Author’s response to reviews

Title: The pathophysiology of hyperuricaemia and its possible relationship to cardiovascular disease, morbidity and mortality

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Author’s response to reviews:

Reviewer Pascal Houillier

“1. Since the renal handling of uric acid/urate is a major determinant of blood urate level, the factors known to alter the renal tubular handling of uric acid/urate should be listed and shortly commented”

More data on the tubular transport of urate have been given on page 2, last paragraph, lines 3-8

“2. "Chronic kidney disease" section, first paragraph. The sentence " However, an alternative explanation..." confuses me a bit. Could the authors be more explicit and quote references supporting the statement if any is available?"

We agree that as written this sentence seems confusing and the explanation in reference 34 (Nashar & Fried) is also slightly confusing (see below) on this point, so we decided to remove the sentence (page 7, first paragraph, lines 6-7). From Nashar and Fried:

“The evidence for UA as a risk factor in CKD is stronger for incident CKD than for progression of stage 3-4 CKD. This could indicate that UA is more of a risk factor for the initiation of CKD than its progression. An alternative explanation is that the incident CKD studies are more confounded by inaccurate estimates of baseline kidney function. eGFR formulas are less accurate above the level of 60 mL/min/1.73 m2. It is possible that elevated UA levels are a marker of subtle kidney damage that is not detected by the eGFR level and this is why UA is a predictor of incident CKD.”

“3. A few typos need to be corrected:

Abstract : second line "of" is missing after "pathophysiology"
Conclusion, 3rd line: "Understanding"

Figure 1: bottom of the figure: tubular instead of tubular”

Thank you. The typos have been corrected.

“Discretionary revision

1. The intriguing observation that UMOD mutations are associated with hyperuricemia suggest that urate transport (in the proximal tubule) might be directly or indirectly affected by UMOD. Would the authors comment on this?”

We have added a few lines about uromodulin on page 3, second paragraph, lines 17-25, although we think there might be an indirect, rather than a direct, relationship between hyperuricaemia and proximal tubule handling of urate.

Reviewer Bertrand Knebelmann

“Discretionary Revisions

1) Recent dat from kotgen et al should be added (Genome-wide association analyses identify 18 new loci associated with serum urate concentrations. Nat Genet. 2013 Feb;45(2):145-54. doi: 10.1038/ng.2500. Epub 2012 Dec 23. )”

We have added data from this large GWAS study on page 3, second paragraph, lines 12-17.

“2) The paragraph "Pathophysiology of Hyperuricemia" could be renamed "Pathophysiology of Hyperuricemia associated conditions”"

We have changed the headline, page 5, second paragraph

“3) CKD section: For the four randomized trials mentioned, precise figures of the effect of lowering SUA on kidney function should be given.”

The data are given on page 7, second paragraph, lines 3-14

“4) In the figure there is a misspelling: "...Tibular reuptake..."

Thank you. The spelling has been corrected
“5) A figure summarizing the different states of uric acid/urate and the potential effects of uric acid on ROS production, endothelial dysfunction, etc would be useful to the reader.”

We understand and appreciate this suggestion, but we wonder if such a figure (which is difficult to compose as a summary), given the debate and uncertainty over whether urate is pro- or antioxidant, risks being an over-simplified and perhaps even misleading. However, we have slightly modified the text and included a more specific reference to this controversial issue on page 5, last paragraph, line 1-7 which we hope will prove an acceptable alternative to a figure.