Author’s response to reviews

Title: Impact of nephrolithiasis on kidney function

Authors:

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Author's response to reviews: see over
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BMC Nephrology
BioMed Central
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Re: MS: 1199529082159519 - revised manuscript, entitled “Impact of nephrolithiasis on renal function”, authored by Vaka K Sigurjonsdottir, Hrafnhildur L Runolfsdottir, Olafur S Indridason, Runolfur Palsson and Vidar O Edvardsson. Previous title: “Kidney Function and Comorbid Disorders in Patients with Kidney Stone Disease.”

To whom it may concern:

Enclosed is our revised manuscript, entitled “Impact of nephrolithiasis on renal function”. We would like to take this opportunity to thank the reviewers for their thoughtful comments which have helped us improve the quality of the manuscript. In this document you will find the point by point responses to reviewer comments and other changes that the authors have made in the manuscript. All manuscript changes are highlighted with a yellow color.

We hope you will find this version of our paper worthy of publication in BMC Nephrology.

Sincerely,

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Responses to reviewer comments:
Reviewer 1
Comment 1: I think this manuscript was well written and is definitely very publishable. The authors have been successful in directly answering the question posed, that is, to show some correlation between kidney function and other co-morbidities in recurrent stone formers. The study is primarily 'observational' and has its inherent limitations. The authors also rightfully acknowledged such limitations, e.g., small sample size as well as lacking information about stone analysis in some of the subjects.

Author's reply: No reply needed.

Reviewer 2

Major Compulsory Revisions:

Comment 1. In the Methods section it is stated that stone patients with known causes of CKD were excluded. Since patients with hypertension and diabetes were included in the study, what criteria were used to link the diagnosis of CKD to another disorder. For example, if a patient had diabetes, proteinuria, and diabetic retinopathy were they excluded from the analysis? Please clarify how patients were excluded for “known causes of CKD”.

Author's reply:
The research strategy was designed to exclude from the analysis all stone patients with other known potential causes of CKD than nephrolithiasis. All stone patients were interviewed by two of the researchers where they were asked about other kidney disorders. In addition, all medical records of the cases were thoroughly reviewed for the same information and the medical information systems at Landspitali – The National University Hospital of Iceland (LUH) in Reykjavik, were searched for all ICD-9 and ICD-10 codes suggestive of underlying renal disease. LUH in Reykjavik is the only referral institution in the country for kidney disease.

Our strategy identified only one stone former with CKD due to other renal diseases. This patient, who had IgA nephropathy and had developed stones in a transplanted kidney, was excluded from the study. Further, none of the other cases were found to have CKD that could with certainty be attributed to diabetic or hypertensive kidney disease. We do, however, acknowledge that it can be difficult to exclude a potential negative impact of diabetes and/or HTN on GFR. Therefore, in our comparison of serum creatinine and eGFR between cases and controls we adjusted for diabetes, hypertension, cardiovascular disease and BMI, factors that all potentially contribute to reduction in GFR and CKD. The difference in serum creatinine and eGFR between cases and control individuals was independent of these comorbid conditions as pointed out in the discussion, lines 298-299.

The following changes have now been made to the methods section (page 4, lines 122-127) where we describe how the presence or absence of underlying renal diseases other than
kidney stone disease was ascertained: “The presence of renal disorders other than kidney stone disease was excluded by self-report (interview), thorough medical record review in all the cases and by searching the medical information systems at LUH in Reykjavik for all ICD-9 and ICD-10 codes suggestive of a specific renal disease. The above strategy led to the exclusion of one patient with IgA nephropathy who developed stones in a transplanted kidney, leaving the total number of cases at 195.” The following sentence: “Patients with other known causes for CKD (only one patient with history of IgA nephropathy who had developed stones in a transplanted kidney) were excluded from the study”, has been deleted.

Comment 2. In definition of comorbid conditions, they do not define how they determined cardiovascular disease. That should be included since it is part of the analysis in Tables 2 and 3.

Author’s reply:
We defined cardiovascular disease broadly as evidence for coronary artery disease, cerebrovascular disease or peripheral vascular disease according to ICD-9 (410-414, 430-438 and 440-448) and ICD-10 (I20-I25 and I60-I79) diagnostic codes retrieved from the medical information systems at LUH in Reykjavik.

We have now clarified the definition of cardiovascular disease in the methods section (page 6, lines 164-169): “Cardiovascular disease was defined as evidence for coronary artery disease, cerebrovascular disease or peripheral vascular disease by ICD-9 (410-414, 430-438 and 440-448) and ICD-10 (I20-I25 and I60-I79) diagnostic codes suggestive of these disorders. The presence of cardiovascular disease was further confirmed with review of individual medical records.”

Comment 3. In the Results section, they mention how many subjects had ESWL etc, but they do not provide information on the number of subjects who had multiple surgical or ESWL treatments. Later in the paper they mention that the number of surgeries, stones etc do not correlate with the severity of CKD, so it would make sense to give the reader some idea of how frequent multiple treatments were.

Author’s reply:
The following sentence has been added to the results section, page 6 lines 189-193: “Of 131 patients (67%) who underwent ESWL, 99, 18 and 10 required 1-4, 5-10 and more than 10 treatments, respectively. In addition, 2 patients required open surgery for stone removal and 8 underwent percutaneous procedures. Finally, 80 patients had endoscopic ureteral catheter insertions performed 1-4 times during stone events and 4 patients on 5-10 occasions. “

The following sentence has been deleted: “The majority of patients needed extracorporeal shock wave lithotripsy (ESWL) treatment (67%), 44% had endoscopic ureteral catheter insertion performed during a stone event and 5% underwent surgical stone removal.”

Comment 4. The authors exclude 8 patients from the analysis of Ca stones and CKD. These 8 patients should just be excluded from the whole study and not be included in Table 1.
Author’s reply:
As recognized by the reviewer, we performed a separate analysis comparing measures of renal function and comorbidity in calcium stone formers and their respective controls, excluding these 8 patients (Table 3). In our opinion, including these 8 patients in the analysis of all recurrent stone formers vs controls, draws attention to the fact that recurrent stone formers may have a treatable underlying cause of their renal stone disease which needs to be identified and treated. We have, therefore, elected to include these 8 patients in the study, and Table 1.

Discretionary Revisions
Comment 5. In Methods section, describing Stone Composition, the authors used plain films to determine radio-opaque vs radio-lucent. Did they make an attempt to use stone density as measured by CT to categorize those without a plain film or stone analysis?

Author’s reply:
Unfortunately, we did not have CT stone density data available to categorize stones as radiopaque or radiolucent.

Comment 6. In the Discussion, the authors refer to outcomes being worse for uric acid stones. It would be more accurate to use the term radio-lucent stones since a significant number of patients in this group (5 of 18) did not have a stone analysis available.

Author’s reply:
The term “uric acid stones” has been replaced with the term “radiolucent stones” throughout the paper, where appropriate.

Comment 7. At the end of the 1st paragraph of Results, it is stated that 5% of subjects had surgical stone removal. I assume these are percutaneous procedures. Please clarify.

Author’s reply:
Please refer to Author’s reply to comment 3, reviewer 2.

Reviewer 3
Comment 1: “Title: inappropriate title. Something clearer would be better. For example: "Impact of renal stone disease on kidney function".

Authors’ reply:
The title has now been edited and now reads: “Impact of nephrolithiasis on kidney function”.

Comment 2: “A clinical stone event was defined as acute flank pain associated with hematuria and/OR the detection of a stone by imaging. Does that mean that flank pain and hematuria alone were considered as an acute stone event (without imaging)?
Please clarify. If this is the case than an obstructing tumor or pyelonephritis would have been considered as a stone event?

Authors’ reply:
We defined clinical stone event as: a) acute flank pain associated with hematuria and b) acute flank pain and the detection of a stone by imaging. We feel this is adequate as an obstructing tumour would not resolve spontaneously without a surgical intervention. The combination of acute flank pain, hematuria, documented urinary tract infection and negative imaging study, was not considered a clinical stone event. Further, the fact that all included patients had a physician-confirmed recurrent stone disease and multiple imaging studies available over the course of their disease makes other reasons for acute flank pain than kidney stones much less likely.

Comment 3: “Results: overall adequate however I don't think radiolucent stones can be considered uric acid. Many times stones not seen on x-ray are just hidden by bowel gas. Uric acid stone should only be considered uric acid unless they are confirmed on stone analysis.”

Authors’ reply:
The term “uric acid stones” has been replaced with the term “radiolucent stones” throughout the paper, as appropriate. See also response to comment 6 by reviewer 2.

Comment 4: “Discussion: Limitations of the study need to be expanded to include the above mentioned critics.”

Authors’ reply:
The following sentence has been added to the paragraph on limitations in the discussion section of the paper, page 10, lines 313-317. “Finally, the definition of clinical stone event as acute flank pain associated with hematuria without confirmation by imaging, can be considered a limitation. However, the fact that all patients included in the study had recurrent kidney stone disease confirmed by a physician and a number of imaging studies carried out during the course of their disease makes other diagnoses unlikely.” See also author’s reply to comment 2 by reviewer 3.