Diabetes, Metabolic Syndrome and Obesity

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LETTER

Comment on: Comparative Evaluation of Responsiveness of Insulin Counter-Regulatory Hormones and Insulin Resistance to Hypoglycemia in Newly Diagnosed Type 1 Diabetes Mellitus Man [Letter]

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Dear editor

We read with interest the article by Zhou et al concerning counter-regulatory hormone responses in newly diagnosed men with type 1 diabetes mellitus (T1DM) using a hyperinsulinemic–hypoglycemic clamp.[1] While clinically relevant, several methodological issues weaken the causal interpretation of their results.

First, the authors treat the glucose infusion rate during hypoglycemia (M value) as a direct index of insulin sensitivity, correlating it with hormonal changes.[1] However, the accepted reference for quantifying insulin resistance is the hyperinsulinemic–euglycemic clamp performed under stable normoglycemia.[2,3] During a hypoglycemic clamp, counter-regulatory hormones activate to reduce glucose uptake; thus, their effects are inherently embedded in the observed M value.[1] Interpreting negative correlations between M and hormone responses as evidence that higher hormone levels cause insulin resistance risks circular reasoning, as both arise from the same induced hypoglycemic stress. These data represent associations, not proof of causality.[2,3]

Second, the statistical analysis complicates interpretation. Numerous comparisons are presented without correction for multiple testing, increasing the risk of spurious significance in a small cohort.[1] Furthermore, the multivariable regression is summarized without providing full outputs (coefficients, confidence intervals), preventing readers from judging model robustness.[2] Omission of these details is problematic, especially when used to downplay univariate associations.[1]

Finally, hormonal profiling and confounding assessment are incomplete. Sparse sampling at only 0 and 30 minutes may miss true peaks.[1] Catecholamines, central to hypoglycemic counter-regulation, were not assessed, providing only a partial view of the counter-regulatory axis.[4,5] Furthermore, limited information on potential confounders like prior hypoglycemia history restricts generalizability in this small cohort.[1,4]

In summary, due to using a hypoglycemic M value as a stand-alone index of insulin resistance and the methodological limitations noted, the causal implications of their findings remain uncertain.[1] Clarifying these roles requires separate euglycemic and hypoglycemic clamps, rigorous statistical reporting, broader hormonal panels with finer sampling, and thorough addressing of confounding.

Data Sharing Statement

No new data were generated or analyzed in this communication.

Received: 1 December 2025
Accepted: 3 December 2025
Published: 11 December 2025

Author Contributions

Lu Xing Xu and Yong Gang Duan: Conceptualization; Writing – original draft. Xue Lin Wang: Conceptualization, Investigation, Writing – review & editing.

All authors gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

Funding

The authors declare that no funding was received for this article.

Disclosure

The authors report no conflicts of interest in this communication.

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https://doi.org/10.2147/DMSO.S585625