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Discordantly Low Hemoglobin A1c in the Context of Marked Hyperglycemia: A Case Report Implicating Elevated Fetal Hemoglobin (4.1%)

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Abstract

Hemoglobin A1c (HbA1c) is main biomarker for assessing long-term hypo and hyperglycemic management. However, depending on the technique, elevated levels of fetal hemoglobin (HbF) can impact the precision of HbA1c tests, potentially producing deceptively low HbA1c values even in cases of significant hyperglycemia. An outpatient evaluated on 2025-06-16 had highly positive urine ketones (+++) and significant hyperglycemia (random blood glucose: 433 mg/dL), which are consistent with a diagnosis of diabetic ketoacidosis. Paradoxically, the HbA1c measured by conventional immunoassay was 6.5%, falling into the non-diabetic category. An elevated fetal hemoglobin (HbF) concentration of 4.1% was revealed by follow-up hemoglobin fractionation, raising concerns about assay interference and prompting a reevaluation of the HbA1c result. Elevated HbF hemoglobin of greater than 4% can mistakenly reduce HbA1c, particularly when employing immunoassay or boronate-affinity methods. To precisely guide management, clinicians should incorporate other glycemic indicators or continuous glucose monitoring, and ion-exchange HPLC or electrophoresis is advised.

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). However, hemoglobin variations or structural changes may impair its analytical precision, especially when fetal hemoglobin (HbF) levels are high. Depending on the assay technique employed, elevated HbF has been demonstrated to disrupt HbA1c tests, resulting in abnormally low HbA1c readings (Gallagher et al., 2009; Little et al., 2012; Abdalla et al., 2023). Low levels of HbF are typical in the general population. For instance, even in the absence of hemoglobinopathies, genome-wide association studies suggest that roughly 10–15% of people may have a mild rise in HbF (~0.8–5%) (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; Aktas et al., 2024). 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.

Materials and methods

Case Presentation

An outpatient admitted to Wad Medani Teaching Hospital on June 2025 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. 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

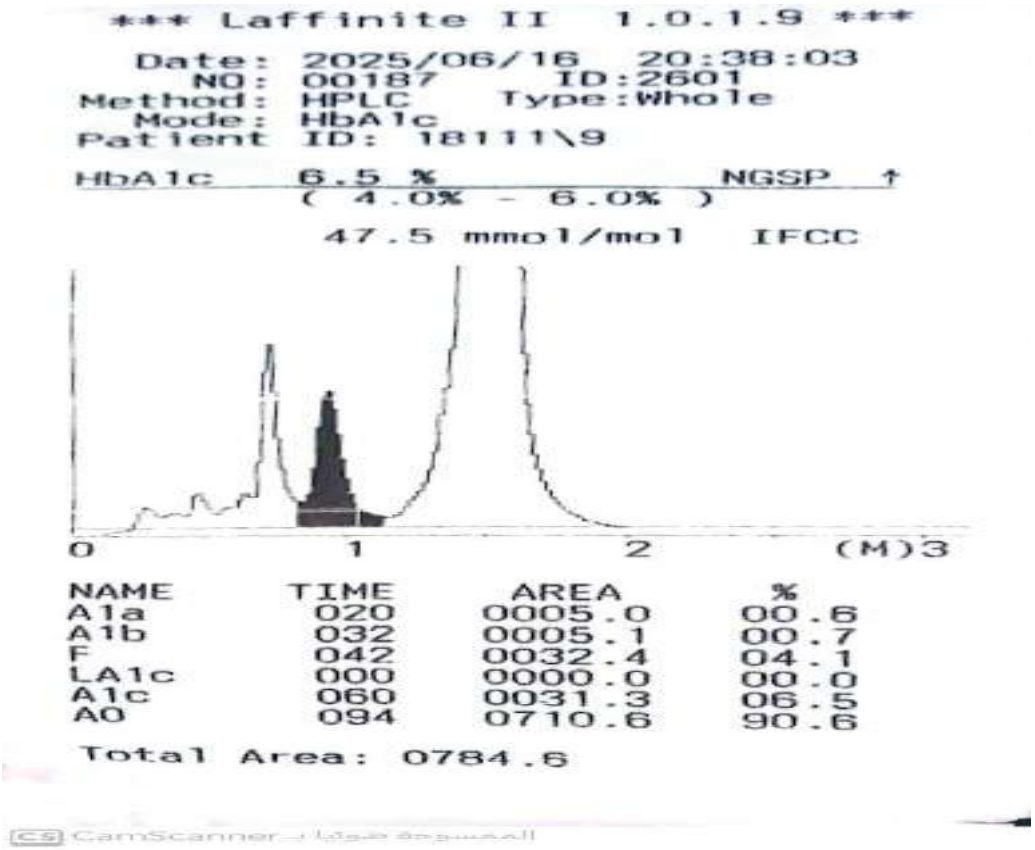

Figure 1: Results of HPLC (Laffinite II instrument)

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; Marin et al., 2024). This case underscores the established limitation of HbA1c as a glycemic biomarker in the presence of elevated fetal hemoglobin (HbF). The analytical technique affects how much HbF interference there is. Because of decreased gamma chain glycation and decreased antibody binding effectiveness, immunoassay and boronate affinity-based methods are especially susceptible to underestimating HbA1c when HbF is increased (Nitta et al., 2015; Little et al., 2014). On the other hand, capillary electrophoresis and ion-exchange high-performance liquid chromatography (HPLC) platforms, including Tosoh G7/G8 systems, are more reliable and can maintain analytical accuracy even at 10–30% HbF concentrations (Jeppsson et al., 2016; Di Resta et al., 2024). These results highlight how crucial it is to choose the right assay depending on the patient's hemoglobin profile in order to prevent inaccurate results.

In the clinical setting, using HbA1c alone in patients with high HbF can have serious consequences. Glycemic burden underestimation can result in inadequate treatment, less than ideal glycemic control, and a higher risk of complications. Clinicians should take a multifaceted approach to reducing these risks, which includes using continuous glucose monitoring (CGM) when necessary, choosing assays carefully, and taking into account alternative glycemic indices like fructosamine or glycated albumin (Gallagher et al., 2009; Shimizu et al., 2016). Furthermore, as these factors may further change HbA1c reliability, it is crucial to be aware of hemoglobinopathies, recent transfusions, and hereditary persistence of fetal hemoglobin (HPFH). This instance highlights even more how important customized laboratory interpretation is. Patient-specific characteristics, particularly hemoglobin composition, must be taken into account even when using commonly used indicators such as HbA1c. Accurate evaluation of glycemic control and better therapeutic decision-making are ensured by integrating laboratory data with clinical context and supplementary diagnostic tools. Finally, the identification of HbF-related interference draws attention to a more general idea in clinical laboratory medicine: in order to prevent diagnostic errors, it is crucial to comprehend assay limitations and patient-specific factors. HbF levels above 4% resulted in erroneously low HbA1c results, especially when assessed using platforms based on boronate affinity or immunoassay. When HbF is increased, capillary electrophoresis or ion-exchange HPLC yield more accurate results. As a result, physicians should be cautious when interpreting HbA1c in these situations and refrain from using it as the only indicator of glycemic control. To guarantee accurate assessment and proper management of hyperglycemia, the patient's hemoglobin profile should instead serve as the basis for test selection. Complementary instruments like fructosamine, glycated albumin, or continuous glucose monitoring should also be included.

Conclusion

Elevated HbF hemoglobin of greater than 4% can mistakenly reduce HbA1c, particularly when employing immunoassay or boronate-affinity methods. To precisely guide management, clinicians should incorporate other glycemic indicators or continuous glucose monitoring, and ion-exchange HPLC or electrophoresis is advised.

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Ethics Approval

All research methods received approval from the Research and Ethics Committees (REC) of the Ministry of Health (No: 15-6-2025), Gezira State, Sudan.

Conflicting Interests

The authors have stated that there are no competing interests.

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