Diabetes, Metabolic Syndrome and Obesity

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RESPONSE TO LETTER

Comment on: "Association Between the Hemoglobin Glycation Index (HGI) and Risk of Diabetic Nephropathy: A Retrospective Cohort Study" [Response to Letter]

Weiyi Zhou[1], Lingyu Zhang[2], Tongqiang Liu[1]

[1]Department of Nephrology, The Affiliated Changzhou Second People's Hospital of Nanjing Medical University, Changzhou Medical Center, Changzhou, Jiangsu, People's Republic of China; [2]Department of Endocrinology, The Affiliated Changzhou Second People's Hospital of Nanjing Medical University, Changzhou Medical Center, Changzhou, Jiangsu, People's Republic of China

Correspondence: Tongqiang Liu, Department of Nephrology, The Affiliated Changzhou Second People's Hospital of Nanjing Medical University, 68 Middle Gehu Road, Changzhou, Jiangsu, 213000, People's Republic of China, Email liuyf1106@126.com

Dear editor

We have received the correspondence from Ren et al regarding our recently published study and appreciate their insightful comments. Our research was to reveal a significant U-shaped relationship between the Hemoglobin Glycation Index (HGI) and the risk of Diabetic Nephropathy (DN) in patients with Type 2 Diabetes Mellitus.[1,2]

In response to the two main points raised in the letter, we provide the following clarifications:

First, regarding the potential interaction between HGI and different glucose-lowering treatment regimens, we have conducted supplementary analyses as suggested. We constructed both a base model and an extended model incorporating interaction terms between HGI and specific medications (Table 1). The results show that the association between HGI and DN was not significantly modified by the use of insulin, metformin, or DPP-4 inhibitors (Interaction *P*-values = 0.3801, 0.1028, and 0.2, respectively). It is important to note that our study was conducted before newer antidiabetic agents with demonstrated renal benefits, such as SGLT-2 inhibitors and GLP-1 receptor agonists, were widely available in China.[3,4] Consequently, our study could not evaluate their potential interaction with HGI. Subsequent research should indeed prioritize investigating these novel therapeutic classes.

Second, concerning the clinical operability and generalizability of HGI, we fully agree with the points raised. While the linear regression model we developed, based on fasting blood glucose and HbA1c, performed well within our cohort, its generalizability across diverse ethnicities, age groups, and comorbid conditions certainly requires further validation. Particularly noteworthy is the strong association between HGI and hypertension, which represents a crucial consideration for clinical application.[5] The question of whether the HGI threshold should be adjusted for diabetic patients with comorbidities such as hypertension is a highly relevant clinical direction. We encourage research teams from different centers to utilize

Table 1 Interaction Between HGI and Drugs and Its *P*-value

Interaction Term	*P* for Interaction
HGI*Insulin	0.3801
HGI*Metformin	0.1028
HGI* DPP-4 inhibitors	0.2

Abbreviations: HGI, Hemoglobin Glycation Index; DPP-4, Dipeptidyl peptidase-4.

Received: 1 October 2025
Accepted: 2 October 2025
Published: 22 October 2025

prospective designs and more comprehensive clinical data to jointly develop and validate more individualized and universally applicable HGI assessment tools, thereby facilitating its transition from a research indicator to a practical clinical instrument.

We thank the commentators once again for their valuable suggestions, which have significantly enhanced our discussion and provided clear direction for future research.

Data Sharing Statement

The data used to support the findings of this study are available from the corresponding author upon reasonable request.

Author Contributions

All authors approved of the final version accepted for publication; agreed on the journal to which this communication was submitted; and agree to be accountable for all aspects of the work. WZ: Formal analysis, Writing – original draft; LZ: Formal analysis, Writing – review and editing; TL: Conceptualization, Writing – review and editing.

Funding

The authors declare that no funds, grants, or other support were received during the preparation of this communication.

Disclosure

The authors declare no competing interests.

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https://doi.org/10.2147/DMSO.S571661