PEER REVIEW HISTORY

ARTICLE DETAILS

TITLE (PROVISIONAL)	Does Chronic Hyperglycaemia Increase the Risk of Kidney Stone disease? Results from a Systematic Review and Meta-Analysis
AUTHORS	Geraghty, Robert; Abdi, Abdihakim; Somani, Bhaskar; Cook, Paul; Roderick, Paul

VERSION 1 - REVIEW

REVIEWER	Khashayar Sakhaee UTSW Medical Center
REVIEW RETURNED	10-Jul-2019

GENERAL COMMENTS	In this manuscript the authors described the relationship of chronic hyperglycemia with a risk of kidney stone disease in a systematic review and meta-analysis of the literature. The results showed chronic hyperglycemia increases the risk of developing kidney stone disease. I have the following comments that may improve the paper: 1. Such a study showing the relationship between body size and obesity has been previously reported by the Taylor et. al. In addition, the study of West et el. has shown the relationship of the feature of metabolic syndrome and risk of kidney stone disease. Citations 29, 37. The authors should specify how this study was different from previously published papers. 2. One shortcoming of the paper is the lack of explanation of how the kidney stones were diagnosed. Was this on the basis on self reported incidence or documented by imaging? 3. The authors should indicate whether the subjects were taking any hypoglycemic agents and also stone analysis was available in any number of them. I agree with the authors that there is a relationship with body weight, obesity, metabolic syndrome and uric acid stones. However, to date this link has not been shown between calcium stones and the cluster of conditions associated with metabolic syndrome as cited in citation 21 and 22 of this manuscript. Could the authors speculate of how obesity may lead to calcium stones.

REVIEWER	POZDZIK CHU Brugmann
REVIEW RETURNED	13-Aug-2019

GENERAL COMMENTS	Thank you for the review of a hot topic concerning the KSD.

	The aim of the study is interesting and relevant. However please not the some major Remarks: -the abstract need to be reviewed and the association between the MD, IGT (the abbreviation was not introduced in the abstract), MetS need to appear more clearly. -the presentation of figures and tables need to be more descriptive in term of significance of symboles, and they significance -some Figures do not have the title the discussion is well done but please underline the differences in the group DM and IGT.

REVIEWER	Wisit Cheungpasitporn University of Mississippi Medical Center, USA
REVIEW RETURNED	09-Sep-2019

GENERAL COMMENTS	Major modifications and additional analysis are strongly needed to improve this systematic review and meta-analysis as described below. 1. Literature Searches and Search terms are incomplete. This is suboptimal for publication for systematic review. Search terms in Ovid Medline, Cochrane Library, CINAHL, Clinicaltrials.gov, Google Scholar are different. Please attach search terms that were used in each database as supplement for Data source and search strategies in the manuscript. Please provide details search terms in supplementary documents. Please attach syntax used in each database as supplementary. 2. "individual urologic, renal, metabolic and epidemiologic journals" is too vague for systematic review. The name of journals that were screened; need to additionally be provided. 3. Significant numbers of article 2301 of 2340 (98%) articles were excluded at the initial step on the basis of the title. This raised the concern of incomplete literature search. 4. There is still a considerable heterogeneity as in your limitation. Meta-regression analysis is then strongly recommended. 5. Type of stones e.g. Calcium oxalate, Calcium phosphate, Uric acid stones and others should be taken into consideration. 6. Data on glycemic control e.g. A1C and poor vs controlled DM should be taken into consideration 7. There is substantive heterogeneity in some outcomes. It also is unclear whether the t-statistic is being used for the degrees of freedom in the random effects analysis (i.e., N-1 d.f. not asymptotic [1.96] value multiplied by tau). Please assure that the t-statistic (or Satterthwaite correction) is being used and add that information to the Methods, when the number of studies is small (e.g., < 10). Apply this principle throughout the author's paper. For reference, the authors can refer the article "IntHout J, Ioannidis JP, Borm GF. The Hartung-Knapp-Sidik-Jonkman method for random effects meta-analysis is straightforward and considerably outperforms the standard DerSimonian-Laird method. BMC Medical Research Methodology 2014;14:25." The issue is the Student t statistic. 8. Authors should better discuss the reason of heterogeneity in more details. 9. It will be better to show kappa for the selection and data extraction. Please show the data of kappa of agreement during the systematic searches. How disagreements were solved during the systematic search among two independent reviewers?

	10. The authors should apply the ROBINS-I (Risk of Bias in Nonrandomized studies of Interventions) tool in addition to NOS. The authors already applied the Newcastle Ottawa Scale, which is a validated tool and was an acceptable choice. However, to enhance the reproducibility and comparability of this review to future reviews of a similar topic (possibly an update of this review) I recommend including a risk of bias assessment using ROBINS-I, since it is the newest and most robust method of assessing risk of bias in systematic reviews/meta-analyses. 11. Please make the data for this review publicly available, possibly through the Open Science Framework (osf.io). Items to include: list of excluded studies, commands for statistical analysis, spreadsheets or data used for the meta-analyses, etc. Making data publicly available will promote the reproducibility of the review and is best practices for systematic reviews and meta-analyses. 12. Limitations should also mention this systematic review included only English language articles 13. Limitations should also include lack of data on supersaturation study profile, stone type?

VERSION 1 – AUTHOR RESPONSE

Reviewer: 1

Reviewer Name: Khashayar Sakhaee

Institution and Country: UTSW Medical Center Please state any competing interests or state 'None declared': None declared

1. Such a study showing the relationship between body size and obesity has been previously reported by the Taylor et. al. In addition, the study of West et el. has shown the relationship of the feature of metabolic syndrome and risk of kidney stone disease. Citations 29, 37. The authors should specify how this study was different from previously published papers.

Reply: These two studies were large cohort studies, the current study differs as it is a systematic review and meta-analysis, thus incorporating all studies in the area and is therefore a different study design.

2. One shortcoming of the paper is the lack of explanation of how the kidney stones were diagnosed. Was this on the basis on self reported incidence or documented by imaging?

Reply: This would vary from study to study and is detailed in table 1. We agree with the reviewer that this is a limitation of the study. However, this is a limitation of any meta-analysis which is reliant on the original data provided.

3. The authors should indicate whether the subjects were taking any hypoglycemic agents and also stone analysis was available in any number of them. I agree with the authors that there is a relationship with body weight, obesity, metabolic syndrome and uric acid stones. However, to date this link has not been shown between calcium stones and the cluster of conditions associated with metabolic syndrome as cited in citation 21 and 22 of this manuscript. Could the authors speculate of how obesity may lead to calcium stones.

Reply: We thank the reviewer for this comment. Again, the studies examined in this review dictate the answers to these questions. Table 1 details how diabetes was defined – in some cases the use of antidiabetic medications. Stone analysis was not performed in any of the studies.

Reviewer: 2

Reviewer Name: POZDZIK

Institution and Country: CHU Brugmann

Please state any competing interests or state 'None declared': Non declared

Please leave your comments for the authors below Thank you for the review of a hot topic concerning the KSD.

The aim of the study is interesting and relevant.

However please not the some major Remarks:

-the abstract need to be reviewed and the association between the MD, IGT (the abbreviation was not introduced in the abstract), MetS need to appear more clearly.

Reply: We agree, and we have now clarified this in the abstract. We apologise for not being more clear initially.

-the presentation of figures and tables need to be more descriptive in term of significance of symboles, and they significance -some Figures do not have the title

Reply: We have now amended this as per reviewers suggestion.

-the discussion is well done but please underline the differences in the group DM and IGT.

Reply: We have now amended this as per reviewers suggestion, see lines 418-475

Reviewer: 3

Reviewer Name: Wisit Cheungpasitporn

Institution and Country: University of Mississippi Medical Center, USA Please state any competing interests or state 'None declared': None declared

Please leave your comments for the authors below Major modifications and additional analysis are strongly needed to improve this systematic review and meta-analysis as described below.

1. Literature Searches and Search terms are incomplete. This is suboptimal for publication for systematic review. Search terms in Ovid Medline, Cochrane Library, CINAHL, Clinicaltrials.gov, Google Scholar are different. Please attach search terms that were used in each database as supplement for Data source and search strategies in the manuscript. Please provide details search terms in supplementary documents. Please attach syntax used in each database as supplementary.

Reply: Attached as supplementary files

2. "individual urologic, renal, metabolic and epidemiologic journals" is too vague for systematic review. The name of journals that were screened; need to additionally be provided.

Reply: We apologies for this, this has now been amended – see lines 147-148

3. Significant numbers of article 2301 of 2340 (98%) articles were excluded at the initial step on the basis of the title. This raised the concern of incomplete literature search.

Reply: The large numbers initially identified and then excluded were based largely on the Google Scholar search, which brings up large numbers of papers due to the limited search functions. The other more refined searches produced far fewer papers that were subsequently excluded.

4. There is still a considerable heterogeneity as in your limitation. Meta-regression analysis is then strongly recommended.

Reply: Apologies this wasn't clear. See line 186-187 in methods, meta-regression was performed and is evidenced by adjusted values in the forest plots.

5. Type of stones e.g. Calcium oxalate, Calcium phosphate, Uric acid stones and others should be taken into consideration.

Reply: We agree with the reviewer that having stone type would have been helpful. Unfortunately the data on stone type was not available in majority of studies. We agree that stone type should be examined in future studies.

6. Data on glycemic control e.g. A1C and poor vs controlled DM should be taken into consideration

Reply: Again, unfortunately this data is not available in the majority of the studies examined, although as per reviewers suggestion, we have included this under the discussion.

7. There is substantive heterogeneity in some outcomes. It also is unclear whether the t-statistic is being used for the degrees of freedom in the random effects analysis (i.e., N-1 d.f. not asymptotic [1.96] value multiplied by tau). Please assure that the t-statistic (or Satterthwaite correction) is being used and add that information to the Methods, when the number of studies is small (e.g., < 10). Apply this principle throughout the author's paper. For reference, the authors can refer the article "IntHout J, Ioannidis JP, Borm GF. The Hartung-Knapp-Sidik-Jonkman method for random effects meta-analysis is straightforward and considerably outperforms the standard DerSimonian-Laird method. BMC Medical Research Methodology 2014;14:25." The issue is the Student t statistic.

Reply: See line 187-188 – student T statistic was used, this has been amended in methods section.

8. Authors should better discuss the reason of heterogeneity in more details.

Reply: Amended - Heterogeneity discussed on lines 385-412

9. It will be better to show kappa for the selection and data extraction. Please show the data of kappa of agreement during the systematic searches. How disagreements were solved during the systematic search among two independent reviewers?

Reply: Kappa added see line 216 . As stated in line 158, the senior authors made the decision regarding inclusion.

10. The authors should apply the ROBINS-I (Risk of Bias in Nonrandomized studies of Interventions) tool in addition to NOS. The authors already applied the Newcastle Ottawa Scale, which is a validated tool and was an acceptable choice. However, to enhance the reproducibility and comparability of this

review to future reviews of a similar topic (possibly an update of this review) I recommend including a risk of bias assessment using ROBINS-I, since it is the newest and most robust method of assessing risk of bias in systematic reviews/meta-analyses.

Reply: We appreciate the comment by the reviewer and are thankful to them for this. We also agree that Newcastle Ottawa Scale is validated for this. Given that we have already done the work using this which is an acceptable choice, using ROBINS-I would mean repeating the whole exercise. We hope that given that the scale we have used is ok given that the reviewer found it acceptable and we would use ROBINS-I in any future studies.

11. Please make the data for this review publicly available, possibly through the Open Science Framework (osf.io). Items to include: list of excluded studies, commands for statistical analysis, spreadsheets or data used for the meta-analyses, etc. Making data publicly available will promote the reproducibility of the review and is best practices for systematic reviews and meta-analyses.

Reply: Data has been added to PROSPERO

12. Limitations should also mention this systematic review included only English language articles

Reply: Added see line 79

13. Limitations should also include lack of data on supersaturation study profile, stone type?

Reply: Added see line 80

VERSION 2 – REVIEW

REVIEWER	Sakhaee
	UTSW
REVIEW RETURNED	18-Dec-2019

| GENERAL COMMENTS | The reviewer completed the checklist but made no further comments. |

REVIEWER	Wisit Cheungpasitporn, MD
	University of Mississippi Medical Center
REVIEW RETURNED	04-Dec-2019

| GENERAL COMMENTS | It appears that all comments have been appropriately responded to. I have no further comments and recommend publication. |