



PEER-REVIEW REPORT

Name of journal: *World Journal of Diabetes*

Manuscript NO: 83936

Title: Klotho: a new therapeutic target in diabetic retinopathy?

Provenance and peer review: Invited Manuscript; Externally peer reviewed

Peer-review model: Single blind

Reviewer's code: 02862753

Position: Editorial Board

Academic degree: MD

Professional title: Full Professor

Reviewer's Country/Territory: Lebanon

Author's Country/Territory: Italy

Manuscript submission date: 2023-02-16

Reviewer chosen by: AI Technique

Reviewer accepted review: 2023-02-17 18:31

Reviewer performed review: 2023-02-18 05:29

Review time: 10 Hours

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| Scientific quality | <input checked="" type="checkbox"/> Grade A: Excellent <input type="checkbox"/> Grade B: Very good <input type="checkbox"/> Grade C: Good <input type="checkbox"/> Grade D: Fair <input type="checkbox"/> Grade E: Do not publish |
| Novelty of this manuscript | <input checked="" type="checkbox"/> Grade A: Excellent <input type="checkbox"/> Grade B: Good <input type="checkbox"/> Grade C: Fair <input type="checkbox"/> Grade D: No novelty |
| Creativity or innovation of this manuscript | <input checked="" type="checkbox"/> Grade A: Excellent <input type="checkbox"/> Grade B: Good <input type="checkbox"/> Grade C: Fair <input type="checkbox"/> Grade D: No creativity or innovation |



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| Scientific significance of the conclusion in this manuscript | <input checked="" type="checkbox"/> Grade A: Excellent <input type="checkbox"/> Grade B: Good <input type="checkbox"/> Grade C: Fair <input type="checkbox"/> Grade D: No scientific significance |
| Language quality | <input checked="" type="checkbox"/> Grade A: Priority publishing <input type="checkbox"/> Grade B: Minor language polishing <input type="checkbox"/> Grade C: A great deal of language polishing <input type="checkbox"/> Grade D: Rejection |
| Conclusion | <input checked="" type="checkbox"/> Accept (High priority) <input type="checkbox"/> Accept (General priority) <input type="checkbox"/> Minor revision <input type="checkbox"/> Major revision <input type="checkbox"/> Rejection |
| Re-review | <input type="checkbox"/> Yes <input checked="" type="checkbox"/> No |
| Peer-reviewer statements | Peer-Review: <input type="checkbox"/> Anonymous <input checked="" type="checkbox"/> Onymous |
| | Conflicts-of-Interest: <input type="checkbox"/> Yes <input checked="" type="checkbox"/> No |

SPECIFIC COMMENTS TO AUTHORS

The authors have performed a complete systematic review and yielded a well written well connected easy to read manuscript about a subject that has not been well known among clinicians and this authoritative paper would entice researchers to pursue further research in this promising avenue. I need to enhance the paper by adding one more sentence with 3 references: To add more evidence for Klotho as biomarker for diabetic retinopathy, the authors need to add that Klotho is also considered as a new biomarker for early diabetic nephropathy and as an emergent exerkin. This systematic review was the first to evaluate the relationship between sKlotho levels and DN. The sKlotho level was significantly lower in the early stages of DN, indicating that sKlotho might be a new biomarker of DN in the future. Xin C, Sun X, Li Z, Gao T. Relationship of Soluble Klotho and Early Stage of Diabetic Nephropathy: A Systematic Review and Meta-Analysis. *Front Endocrinol (Lausanne)*. 2022 May 27;13:902765. doi: 10.3389/fendo.2022.902765. Piwkowska A, Zdrojewski Ł, Heleniak Z, Dębska-Ślizień A. Novel Markers in Diabetic Kidney Disease-Current State and Perspectives. *Diagnostics (Basel)*. 2022 May 11;12(5):1205. doi: 10.3390/diagnostics12051205. Available evidence



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suggests that exercise increases Klotho levels, regardless of the condition or intervention, shedding some light on this anti-aging protein as an emergent and promising exerkin.

Corrêa HL, Raab ATO, Araújo TM, Deus LA, Reis AL, Honorato FS, Rodrigues-Silva PL, Neves RVP, Brunetta HS, Mori MADS, Franco OL, Rosa TDS. A systematic review and meta-analysis demonstrating Klotho as an emerging exerkin. *Sci Rep.* 2022 Oct 20;12(1):17587. doi: 10.1038/s41598-022-22123-1.



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Peer-review model: Single blind

Reviewer's code: 05573818

Position: Peer Reviewer

Academic degree: MD, PhD

Professional title: Chief Doctor, Surgeon

Reviewer's Country/Territory: China

Author's Country/Territory: Italy

Manuscript submission date: 2023-02-16

Reviewer chosen by: Geng-Long Liu

Reviewer accepted review: 2023-03-27 14:49

Reviewer performed review: 2023-04-04 14:29

Review time: 7 Days and 23 Hours

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| Scientific quality | <input type="checkbox"/> Grade A: Excellent <input checked="" type="checkbox"/> Grade B: Very good <input type="checkbox"/> Grade C: Good <input type="checkbox"/> Grade D: Fair <input type="checkbox"/> Grade E: Do not publish |
| Novelty of this manuscript | <input checked="" type="checkbox"/> Grade A: Excellent <input type="checkbox"/> Grade B: Good <input type="checkbox"/> Grade C: Fair <input type="checkbox"/> Grade D: No novelty |
| Creativity or innovation of this manuscript | <input type="checkbox"/> Grade A: Excellent <input checked="" type="checkbox"/> Grade B: Good <input type="checkbox"/> Grade C: Fair <input type="checkbox"/> Grade D: No creativity or innovation |



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| Scientific significance of the conclusion in this manuscript | <input type="checkbox"/> Grade A: Excellent <input checked="" type="checkbox"/> Grade B: Good <input type="checkbox"/> Grade C: Fair <input type="checkbox"/> Grade D: No scientific significance |
| Language quality | <input type="checkbox"/> Grade A: Priority publishing <input checked="" type="checkbox"/> Grade B: Minor language polishing <input type="checkbox"/> Grade C: A great deal of language polishing <input type="checkbox"/> Grade D: Rejection |
| Conclusion | <input type="checkbox"/> Accept (High priority) <input type="checkbox"/> Accept (General priority) <input checked="" type="checkbox"/> Minor revision <input type="checkbox"/> Major revision <input type="checkbox"/> Rejection |
| Re-review | <input checked="" type="checkbox"/> Yes <input type="checkbox"/> No |
| Peer-reviewer statements | Peer-Review: <input checked="" type="checkbox"/> Anonymous <input type="checkbox"/> Onymous |
| | Conflicts-of-Interest: <input type="checkbox"/> Yes <input checked="" type="checkbox"/> No |

SPECIFIC COMMENTS TO AUTHORS

Comments: The authors reviewed the relation between Klotho and DR. They focused on the role of Klotho in DR, highlighting the importance of Klotho in maintaining retinal homeostasis and its positive effects on several mechanisms involved in DR onset and progression. Therefore, they proposed Klotho could be a novel biomarker and a good candidate for the treatment of DR. This manuscript is interesting and creative. I have several suggestions. 1. Please provide a figure concerning the signal pathway related with Klotho. 2. Please add the full name of POS when it first appears. 3. Please delete irrelevant part of Klotho and DR. Authors need to re-focus the and better structure the content. Especially, Table and figures could be an effective way to follow the topic directly.



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Peer-review model: Single blind

Reviewer’s code: 05111420

Position: Peer Reviewer

Academic degree: PhD

Professional title: Attending Doctor

Reviewer’s Country/Territory: China

Author’s Country/Territory: Italy

Manuscript submission date: 2023-02-16

Reviewer chosen by: Geng-Long Liu

Reviewer accepted review: 2023-03-31 02:41

Reviewer performed review: 2023-04-05 03:37

Review time: 5 Days

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| Scientific quality | <input type="checkbox"/> Grade A: Excellent <input type="checkbox"/> Grade B: Very good <input checked="" type="checkbox"/> Grade C: Good <input type="checkbox"/> Grade D: Fair <input type="checkbox"/> Grade E: Do not publish |
| Novelty of this manuscript | <input type="checkbox"/> Grade A: Excellent <input checked="" type="checkbox"/> Grade B: Good <input type="checkbox"/> Grade C: Fair <input type="checkbox"/> Grade D: No novelty |
| Creativity or innovation of this manuscript | <input type="checkbox"/> Grade A: Excellent <input checked="" type="checkbox"/> Grade B: Good <input type="checkbox"/> Grade C: Fair <input type="checkbox"/> Grade D: No creativity or innovation |



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| Language quality | <input type="checkbox"/> Grade A: Priority publishing <input checked="" type="checkbox"/> Grade B: Minor language polishing <input type="checkbox"/> Grade C: A great deal of language polishing <input type="checkbox"/> Grade D: Rejection |
| Conclusion | <input type="checkbox"/> Accept (High priority) <input type="checkbox"/> Accept (General priority) <input type="checkbox"/> Minor revision <input checked="" type="checkbox"/> Major revision <input type="checkbox"/> Rejection |
| Re-review | <input checked="" type="checkbox"/> Yes <input type="checkbox"/> No |
| Peer-reviewer statements | Peer-Review: <input checked="" type="checkbox"/> Anonymous <input type="checkbox"/> Onymous |
| | Conflicts-of-Interest: <input type="checkbox"/> Yes <input checked="" type="checkbox"/> No |

SPECIFIC COMMENTS TO AUTHORS

Thanks for the invitation for reviewing the paper. Major concerns: 1.The logical structure of the article is loose. There are 5 parts of this article:KLOTHO , KLOTHO AND DIABETES , DIABETIC RETINOPATHY , KLOTHO AND RETINAL HOMEOSTASIS, KLOTHO AND DIABETIC RETINOPATHY. As we know, the topic of the article is “klotho” and “diabetes retinopahthy”.Some part is a little bit digress from the main subject. Some parts can be merged into one part.For instance, in part “klotho”, author mentioned 3 proteins of klotho,which one is closely related to diabetes or diabetes retinopahthy should point out.In part “diabetic retinopathy” ,it contains some unnecessary repetition. If simply talk about “klotho” or diabetic retinopathy or diabtes and can’t sufficiently prove the relationship of “klotho” and “diabetes retinopahthy”, the novel point of this review can’t be shown and I will reject this article. 2.Insufficient literature citation. Only 20 out of the 85 references were published within the past 3 years, more fresh references were needed. The proportion of the literature in the last 5 years is better to be more than 50%, and try to avoid citing review articles as references.Search for lastest research of diabetic retionpathy,and figure out possible



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target with klotho. Page10, line28: About autophagy, more recent studies in diabetic patients can be further elaborated. 3.Add pictures and tables for display"Klotho,: therapeutic target; diabetic retinopathy" Minor concerns 1.Page4, line25: The logic here is not clear, the increased level of Klotho during the worsening of diabetic CKD versus the increased level of Klotho inhibit the progression of kidney diseases , this two conditions can be further elaborated. 2.Page4, line27: For the early biomarker of diabetic nephropathy (DN) , the author fail to explain exactly how Klotho can be detected and measured, and to what level can be called increase or decrease. 3.Page5, line20: Proliferative diabetic retinopathy (PDR) , the author should not start the name of a disedase with abbreviated term, wihch makes understanding of the sentence difficult. 4.Page8, line18: The logic here is not clear. The lower level of the index in diabetic patients with retinopathy does not mean that the index must be protective and relevant when the level is elevated. Final comment Klotho (Kl) is considered an antiaging gene.This paper reviews "koltho" from a new perspective that relationship between klotho and retinopathy.The conclusion of the paper is not convinced. This paper need major revision.



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Position: Peer Reviewer

Academic degree: MD

Professional title: Doctor

Reviewer's Country/Territory: China

Author's Country/Territory: Italy

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Review time: 13 Days

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| Scientific quality | <input type="checkbox"/> Grade A: Excellent <input checked="" type="checkbox"/> Grade B: Very good <input type="checkbox"/> Grade C: Good <input type="checkbox"/> Grade D: Fair <input type="checkbox"/> Grade E: Do not publish |
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| Language quality | <input checked="" type="checkbox"/> Grade A: Priority publishing <input type="checkbox"/> Grade B: Minor language polishing <input type="checkbox"/> Grade C: A great deal of language polishing <input type="checkbox"/> Grade D: Rejection |
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| Re-review | <input checked="" type="checkbox"/> Yes <input type="checkbox"/> No |
| Peer-reviewer statements | Peer-Review: <input checked="" type="checkbox"/> Anonymous <input type="checkbox"/> Onymous |
| | Conflicts-of-Interest: <input type="checkbox"/> Yes <input checked="" type="checkbox"/> No |

SPECIFIC COMMENTS TO AUTHORS

This manuscript summarizes the positive effect of Klotho on diabetic retinopathy. However, as a narrative review, this manuscript lacks a rigorous format and the authors are recommended to make revisions. Additionally, it is suggested that the authors delve deeper into the related targets and mechanisms of Klotho's effect on improving DR.