



PEER-REVIEW REPORT

Name of journal: *World Journal of Diabetes*

Manuscript NO: 101966

Title: Increased blood urea nitrogen levels and compromised peripheral nerve function in patients with type 2 diabetes

Provenance and peer review: Unsolicited Manuscript; Externally peer reviewed

Peer-review model: Single blind

Reviewer's code: 07918561

Position: Peer Reviewer

Academic degree: PhD

Professional title: Assistant Professor

Reviewer's Country/Territory: Iraq

Author's Country/Territory: China

Manuscript submission date: 2024-10-03

Reviewer chosen by: Yu Bai

Reviewer accepted review: 2024-10-28 01:24

Reviewer performed review: 2024-11-07 11:00

Review time: 10 Days and 9 Hours

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 Grade E: Do not publish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



Scientific significance of the conclusion in this manuscript	<input type="checkbox"/> Grade A: Excellent <input type="checkbox"/> Grade B: Good <input checked="" type="checkbox"/> Grade C: Fair <input type="checkbox"/> Grade D: No scientific significance
Language quality	<input type="checkbox"/> Grade A: Priority publishing <input type="checkbox"/> Grade B: Minor language polishing <input checked="" 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 type="checkbox"/> Yes <input checked="" 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

The letter provides constructive feedback on the manuscript exploring the role of BUN (blood urea nitrogen) as a risk factor for diabetic peripheral neuropathy (DPN) in type 2 diabetes (T2D). The main points of the feedback are: 1. Introduction: • It would help to briefly define DPN and explain how it develops, linking it to the study's exploration of risk factors like BUN. • The introduction should include a brief mention of known mechanisms behind DPN (e.g., oxidative stress, inflammation) to provide context for why studying BUN as a risk factor is important. • The mechanistic link between elevated BUN levels and DPN is underdeveloped. The introduction could elaborate on how BUN might contribute to vascular damage, inflammation, or renal dysfunction, which could affect nerve function. • The introduction should emphasize how identifying BUN as a risk factor could lead to earlier diagnosis or targeted treatments for DPN, potentially improving patient outcomes and reducing long-term complications. • The study's objective should be more clearly stated and specific research questions should be outlined to guide the reader's understanding of the study's aims. • The hypothesis could be made more specific, such as examining whether elevated BUN levels are associated



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with both the presence and severity of DPN, to provide clearer focus. 2. Methods: o Clarify participant recruitment and include a control group to differentiate diabetes-specific effects. o Address how confounding variables, such as medications, are controlled for. o Provide more details on standardization of nerve conduction measurements, handling of missing data, and statistical power analysis. 3. Results: The footnotes for figures should clearly explain key aspects of the data, including the methodologies, statistical analyses, and interpretation of results. They must contextualize the figure within the study, helping readers understand the significance of the findings and their potential impact on clinical practice and future research. The goal is to provide clarity and depth in the explanations, ensuring that the reader fully grasps the relevance and implications of the data presented in each figure. 4. Discussion: o Discuss the causal relationship between BUN and nerve dysfunction and the potential mechanisms involved. o Explore the clinical implications of using BUN as a diagnostic or prognostic tool for DPN. o Address the generalizability of findings and integrate BUN's relationship with other DPN risk factors like glycemic control and inflammation. o Suggest future research to investigate the specific mechanisms linking BUN to nerve damage in T2D.



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Reviewer’s code: 08339407

Position: Peer Reviewer

Academic degree: MD

Professional title: Assistant Professor, Senior Researcher

Reviewer’s Country/Territory: Indonesia

Author’s Country/Territory: China

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Reviewer chosen by: Hong-Xin Jiang

Reviewer accepted review: 2024-11-25 02:58

Reviewer performed review: 2024-11-26 22:52

Review time: 1 Day and 19 Hours

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
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	Conflicts-of-Interest: <input type="checkbox"/> Yes <input checked="" type="checkbox"/> No

SPECIFIC COMMENTS TO AUTHORS

For abstract Background: The statement "Increased blood urea nitrogen (BUN) levels have been shown to be associated with the incidence of type 2 diabetes (T2D)" lacks specificity and appears overly general. It should clarify whether BUN is an independent factor or merely associated with broader metabolic disturbances. Results: The trends for Z-scores (latency, amplitude, and NCV) are mentioned but lack specific statistical values to support the claims. Including key p-values or effect sizes would make the results more compelling. Conclusion: The statement "Monitoring BUN levels can help proactively identify the risk of peripheral nerve dysfunction early" is overly optimistic without explicitly linking it to actionable intervention For Introduction The introduction extensively discusses DPN but repeats information unnecessarily about its complications and prevalence. This redundancy detracts from the focus on BUN as a central hypothesis. The hypothesis that BUN contributes to peripheral nerve dysfunction in T2D is implied but not explicitly stated. This weakens the rationale for the study. Methods Patient Recruitment: While inclusion and exclusion criteria are detailed, the rationale for excluding conditions like anemia or vitamin B12 deficiency is not provided. This



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omission could raise questions about the generalizability of the findings. Z-Score Standardization: The justification for using Z-scores to analyze nerve function is not clearly explained. This may confuse readers unfamiliar with the method's advantages. Discussion The discussion heavily relies on speculation about mechanisms linking BUN to peripheral nerve dysfunction, such as oxidative stress and endothelial dysfunction, without direct evidence from this study. The statement that "Elevated BUN levels may increase the risk of compromised peripheral nerve function" is overly definitive for an observational study. The discussion should emphasize the need for future research to establish causality. The clinical implications are underdeveloped. Although BUN is identified as a potential biomarker, there is no clear explanation of how monitoring or reducing BUN would translate into improved outcomes for DPN patients. Results The trends presented in the tables and text often lack interpretation. For example, the increase in latency with higher BUN quartiles is statistically significant, but the clinical importance is not discussed. The correlation analyses (Table 2) show strong statistical results but do not address whether these correlations remain robust after adjusting for potential confounders like hydration status or dietary intake. Some trends, such as the association of BUN with NCV, appear weak despite being statistically significant (e.g., low r-values). This could be misleading without context.



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Reviewer's code: 06209780

Position: Peer Reviewer

Academic degree: MD

Professional title: Professor

Reviewer's Country/Territory: India

Author's Country/Territory: China

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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
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	Conflicts-of-Interest: <input type="checkbox"/> Yes <input checked="" type="checkbox"/> No

SPECIFIC COMMENTS TO AUTHORS

The article is very well written. 1 Title: The title contains important information about the study. The type of study to be included in the title/abstract as per STROBE guidelines. 2 Authors: The author’s details and affiliations are mentioned. 3 Abstract: The abstract reflects the importance, purpose and significant of the study. 4 Key Words: Keywords reflect the content of the manuscript. 5 Introduction: Introduction is written concisely with relevance to the study topic. The purpose of the study is clearly mentioned. Kindly don’t brand the participants as diabetic patients. It can be modified as patients with diabetes. 6 Materials and Methods/Experimental Procedure: Well written. The methods and procedures and sample analysis and statistical analysis are mentioned. How did the authors divide the patients into 4 groups? What is the cut off value BUN for each group? 7 Results: The results are understandable, and data are represented clearly. Statistics and interpretation of data are very well explained. The Table is represented as the format. All the correlation values are weak, kindly mention as weak correlation in the results. The authors have done the multivariable linear regression using BUN. My suggestion would be to do the multivariable linear regression



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using individual groups BUN with nerve latency, amplitude, and NCV; it will define the risk of BUN with DPN appropriately. 8 Discussion: Very well discussed. The results are discussed properly in comparison to other relevant studies. The limitations of the study are undoubtedly mentioned. Future perspective of the study is also mentioned. The authors need not to mention as their previous study in reference 16; instead they can mention as Xu F et al. found that lower levels of 1,5-anhydro-D-glucitol, a marker for short-term glycemic fluctuation, were significantly associated with compromised peripheral nerve function. 9 Conclusion: Conclusion is concise and clear. The study reports support the conclusion. 10 Acknowledgments: Acknowledgement is not mentioned. 11 References: references are relevant. The references are mentioned in order. Few of the references are more than 10 years old. Authors are requested to update the references. 12 Abbreviations: Abbreviations are mentioned. 13 Language: language quality is good. 14 Manuscript type: Observational study. 15 Scientific research ethics: Authors have mentioned the ethical approval details, study duration in the Methods.