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Author(s)' Response to Comments on "Effect of Iron Deficiency Anemia on HbA1c in Non-Diabetics: An Analytical Study from Eastern India"

Thank you for your interest in our article titled "Effect of Iron Deficiency Anemia on HbA1c in Non-Diabetics: An Analytical Study from Eastern India"[1] and for your thoughtful commentary. We appreciate the opportunity to address the points raised.

Our cross-sectional analytical study demonstrated an inverse correlation between HbA1c and iron deficiency anemia in non-diabetic individuals. While patients were managed according to standard guidelines based on the severity of anemia and iron deficiency, data on treatment outcomes were not incorporated due to the inherent nature of the study and its primary focus on baseline observations. Nonetheless, it is now well-established in the literature that iron supplementation therapy effectively lowers HbA1c levels and is beneficial for managing iron deficiency anemia (IDA) in patients with falsely diagnosed poor glycemic control.[2]

Beyond the variations attributed to diverse medical conditions and technical factors (as highlighted in our study), HbA1c also fails to precisely reflect fluctuations in blood glucose levels and hypoglycemic episodes. The use of predicted HbA1c derived from fasting plasma glucose (FPG) is a promising approach; however, the efficacy of FPG in calculating predicted HbA1c may demonstrate variability.

The study by Ghazanfari et al[3] found that the association between HbA1c and FPG was relatively strong, particularly in diabetic subjects. The crude and adjusted regression coefficients for FPG in predicting HbA1c were higher in the FPG > 126 mg/dL subgroup than those with normal FPG levels (crude coefficients: 0.18 versus 0.13, adjusted coefficients: 0.18 versus 0.09). This suggests that FPG predicts HbA1c more accurately in diabetic individuals, while the relationship is weaker in those with normal FPG levels. Studies also suggest that mean blood glucose (MBG) correlates with HbA1c and predicted HbA1c can be calculated by inputting data-matched MBG into a population regression equation, demonstrating potential utility for assessing diabetes risk and complications.[4] Additionally, Rohlfing et al[5] found a strong correlation between MBG and HbA1c, particularly in the afternoon and evening readings, with an *R*-value of 0.82, while the correlation was weaker for morning time values (pre-breakfast, post-breakfast, and pre-lunch). The hemoglobin glycation index (HGI = observed HbA1c – predicted HbA1c) has been used in various studies. However, findings from major studies, such as the DEVOTE trial by Klein et al[6] and the ADVANCE trial by van Steen, Sigrid C et al [7], have indicated that actual HbA1c, may be a more reliable predictor of major adverse cardiovascular events than HGI.[7] It is also important to recognize the limitations of using predicted HbA1c. Desai and Bubanale[8] observed significant discrepancies when comparing predicted HbA1c to actual measured values, suggesting it may not be a suitable alternative. Similarly, Temsch et al[9] highlighted that mathematical models for calculating HbA1c, such as those employing truncated Fourier series, may result in misinterpretations, particularly in patients with variable glucose control.

For patients with conditions that impact the relationship between HbA1c and FPG, alternative markers like fructosamine, glycated albumin, and 1,5 anhydroglucitol may be valuable. These reflect shorter-term glycemia over 2-3 weeks and are not affected by erythrocyte lifespan or hemoglobin variants. Additionally, advanced glycation end products have the potential to identify patients at risk of diabetes complications independent of HbA1c.

In conclusion, while the use of predicted HbA1c is an interesting and potentially cost-effective strategy in certain situations, its limitations must be acknowledged. Comprehensive

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monitoring, supplemented by clinical assessment, remains essential for accurate diabetes management.

Availability of Data and Materials: The data that support the findings of this study are available on request from the corresponding author.

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