristics of the reviewed articles. Perhaps it would benefit from including
the number of observations (where appropriate) as it is stated that some papers presented a single observation.

We thank the reviewer for this comment and have added the number of articles that investigated each of the three stages of MSU crystallization (urate solubility, nucleation and growth) to the results section (page 6, lines 109). We have also included the number of articles that utilised each different type of assay (in vitro, ex vivo and in vivo) in the results section (page 6, lines 115 and 117).

Referee 2

1. Please clarify on how many articles the full text review was done (109 instead of 91).

The full text review was done on 109 articles, not 91. This has been changed in the search results section (page 6, line 107). We are grateful to the reviewer for finding this discrepancy in our results.

2. Explain the abbreviation SEM in the discussion section.

SEM refers to “scanning electron microscopy”. This has been clarified in the discussion section (page 20, line 438).

3. Experimental data have shown that slightly basic conditions promote MSU crystallization. This seems to be somewhat in contrary to the clinical opinion that MSU crystallization preferentially might occur during acid conditions e.g. during inflammation (activated osteoarthritis). Is there any explanation? If so, probably this could be very shortly discussed.

We thank the reviewer for raising this interesting point. As outlined by the reviewer, the experimental data summarized in our review does show that MSU crystallization is promoted at pH 7-9. Previous research has shown that the pH of osteoarthritic cartilage is indeed slightly acidic (Konttinen et al., 2002 Arthritis Rheum). While the majority of in vitro research investigating urate solubility did show that urate solubility was lowest between pH 7-9, some of the research also showed that urate solubility is still actually very low in slightly acidic conditions as well, including pH levels similar to those reported for osteoarthritic cartilage (pH 5.5-6.2). In addition, enzymes (e.g. cathepsin K) that are activated in these acidic conditions (Lang et al., 2000 J Rheum, and Morko et al., 2004 Ann Rheum Dis) may further promote MSU crystallization in osteoarthritic joints by breaking down cartilage matrix into components which may act as nucleation sites for MSU. These points have been added to the discussion section (page 19, line 447).