Letters and Replies

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The relationship between serum uric acid and chronic kidney disease among Appalachian adults

Dear Editor,

We read the article by Cain et al. [1] with great interest. This study deals with the never-ending issue of whether serum uric acid (SUA) is independently associated with kidney disease. However, the same shortcomings, unfortunately inherent to many of the similar studies investigating this issue, are at play here.

First, the secondary elevation of SUA after reduction of glomerular filtration rate is a well-known fact. Thus, unless longitudinal data clearly showing that increases of SUA elevations precede renal damage, it is difficult to ascertain that hyperuricaemia causes renal damage. Another way of suggesting such a causal relation is near-complete control of confounding factors affecting the outcome parameters. In this example, there are numerous causes of chronic kidney disease (CKD) in the general population beyond just diabetes mellitus and hypertension. Unfortunately, there is no mention of them in the study. Thus, the observed relation of CKD and high SUA may just be due to reduced glomerular filtration rate from another cause.

Second, many risk factors or comorbid conditions like metabolic syndrome may cause increased serum uric acid levels [2]. Despite the fact that the frequency of metabolic syndrome in each quartile is not specifically mentioned, the individual components of metabolic syndrome such as dyslipidaemia, obesity and hypertension are shown to be more prevalent while advancing to quartile 4. Thus, the observed increase in SUA levels may be an indirect consequence of this trend.

Third, not only uric acid-lowering drugs alter SUA levels, a number of other drugs including losartan, diuretics, fenofibrate and nonsteroidal anti-inflammatory drugs affect levels [3]. Thus, the observed difference of SUA levels in the different quartiles may be ascribed to different patterns of drug use in the absence of such data. Furthermore, dietary patterns, particularly fructose intake, has recently been implicated in increased SUA levels.

Fourth, to eliminate the effect of reverse causality, the authors stated that they made a sensitivity analysis excluding the patients who had serum creatinine values ≥2 mg/dL. I think with this approach they did not exclude very many patients with moderate CKD. For example, a non-African-American female patient with a 2 mg/dL serum creatinine value has an estimated GFR of 28 mL/min/1.73 m². It would be better if the authors had used eGFR instead of creatinine value. Thus, the effect of reduced eGFR on SUA levels cannot be fully excluded.

In conclusion, the controversy continues regarding the causative role of SUA on CKD. Because each variable is strongly interrelated with one another and adequately controlling each confounding factor is challenging. It seems we will be debating this issue until more definitive data become available emanating from longitudinal studies.

Conflict of interest statement. None declared.

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Reply

Dear Editor,

Dr Solak raises several interesting questions regarding our recent paper [1] on the association between serum uric acid and chronic kidney disease (CKD). While keeping in mind that our data are based on an observational study and therefore cannot provide definitive evidence for a causal association, we would like to share our thoughts on Dr Solak’s points.

First, we agree with Dr Solak that unless longitudinal data are available, it is difficult to ascertain that hyperuricaemia precedes renal damage. We are following up the cohort. So, hopefully, in the near future, this data can be presented. Further, Dr Solak raises the concern that in addition to diabetes mellitus and hypertension, there are other causes of CKD that we did not consider as confounders. To address this point, we are now providing a new multivariable analysis (see the multivariable model 2 in Table 1) additionally adjusting for other causes of CKD, including polycystic kidney disease, those who have a history of hospitalization for urinary tract infection and those