Journal of Medical Surgical and Allied Sciences

Case Report

Discordantly low hemoglobin A1c in the context of marked hyperglycemia

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Volume: 2, Issue: 1, Pages: 1-4
DOI: https://doi.org/10.37446/jmedsurg/cr/2.1.2024.1-4
Received: 21 January 2024 / Accepted: 10 May 2024 / Published: 30 June 2024

Background: Hemoglobin A1c (HbA1c) acts as the primary biomarker for evaluating long-term glucose regulation. Nevertheless, high concentrations of fetal hemoglobin (HbF) can affect the accuracy of HbA1c assays in a manner dependent on the method used, possibly leading to falsely low HbA1c readings even when there is considerable hyperglycemia.

Case Presentation: The outpatients showed significant hyperglycemia (random blood glucose: 433 mg/dL) and highly positive urine ketones (+++), aligning with a diagnosis of diabetic ketoacidosis. Ironically, HbA1c obtained through standard immunoassay was 6.5%, which is categorized within the non-diabetic range. Follow-up hemoglobin fractionation showed an increased fetal hemoglobin (HbF) concentration of 4.1%, causing worry about assay interference and leading to a reassessment of the HbA1c outcome.

Conclusion: Elevated fetal hemoglobin (>4%) can falsely lower HbA1c, especially with immunoassay or boronate-affinity methods. Ion-exchange HPLC or electrophoresis is recommended, and clinicians should integrate alternative glycemic markers or continuous glucose monitoring to guide management accurately.

Keywords: *hemoglobin A1c, fetal hemoglobin, HbF interference, Ion-exchange HPLC, capillary electrophoresis, glycemic markers*

Introduction

Hemoglobin A1c (HbA1c) is the gold-standard biomarker for assessing long-term glycemic control, as it reflects the average proportion of glycated adult hemoglobin (HbA) over the preceding 2–3 months. Nevertheless, its analytical accuracy can be compromised by hemoglobin variants or structural alterations, particularly in the presence of elevated fetal hemoglobin (HbF). Elevated HbF has been shown to interfere with HbA1c assays, producing spuriously low HbA1c values depending on the assay method used (Gallagher et al., 2009; Little et al., 2012; Abdalla et al., 2023). In the general population, modest elevations of HbF are not uncommon. For example, genome-wide association studies estimate that approximately 10–15% of individuals may display a moderate increase in HbF (~0.8–5%) even in the

absence of hemoglobinopathies (Galarneau et al., 2007). Numerous studies have investigated assay-specific interference affecting HbA1c measurement. Ion-exchange high-performance liquid chromatography (HPLC) platforms, such as the Tosoh G7 and G8 systems, generally maintain analytical accuracy in the presence of elevated fetal hemoglobin (HbF) concentrations up to 15–30%, with minimal clinically significant bias (Jeppsson et al., 2016). In contrast, boronate-affinity chromatography and immunoassay-based methods are more susceptible to underestimating HbA1c levels when HbF is elevated, due to reduced glycation of gamma chains and decreased antibody binding (Nitta et al., 2015). Case reports further corroborate that increased HbF can result in deceptively low HbA1c values, potentially obscuring the diagnosis or severity of underlying hyperglycemia (Adekanmbi et al., 2016; Ahmed et al., 2022). Here, we present a case where significantly elevated random blood glucose (RBS) and urinary ketones, combined with a low HbA1c (4.5%), prompted further investigation that uncovered HbF at 4.1%, highlighting the potential for diagnostic pitfalls and the need for alternative glycemic markers.

Case presentation

An outpatient admitted to Wad Medani Teaching Hospital, suffering from common signs of thirst, polyuria, blurring of vision, and weight loss. No prior documented diagnosis of diabetes; presenting due to routine random blood glucose measurement and lab anomalies. Laboratory findings showed significant hyperglycemia (random blood glucose: 433 mg/dL) and highly positive urine ketones (+++), aligning with a diagnosis of diabetic ketoacidosis. Ironically, HbA1c obtained through standard immunoassay was 6.5%, which is categorized within the non-diabetic range. Follow-up hemoglobin fractionation showed an increased fetal hemoglobin (HbF) concentration of 4.1%, causing worry about assay interference and leading to a reassessment of the HbA1c outcome. Despite severe hyperglycemia and ketosis, likely suggestive of diabetic ketoacidosis, the low HbA1c was discordant, indicating interference. Hemoglobin fractionation revealed elevated HbF (4.1%), sufficient to distort HbA1c results depending on assay method. Given the assay type was a standard immunoassay or boronate-affinity platform (as per lab documentation), the observed HbF interference aligns with known limitations. Recognized HbA1c was unreliable in this context. So recommended to use fructosamine or glycated albumin for better short-term glycemic monitoring and consider ion-exchange HPLC or capillary electrophoresis for more accurate HbA1c in the presence of HbF anomalies (Figure 1). The patient was referred for continuous glucose monitoring (CGM) and repeat assessment with alternate glycemic markers. Counseling on potential diabetic ketoacidosis and follow-up planning were initiated.

Table 1. Laboratory findings

Test	Results	Reference Range
Random Blood Sugar (RBS)	433 mg/dL	80 – 180 mg/dL
Urine Glucose	+++	Negative
Urine Acetone (Ketones)	+++	Negative
HbA1c	6.5 %	< 6.6 % (non-diabetic)
Hemoglobin F (HbF)	4.1 %	~0.0 – 1.0 %
Potassium (K^+)	4.0 mEq/L	3.5 – 5.3 mEq/L

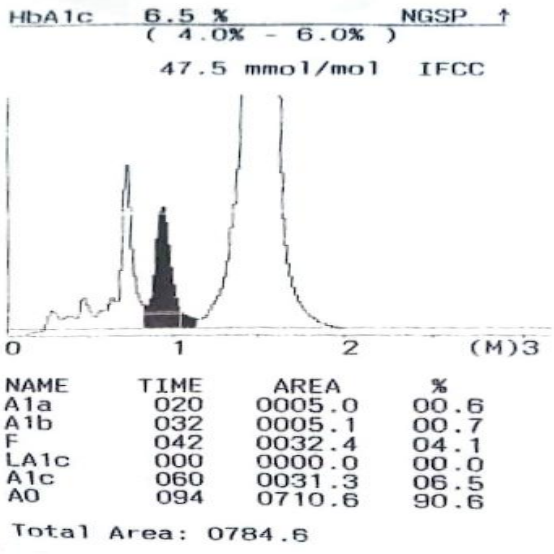

Figure 1. Results of HPLC (Laffinite II instrument)

Discussion

Hemoglobin A1c (HbA1c) is widely recognized as the gold-standard biomarker for long-term glycemic control, reflecting the proportion of glycated adult hemoglobin (HbA) over the preceding 2–3 months (Little et al., 2014; Ibrahim et al., 2021). Its clinical utility relies not only on its ability to correlate with average glucose but also on the assumption of normal hemoglobin composition. However, structural hemoglobin variants or alterations, such as elevated fetal hemoglobin (HbF), can significantly interfere with assay accuracy, leading to misinterpretation of glycemic status (Nitta et al., 2015). In the present case, HbF levels exceeding 4% resulted in spuriously low HbA1c values, which could have masked the severity of hyperglycemia and potentially delayed appropriate management. HbF has fewer accessible glycation sites relative to adult hemoglobin A. Its elevated proportion reduces the fraction of HbA available for glycation. Consequently, assays unable to differentiate HbF from HbA (e.g., boronate-affinity, immunoassay) report falsely low HbA1c values even in the presence of persistent hyperglycemia (Harris et al., 2021). This case underscores the established limitation of HbA1c as a glycemic biomarker in the presence of elevated fetal hemoglobin (HbF). The degree of interference from HbF varies according to the analytical methodology. Immunoassay- and boronate-affinity–based techniques are particularly vulnerable to underestimating HbA1c in the presence of elevated HbF due to reduced glycation of gamma chains and diminished antibody binding efficiency (Nitta et al., 2015; Little et al., 2014). Conversely, ion-exchange high-performance liquid chromatography (HPLC) platforms, such as Tosoh G7/G8 systems, and capillary electrophoresis are more robust, maintaining analytical accuracy even with HbF concentrations up to 15–30% (Jeppsson et al., 2016). These findings underscore the importance of selecting an appropriate assay based on the patient's hemoglobin profile to avoid erroneous results. Clinically, relying solely on HbA1c in individuals with elevated HbF can have significant implications. Underestimation of glycemic burden may lead to under-treatment, suboptimal glycemic control, and increased risk of complications. To mitigate these risks, clinicians should adopt a multifaceted approach: careful assay selection, consideration of alternative glycemic indices such as fructosamine or glycated albumin, and the use of continuous glucose monitoring (CGM) when appropriate (Gallagher et al., 2009; Shimizu et al., 2016). Additionally, awareness of hereditary persistence of fetal hemoglobin (HPFH), hemoglobinopathies, or recent transfusions is essential, as these factors may further alter HbA1c reliability. This case further emphasizes the necessity of individualized laboratory interpretation. Even with widely accepted biomarkers like HbA1c, patient-specific factors—especially hemoglobin composition must be considered. Integrating laboratory data with clinical context and complementary diagnostic tools ensures accurate assessment of glycemic control and guides therapeutic decisions more effectively. Ultimately, the recognition of HbF-related interference highlights a broader principle in clinical laboratory medicine: the critical importance of understanding assay limitations and patient-specific variables to avoid diagnostic errors. HbF levels exceeding 4% led to spuriously low HbA1c values, particularly when measured by immunoassay- or boronate-affinity–based platforms. The ion-exchange HPLC or capillary electrophoresis provides more reliable results in the presence of elevated HbF. Therefore, clinicians should exercise caution in interpreting HbA1c under such circumstances and avoid relying on it as a sole marker of glycemic control. Instead, assay selection should be guided by the patient's hemoglobin profile, and complementary tools such as fructosamine, glycated albumin, or continuous glucose monitoring should be incorporated to ensure accurate assessment and appropriate management of hyperglycemia.

Conclusion

Elevated fetal hemoglobin (>4%) can falsely lower HbA1c, especially with immunoassay or boronate-affinity methods. Ion-exchange HPLC or electrophoresis is recommended, and clinicians should integrate alternative glycemic markers or continuous glucose monitoring to guide management accurately.

Author contribution

Each author made a significant intellectual contribution, reviewed and approved the final manuscript version, and consented to take responsibility for all elements of the work.

Acknowledgment

The authors would like to acknowledge the team of Elmomayaz Advanced Medical Laboratories for their great efforts.

Funding

This report did not have any specific grant from funding agencies in the public, commercial or not-for-profit sectors.

AI tool declaration

The authors declare that no AI tools were used to generate scientific content, data interpretation, or reference citations in this manuscript. However, AI-assisted tools such as Grammarly, ChatGPT, and QuillBot were used solely for grammar correction, language refinement, and improving readability. All scientific content was written by the authors, who carefully reviewed and verified the manuscript for accuracy, originality, and completeness.

Conflict of interest

The authors declare no conflict of interest. The manuscript has not been submitted for publication in other journal.

Ethical concern and Informed consent

All research methods received approval from the Research and Ethics Committees (REC) of the Ministry of Health, Gezira State, Sudan (no. 16/2024). All procedures conducted in research involving human subjects adhered to the ethical guidelines set by the institutional and/or national research committees, along with the Helsinki Declaration. Written informed consent was obtained from the patient's parents.

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