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Name of Journal: ***World Journal of Nephrology***

ESPS Manuscript NO: 24992

Manuscript type: Minireviews

Dr. Shui Qiu

Scientific Editor

Baishideng Publishing Group Inc.

7 April 2016

Dear dr. Qiu,

We would like to thank you and the reviewers for the time invested in reviewing our manuscript and for giving us the opportunity to make a revision. We have carefully read the comments and suggestions, which in our opinion, have resulted in improvement of our manuscript. Here below, we have answered the questions punctually and given our comments on the received feedback (indicated in bold letters). The suggestions given to us have indeed improved our study. In our manuscript, changes are marked in yellow.

The most important changes include:

1. Moderation of our conclusion and recommendation considering which method is preferable to determine the intestinal permeability in future research
2. Clarification of our plots and further explanation that we did not pool results and were not able to perform a meta-analysis on the results of the included studies due to the different methods that were used

3. Adjustment of our exclusion criteria; papers published in other languages than English are now also included
4. Moderation of our conclusion considering the link between an increased intestinal permeability in ESRD

Should you have any further questions, please do not hesitate to contact us at any time.

Yours sincerely,

On behalf of all co-authors,

Matty L. Terpstra, MD

Reviewers code: 00503339

Comments to authors:

No manuscript received.

From this reviewer we didn't receive comments.

Reviewers code 00503043

Comments to authors

1. This systematic review(24992) was aimed to clarify what is the best available method to determine the intestinal permeability in CKD patients. However, there was no golden standard. Furthermore, these included studies didn't compare different methods to determine the intestinal permeability in CKD patients. So, based on this systematic review, authors could not draw the conclusion that quantitative PCR for bacterial DNA in blood was the most accurate method currently available to demonstrate an increased intestinal permeability in patients with CKD.

We fully agree with the above mentioned reviewer. With the currently available data on the assessment of the intestinal permeability in CKD it is indeed not possible to draw a definite conclusion on which method is the most accurate. We are pointing out the limitations of the currently available methods to assess the intestinal permeability and emphasize that results of these methods should be interpret with caution, especially in the CKD patient. This review serves to inform and advice fellow researchers which method could be preferred in future research projects. Although each method has it own limitations, after weighing the advantages and disadvantages, some methods are preferable compared to others. We have however moderated our conclusion and recommendations.

'Even though we aim to oppose the most reliable method, the lack of a gold standard is a limitation of this systematic review. In addition to this, unfortunately none of the included studies used more than one method to measure the intestinal permeability in CKD patients in order to be able to actually compare different methods. '

'Assessing the intestinal permeability in CKD patients remains challenging as the influence of decreased renal function on the test results remains unclear . Quantitative PCR for bacterial DNA in blood and D-lactate levels in plasma seem the least likely to be influenced by a decreased eGFR. It should be noted though that also these methods have not been validated in the CKD patient population and results should still be interpret with caution.'

2. Based on this systematic review, authors draw the conclusion that there was a clear connection between end stage renal disease and intestinal barrier dysfunction. In my opinion, there are two problems. Firstly, the connection between the methods used in the included studies and intestinal permeability in CKD is still unclear.

The lack of a gold standard is a limitation of not only our study but also of each of the studies we (and thus data) we included. However, despite the use of different methods, each study measuring the intestinal permeability in ESRD concludes that there is an increased intestinal permeability. It is true that these results, especially the results published using methods such as the sugar absorption test and PEG's, are probably influenced by a decreased renal function. However, each study assessing the intestinal permeability in ESRD pointed out a significant increased permeability, also the studies that are unlikely to be influenced by a decreased renal clearance. It seems likely that there is a link. However, we moderated our conclusion.

'However each included study measuring the intestinal permeability in patients with ESRD pointed out a significant increased permeability. Thus, it seems likely that there is a connection between renal failure and an increased intestinal permeability. How the permeability evolves in time, the possible link with (recurrent) infection(s), cardiovascular complications and prognosis of these patients has not yet been made and requires further exploration.'

3. Secondly, authors extracted outcome data from included studies and performed meta-analysis using RevMan 5.3. However, the methods used in the included studies were variety. In my opinion, these different methods and outcomes could not be included and calculated in meta-analysis.

We are aware of the fact that when we are comparing results of the studies we are comparing results obtained through different methods. It was thus impossible to pool results and perform a meta-analysis. We used RevMan only to make a graphic design of the results of the different studies and to calculate the standardized mean difference but we did not pool results. In our tables we provide a lot of detailed information, the plot is a short overview of the results published in the different studies. In a forest plot results are pooled in a diamond,

in our plots we are not pooling results. To further clarify and emphasize this we added the following paragraph.

'Results were graphically displayed in two plots, one comparing the intestinal permeability in mild to moderate CKD patients to healthy controls and one comparing the intestinal permeability in ESRD patients to healthy controls. Since different methods were used among the included studies, results were not pooled and no meta-analysis was performed.'

4. It would be better if you can find and include the studies not written in English.

Our search contained two non-English studies possibly meeting the inclusion criteria. After further analyzing these two studies, one study met our inclusion criteria and was included in our study. This paper appeared to present results conducted in the same patient group as an already included paper published by the same research group. Data published by the two articles were combined and are displayed in table 2.

Kovacs et al. 1996 [21] and Kovacs et al. 1996 [23] *Two studies published results measured in the same patient group	IgAN patients (both uremic and non-uremic) vs healthy controls Both in 1989 and after a four year follow up in 1994 No mean creatinine levels of total IgAN group provided	1989: IgAN patients n= 29: (uremic n = 24 non-uremic n = 5) Controls n = 20 1996: IgAN patients n= 21 No controls Follow up patients further divided an analyzed in two groups; increased intestinal permeability group vs non-increased intestinal permeability	Cr-EDTA recovery (urine)	Significantly higher Cr-EDTA recovery in IgAN patients vs controls $p < 0.005$, both in 1989 and in follow up after 5 years IgAN (1989): 3.86 % +- 0.29 IgAN (1994): 4.57 % +- 0.63 Controls: 2.72 % +- 0.23 Only in the increased permeability group significant decrease in renal clearance (Baseline renal clearance 84.4 ± 6.1 ml/min vs 65.4 ± 8.6 ml/min after four years, $p < 0.01$)	Both small and large intestine

5. I could not find the explanations of PROSPERO in the manuscript text. It should be explained where it is first used in the manuscript text.

The PROSPERO register is now further explained in the methods section.

'PROSPERO is an international database of prospectively registered reviews in health and social care in which key features from the review protocol are recorded and maintained as a permanent record. PROSPERO aims to provide a comprehensive listing of systematic reviews registered at inception to help avoid unplanned duplication and enable comparison of reported review methods with what was planned in the protocol. [11]'

Reviewers code 00070143

Comments to authors

Intestinal permeability and bacterial endotoxin is really important for most of the disease. Therefore , methods for detecting intestinal permeability are useful. This study can accepted for publishing . This is well written review article

No issues to address. Thank you for the encouraging feedback.

Reviewers code 00503233

Comments to authors

Authors evaluate here methods of assessing intestinal permeability, with special reference to patients with chronic kidney disease(CKD). The review is detailed, well performed and written. I only have a few minor observations:

1. Please use the term ”renal clearance” when referring to clearance of a specific molecule(creatinine, inulin, …..); other wise use the terms “glomerular filtration rate”, “renal function” as appropriate

We adjusted these terms in the manuscript.

‘decreased glomerular filtration rate on test results’

‘The influence of decreased renal function on’

‘to prevent possible bias obtained by a decreased estimated glomerular filtration rate (eGFR)’

2. Page 9: it is preferable to use the terms “yielded” or “provided” rather than “conducted” , and “proposed” rather than “opposed” 3. Pages 12-13: “rhamnose” not “rhmanose”

We adjusted these language abbreviations.

‘Our search through MEDline and EMBASE yielded 646 articles.’

‘They proposed the biofilm on the surface of the central venous catheter (CVC) as a possible source’

‘rhamnose was’

Note: other similar adjustments are highlighted in the manuscript

Reviewers code 00503014

Comments to authors

1.Page8, last paragraph:----were divided in two categories: studies comparing the intestinal permeability in mild to moderate CKD patients to healthy controls. I suggest that the renal function should be divided as eGFR for readers easy follow-up.

We clarified these groups in our methods section and in the title of Figures 2 and 3.

'In attempt to compare results studies were divided in two categories: studies comparing the intestinal permeability in mild to moderate CKD patients (eGFR 15-90) to healthy controls and studies comparing intestinal permeability in End Stage Renal Disease (ESRD) (eGFR <15; both hemodialysis [HD] and non-hemodialysis non-HD]) patients to healthy controls.'

'Figure 2. Intestinal permeability mild to moderate CKD patients (eGFR 15-90) vs healthy controls'

'Figure 3. Intestinal permeability ESRD patients (eGFR <15) vs healthy controls'

2.As known, hypoalbuminemia will cause change in intestinal permeability change. Beside eGFR staging, diabetic nephropathy or not should be divided.

For this systematic review we are unfortunately depended on data published in the included studies. Not all studies provided sufficient clinical data on their included patient population, this was also part of the quality assessment we performed on each included study. More importantly, even though some studies did provide a percentage of diabetic nephropathy in their population, none of the included studies performed a sub analysis in which the CKD patients with diabetes patients were compared to the CKD patients without diabetes. Due to the design of our study it is thus impossible to perform this analysis. It is however an interesting and important issue that should be addressed in future research.