Author's response to reviews

Title: Association between Asymptomatic Hyperuricemia and New-onset Chronic Kidney Disease in Japanese Male Workers: A Long-term Retrospective Cohort Study

Authors:

Masatoshi Kawashima (m-kawashima@umin.ac.jp)
Koji Wada (kwada-sgy@umin.ac.jp)
Hiroshi Ohta (ohta.hiroshi.md@gmail.com)
Hiroyuki Terawaki (terawaki@jikei.ac.jp)
Yoshiharu Aizawa (aizawa@kitasato-u.ac.jp)

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Replies to Reviewers

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Title: Association between Asymptomatic Hyperuricemia and New-onset Chronic Kidney Disease in Japanese Male Workers: A Long-term Retrospective Cohort Study
Masatoshi Kawashima, Koji Wada, Hiroshi Ohta, Hiroyuki Terawaki and Yoshiharu Aizawa

We thank the reviewers for their constructive comments which have helped us to improve our manuscript.

Reviewer 1
1) Some of the Kaplan-Meier curves appear faulty, especially evident in Fig 1B, where the stepwise increase that reflects individual patients is not identical. I recommend carefully examining the curves, and the corresponding values.

Reply: We re-examined the data and method of analysis. The Kaplan-Meier curves are for estimating the cumulative incidence rate of disease. To estimate the incidence rate (CKD incidence in this study), every time a participant develops CKD, it is necessary to re-calculate the incidence rate in the remaining participants. As the follow-up period became longer, the number of participants who developed CKD increased while the number of remaining participants decreased. Effects of one case developing CKD on the cumulative incidence rate vary depending on the numbers of participants with CKD and remaining participants. Thus, the stepwise increases in the rate reflecting individual participants do not appear to be identical.

2) The authors correctly point out that diabetic nephropathy in its initial stages is generally characterized by hyperfiltration, and not reduction of GFR. As a consequence, it appears much more appropriate to examine rise in urinary albumin in these patients, rather than decline in GFR. I suggest investigating the association of diabetes with increase in urinary albumin and base any conclusion on the association of onset of CKD with diabetes on urinary albumin. If this is not possible
(due to the data not being available), then it seems appropriate to state that no conclusion on an association of diabetes with CKD can be drawn from the data available. Suggesting that diabetes may not be associated with CKD clearly contradicts the current knowledge, and must be based on much more substantial data.

Reply: As the reviewer pointed out, it is difficult to determine the progression of renal dysfunction by GFR because hyperfiltration occurs during the early stage of diabetic nephropathy. Since this is a cohort study conducted over a maximum period of 18 years, we anticipated observing a reduction in GFR after the hyperfiltration phase. The actual data, however, did not clearly show GFR decreases. Since the urinary albumin data are not available, no conclusion regarding an association of diabetes with new-onset CKD could be drawn. We revised the corresponding discussion section as follows (red characters).

Page 13, line 13 (discussion)

Diabetes is an established predictor of renal disease [10-13]. However, we found no significant association between diabetes and new-onset CKD. GFR decreases with the duration of diabetes, but it has been suggested that glomerular hyperfiltration occurs during the early stage of diabetes, leading to a temporary increase in GFR [37]. The mean (± SD) follow-up period was 95.1 (± 66.0) months in our participants with diabetes, but it is possible that the GFR either increased or did not decrease markedly in some participants who were still in the hyperfiltration phase. Thus, it is necessary to determine the presence of new-onset CKD employing urinary albumin measurement in participants with diabetic nephropathy during the early stage. Diabetes reportedly did not significantly affect the progression of CKD in Japanese participants; significant reductions in GFR might not have been observed because of hyperfiltration, as observed in this study [6].

3) The figure legend is sketchy (at best), and must be improved upon.

Reply: We added the following to the figure legend.

The Kaplan-Meier curves show the follow-up periods (in months) and cumulative incidence rate of CKD. Solid lines represent cumulative incidence rates of CKD in participants with hyperuricemia (A), low serum HDL (B), hypertension (C) and
4) Investigation of the correlation of the numeric values of uric acid levels with the decline in GFR may be helpful, and could show the association even more convincingly.

Reply: We appreciate the reviewer’s comment. We examined the correlation coefficient of uric acid levels at the beginning of the follow-up period with GFR reduction after follow-up periods of 5, 10 and 15 years. Those with an estimated GFR over 150 were excluded from the analysis. The correlation coefficients with uric acid levels were -0.01 for 5 years, -0.02 for 10 years, and -0.1 for 15 years. No significant association was observed between uric acid levels before these follow-up periods and GFR reduction thereafter in this study.

Reviewer 2
1) This is a well conducted study examining the association between hyperuricemia and CKD. The paper is well written also. My main suggestion is that he authors should attempt multivariable analysis to examine if hyperuricemia if still positively related to CKD after adjusting for confounders such as age, gender, diabetes, hypertension, etc.

Reply: We agree with the reviewer that adjustment for confounders such as age, gender and diseases is necessary. Since the participants in this study were all male, adjustment for confounders other than gender was performed and multivariate analysis was carried out using Cox regression analysis. We revised the methods section as follows (red characters).

Page 7, line 13 (methods: statistical analysis)

The associations between new-onset CKD and the presence of hyperuricemia, low serum HDL-C, hypertension, diabetes and obesity were analyzed. The covariates included age, hyperuricemia, low serum HDL-C, hypertension, diabetes and obesity. The follow-up period (in months) was the survival variable and new-onset CKD was
a state variable. To adjust for age and the presence of disease as confounders, multivariate analysis was performed using Cox regression analysis[23]. A hazard ratio and 95% confidential interval were derived for each covariate. The hazard ratio was determined to be significant when the P value was < 0.05. In addition, Kaplan-Meier curves and log-rank tests were used to estimate the cumulative incidence of the covariates showing a significant hazard ratio [24]. The Japanese version of SPSS 17.0 for Windows was used for these analyses [25].