

PEER-REVIEW REPORT

Name of journal: World Journal of Nephrology

Manuscript NO: 34073

Title: Podocyturia: Potential applications and current limitations

Reviewer's code: 00503252

Reviewer's country: Japan

Science editor: Jin-Xin Kong

Date sent for review: 2017-03-28

Date reviewed: 2017-04-01

CLASSIFICATION	LANGUAGE EVALUATION	SCIENTIFIC MISCONDUCT	CONCLUSION
<input type="checkbox"/> Grade A: Excellent	<input type="checkbox"/> Grade A: Priority publishing	Google Search:	<input type="checkbox"/> Accept
<input checked="" type="checkbox"/> Grade B: Very good	<input checked="" type="checkbox"/> Grade B: Minor language polishing	<input type="checkbox"/> The same title	<input type="checkbox"/> High priority for publication
<input type="checkbox"/> Grade C: Good		<input type="checkbox"/> Duplicate publication	
<input type="checkbox"/> Grade D: Fair	<input type="checkbox"/> Grade C: A great deal of language polishing	<input type="checkbox"/> Plagiarism	<input type="checkbox"/> Rejection
<input type="checkbox"/> Grade E: Poor	<input type="checkbox"/> Grade D: Rejected	<input checked="" type="checkbox"/> No	<input checked="" type="checkbox"/> Minor revision
		BPG Search:	<input type="checkbox"/> Major revision
		<input type="checkbox"/> The same title	
		<input type="checkbox"/> Duplicate publication	
		<input type="checkbox"/> Plagiarism	
		<input checked="" type="checkbox"/> No	

COMMENTS TO AUTHORS

Trimarchi H reported comprehensive review of podocyturia partially based on his own data. This reviewer has some minor comments. 1. The authors stated that "It appears that glomerulosclerosis starts to occur when the loss of podocytes per glomerulus is approximately between 20 and 40%. Above this number, the glomerulus starts the point of no return and is destined to obliteration." (P4, L6-8). and "Partial detachments are usually reversible to a certain degree." (P7, L10,11). Appropriate references to each statement should be provided. 2. This reviewer wonders the sentence "Considering the fact that about 2 million podocytes are distributed in glomeruli in both kidneys, approximately 1 billion podocytes populate both kidneys. In addition, it has been calculated that around 400 podocytes are lost in the urine every day." (P11, L9-12) does not make sense. 3. misspellings a normal o higher glomerular filtration rate (P13, L3 from last line) disease ore ven at the same stage (P14, L2 from the last line) without delays (L15, L7)

PEER-REVIEW REPORT

Name of journal: World Journal of Nephrology

Manuscript NO: 34073

Title: Podocyturia: Potential applications and current limitations

Reviewer's code: 00503272

Reviewer's country: Nigeria

Science editor: Jin-Xin Kong

Date sent for review: 2017-03-28

Date reviewed: 2017-04-05

CLASSIFICATION	LANGUAGE EVALUATION	SCIENTIFIC MISCONDUCT	CONCLUSION
<input type="checkbox"/> Grade A: Excellent	<input type="checkbox"/> Grade A: Priority publishing	Google Search:	<input type="checkbox"/> Accept
<input type="checkbox"/> Grade B: Very good	<input checked="" type="checkbox"/> Grade B: Minor language polishing	<input type="checkbox"/> The same title	<input type="checkbox"/> High priority for publication
<input checked="" type="checkbox"/> Grade C: Good		<input type="checkbox"/> Duplicate publication	
<input type="checkbox"/> Grade D: Fair	<input type="checkbox"/> Grade C: A great deal of language polishing	<input type="checkbox"/> Plagiarism	<input type="checkbox"/> Rejection
<input type="checkbox"/> Grade E: Poor	<input type="checkbox"/> Grade D: Rejected	<input checked="" type="checkbox"/> No	<input checked="" type="checkbox"/> Minor revision
		BPG Search:	<input type="checkbox"/> Major revision
		<input type="checkbox"/> The same title	
		<input type="checkbox"/> Duplicate publication	
		<input type="checkbox"/> Plagiarism	
		<input checked="" type="checkbox"/> No	

COMMENTS TO AUTHORS

Reviewer's comments 1. Author (Abstract line 10, page 2): '... glomerular filtration barrier: The podocyte.' Reviewer: change to '.... glomerular filtration barrier: the podocyte.' 2. Author (Page 2, line 14): 'When the loss of podocytes in the urine, or podocyturia, is taken place and its glomerular...' Reviewer: change 'taken' to 'taking' in the above line. 3. Author (The podocyte, line 1, page 4): 'The podocyte mass is small when compared of the whole amount of kidney cells.' Reviewer: the sentence should be revised to 'The podocyte mass is small compared to the entire kidney mass.' 4. Author (Page 5, line 9, paragraph 1): '... which is critical for the formation of fenestrae in the capillar endothelium, ...' Reviewer: please change 'capillar' to 'capillary.' 5. Author (Page 6, line 22): '... and also in the lower quality of these synthesized molecules,a...' Reviewer: let there be period between 'molecules,' and letter 'a'. 6. Author (Page 9, line 9, paragraph 1): 'In this regard, our group suggests that a probable...' Reviewer: change 'suggests' to 'suggested.' 7. Author (Page 10, paragraph 3, line 4): 'In addition, it has beencalculated that around 400...' Reviewer: put a period between 'been' and



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'calculated.' 8. Author (Page 12, paragraph 2, line 11): 'a different regenerative potential at distinct stages of life, exhibiting the highest...' Reviewer: put a period between 'life,' and 'exhibiting.' 9. Author (Page 13, lines 9-12, paragraph 1): 'We and others have assessed podocyturia in a wide variety of glomerulopathies, as well as in transplantation and in entities where the glomerulus is not primarily affected, as in polycystic kidney disease....' Reviewer: Remove 'We and others' and revise to read 'Podocyturia has been assessed in a wide....' 10. Author (Page 13, line 13, paragraph 1): 'Podocyturia is ideally employed in hereditary kidney disorders like Alport of Fabry disease.' Reviewer: What is the meaning of 'Alport of Fabry disease' in the above statement? 11. Author (Conclusion): 'Podocytes are HIGHLY DIFFERENTIATED CELLS UNABLE TO REPLICATE under normal conditions. DESPITE PHYSIOLOGIC PODOCYTURIA EXISTS, any insult received by the podocyte either directly or indirectly, would trigger contractile mechanisms DESTINED TO RETAIN THEM ATTACHED to the glomerular basement membrane, DESPITE RESIGNING THEIR CAPACITY TO AVOID PROTEIN LOSS in the urine. Podocytes attach to the glomerular basement membrane via integrins, that anchor cells.' Review: What is the meaning of each of the statements in upper case in the above lines in your conclusion? Please, make them clear.

PEER-REVIEW REPORT

Name of journal: World Journal of Nephrology

Manuscript NO: 34073

Title: Podocyturia: Potential applications and current limitations

Reviewer's code: 00503187

Reviewer's country: Finland

Science editor: Jin-Xin Kong

Date sent for review: 2017-03-28

Date reviewed: 2017-04-11

CLASSIFICATION	LANGUAGE EVALUATION	SCIENTIFIC MISCONDUCT	CONCLUSION
<input type="checkbox"/> Grade A: Excellent	<input type="checkbox"/> Grade A: Priority publishing	Google Search:	<input type="checkbox"/> Accept
<input type="checkbox"/> Grade B: Very good	<input checked="" type="checkbox"/> Grade B: Minor language polishing	<input type="checkbox"/> The same title	<input type="checkbox"/> High priority for publication
<input checked="" type="checkbox"/> Grade C: Good		<input type="checkbox"/> Duplicate publication	
<input type="checkbox"/> Grade D: Fair	<input type="checkbox"/> Grade C: A great deal of language polishing	<input type="checkbox"/> Plagiarism	<input type="checkbox"/> Rejection
<input type="checkbox"/> Grade E: Poor	<input type="checkbox"/> Grade D: Rejected	<input checked="" type="checkbox"/> No	<input checked="" type="checkbox"/> Minor revision
		BPG Search:	<input type="checkbox"/> Major revision
		<input type="checkbox"/> The same title	
		<input type="checkbox"/> Duplicate publication	
		<input type="checkbox"/> Plagiarism	
		<input checked="" type="checkbox"/> No	

COMMENTS TO AUTHORS

The review by Trimarchi introduces podocyturia, covering first an introduction of podocytes followed by mechanisms of podocyte detachment, methods to diagnose podocyturia and finally potentiality and limitations of podocyturia. I have a couple of comments on the manuscript as detailed below. On page 7 the author mentions that 'The vast majority of these cells appear to be viable with normal morphology and organelle distribution in the cell body.', referring to detached podocytes. What is the reference for this? Podocyte apoptosis is also one of the mechanisms of podocyte detachment and loss. However, this is not mentioned in the review. This also reflects back to the comment above. I am wondering about the following two sentences: 'In addition, it has been calculated that around 400 podocytes are lost in the urine every day. Finally, it has been demonstrated that when a glomerulus loses between 20-40% of its podocyte content (around 100-200 podocytes), it renders itself to sclerosis and obliteration [2,4].' The numbers/percentages do not make sense, as based on the above, podocyte loss occurring in one day would be enough to lead to sclerosis. Please, check.



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In the sentence: 'The available methods to study podocyuria are time-consuming, expensive when compared to the classical ones, and time-consuming.' the spot 'when compared to the classical ones' needs clarification. What methods are ment here and referred to as classical ones? Please, remove the duplicated 'and time-consuming'. The review does not touch many diseases or physiological states in which podocyuria has been studied or proposed as a potential method to study the disease state or kidney status, and just Alport and Fabry disease are mentioned. I would like the review to contain a more thorough look-up into literature along these lines. The references are very much concentrated on the papers published by the author himself. Even though Figure 1 is a cartoon depicting certain key proteins in podocytes, I would like to suggest to draw the proteins and mark their names as realistically as possible. In several cases it is not easy to recognize which marking represents the specific protein (actin, actinin-4, synaptopodin). In case of CD2AP, the name is outside of the foot process even though the protein is intracellular and drawn there as well. Catenin and cadherin are marked the wrong way round (cadherins are the transmembrane proteins and catenins cytosolic adaptors). Podocin is not an extracellular protein or a transmembrane protein, it is attached to the innermost plasma membrane leaflet and should be imaged correspondingly in the cartoon. In Figure 2, please mark the tubular cells and podocytes on the image for clarity. Indicate the nature of the blue and green colors on the image. Minor comments: On page 4, it is mentioned that podocyte foot processes self-interdigitate in addition that they interdigitate with the foot processes of the neighboring podocytes; is that so? page 10, change 'protein chain reaction (PCR)' to 'polymerase chain reaction' There are some small mistakes in the English language throughout, so please, go through the text and correct.

PEER-REVIEW REPORT

Name of journal: World Journal of Nephrology

Manuscript NO: 34073

Title: Podocyturia: Potential applications and current limitations

Reviewer's code: 02888410

Reviewer's country: Spain

Science editor: Jin-Xin Kong

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Date reviewed: 2017-04-12

CLASSIFICATION	LANGUAGE EVALUATION	SCIENTIFIC MISCONDUCT	CONCLUSION
<input type="checkbox"/> Grade A: Excellent	<input type="checkbox"/> Grade A: Priority publishing	Google Search:	<input type="checkbox"/> [Y] Accept
<input type="checkbox"/> [Y] Grade B: Very good	<input type="checkbox"/> [Y] Grade B: Minor language polishing	<input type="checkbox"/> [] The same title	<input type="checkbox"/> [] High priority for publication
<input type="checkbox"/> [] Grade C: Good	<input type="checkbox"/> [] Grade C: A great deal of language polishing	<input type="checkbox"/> [] Duplicate publication	<input type="checkbox"/> [] Rejection
<input type="checkbox"/> [] Grade D: Fair	<input type="checkbox"/> [] Grade D: Rejected	<input type="checkbox"/> [Y] No	<input type="checkbox"/> [] Minor revision
<input type="checkbox"/> [] Grade E: Poor		BPG Search:	<input type="checkbox"/> [] Major revision
		<input type="checkbox"/> [] The same title	
		<input type="checkbox"/> [] Duplicate publication	
		<input type="checkbox"/> [] Plagiarism	
		<input type="checkbox"/> [Y] No	

COMMENTS TO AUTHORS

The manuscript is too condensed. To separate paragraphs and introducing subtitles would help to a better text understanding. A figure on the pathogenesis of GSFS after podocyte destruction would be welcome. The phrase "Thus, podocyturia would be useful in clinical grounds when employed routinely for screening purposes in any patient" would be better placed in "Conclusions" rather than in limitations. In any case, a comment on the cost of such measure for screening purposes must be added (this is obviously the limitation). Conclusions: Erase " Podocytes attach to the glomerular basement membrane via integrins, that anchor cells to laminin and other membrane components". This is not a conclusion. The authors discussed the diagnostic use of podocyturia, and this should be included in the conclusions. The last phrase: "Unravelling the mechanisms of podocyte detachment could lead to targeted therapeutic interventions that could delay the progression of chronic kidney diseases" is logical but it is not supported by the matter discussed in the text.