World Journal of Advanced Research and Reviews
eISSN: 2581-9615 CODEN (USA): WJARAI
Cross Ref DOI: 10.30574/wjarr
Journal homepage: https://wjarr.com/

(CASE REPORT)

Falsely Low Hba1c in a Patient with Elevated Blood Glucose Levels: Diagnostic Challenges in Hemoglobinopathies: A Case Report

Anjali S [1,*], Achsah Achu Benoy [1] and Mohan Varghese [2]

[1] *Nazareth College of Pharmacy, Othera, Thiruvalla, Kerala.*
[2] *Believers Church Medical College Hospital, Thiruvalla, Kerala.*

World Journal of Advanced Research and Reviews, 2026, 30(02), 1289-1293

Publication history: Received on 07 April 2026; revised on 15 May 2026; accepted on 18 May 2026

Article DOI: https://doi.org/10.30574/wjarr.2026.30.2.1365

Abstract

Glycated haemoglobin (HbA1c) is commonly used to assess long-term glycaemic control in patients with diabetes mellitus; however, red blood cell survival and haemoglobin variation affects the accuracy of glycated haemoglobin (HbA1c). We present a middle-aged man with a duration of four-year history of type 2 diabetes mellitus who was admitted for left lower limb cellulitis. Although insulin therapy had to be given to manage persistently elevated blood glucose levels, the HbA1c was unusually low at 4.6%. This discrepancy prompted further investigations. Peripheral blood smear revealed microcytic hypochromic anemia with anisopoikilocytosis and associated iron and folate deficiencies. High-performance liquid chromatography demonstrated reduced hemoglobin A, elevated haemoglobin A_2, increased fetal haemoglobin, and abnormal hemoglobin fractions suggestive of an underlying hemoglobinopathy..

Keywords: HbA1c discordance; Hemoglobinopathies; Falsely low HbA1c; Type 2 diabetes mellitus; High-performance liquid chromatography

1. Introduction

Glycated haemoglobin (HbA1c) is the cornerstone for assessing long-term glycaemic control in patients with diabetes mellitus [1], reflecting average plasma glucose levels over the preceding 2–3 months. Normal haemoglobin composition and red blood cell (RBC) lifespan are requirements for its reliability. Conditions that alter haemoglobin structure or erythrocyte turnover can result in discordance between HbA1c values and true glycaemic status, potentially leading to inappropriate clinical decisions [1,2].

Hemoglobinopathies are a well-recognised but rarely overlooked cause of falsely low or misleading HbA1c values [2,3]. Disorders such as β-thalassaemia and compound heterozygous haemoglobin variants are characterized by reduced haemoglobin A (HbA) with compensatory elevation of haemoglobin A_2 (HbA_2) and, occasionally, increased fetal haemoglobin (HbF). High-performance liquid chromatography (HPLC), commonly used for HbA1c estimation, can detect these abnormal haemoglobin fractions; however, variant haemoglobin may interfere with HbA1c measurement due to co-elution or altered glycation kinetics [3]. In addition to analytical interference, shortened RBC survival in hemoglobinopathies reduces glycation time, further contributing to spuriously low HbA1c levels despite persistent hyperglycaemia. Coexisting iron deficiency anaemia may compound this effect by altering erythropoiesis and red cell turnover [4,5].

This case highlights the importance of recognising haemoglobin variants on HPLC when HbA1c values are discordant with clinical glycaemic status.

* Corresponding author: Anjali S

2. Case report

A middle-aged gentleman presented to the OPD department with complaints of left lower limb cellulitis. He had a medical history of type 2 diabetes mellitus, systemic hypertension, road traffic accident and varicose vein surgery.

On clinical examination, his vital parameters were normal. The systemic examination revealed nothing abnormal. On local examination it revealed features consistent with left lower limb cellulitis. Laboratory investigations showed anemia (HB-10.2) and leucocytosis (TLC- 14370). A peripheral blood smear showed neutrophilic leucocytosis and

mild microcytic hypochromic anaemia. Low serum iron, low total iron binding capacity and low transferrin saturation were found in iron studies, co-existential suggestive of iron deficiency anaemia. Folate deficiency was also revealed on further investigation.

Venous Doppler study was performed for left lower limb to rule out deep vein thrombosis and showed no evidence of thrombosis, with diffuse subcutaneous edema involving the leg and foot. Ultrasonography of abdomen and pelvis have an impression of mild fatty liver and normal spleen life. No abnormal growths were seen in blood cultures. The patient was managed with intravenous antibiotics, insulin, oral hypoglycaemic agents, and supportive care.

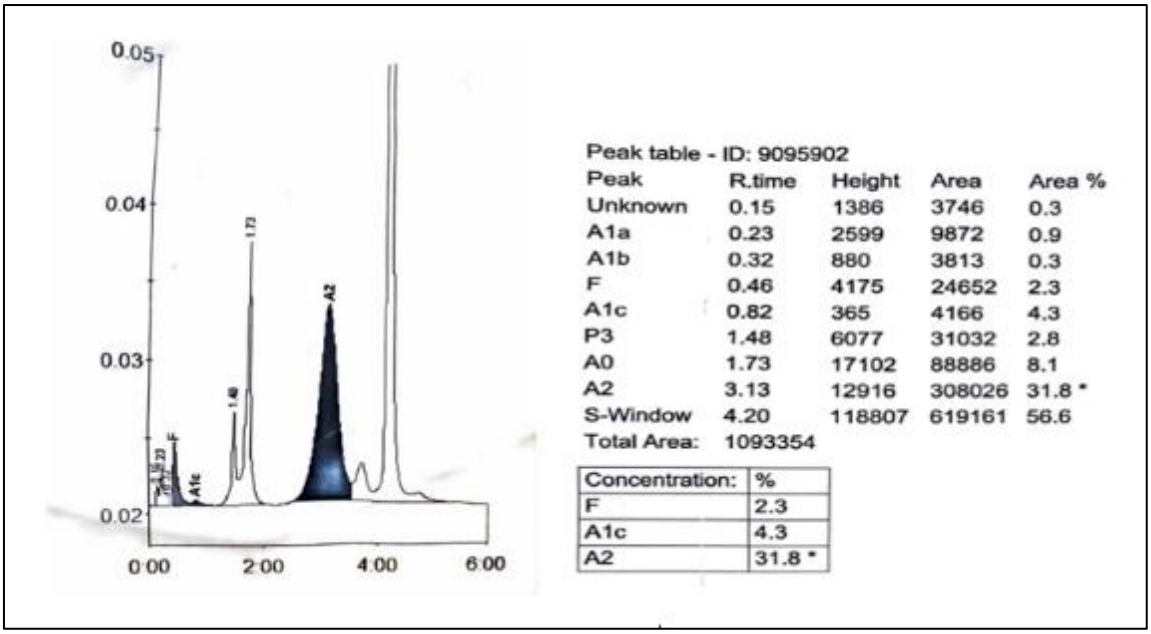
During the investigations, an unexpectedly low HbA1C value of 4.6% was noted as the patient already a known case of T2DM requiring insulins and oral hypoglycaemic agents, raising suspicions of falsely low HbA1C. Considering this discordance between clinical glycaemic status and HbA1C, haemoglobin variant analysis by high- performance liquid chromatography (HPLC) was performed. HPLC revealed significantly reduced HbA at 13.9%, markedly elevated HbA2 at 31.8%, and increased HbF at 2.3%. The chromatogram also showed the presence of abnormal haemoglobin fractions, including HbS(56.6)-related peaks. Peripheral smear findings of target cells, anisopoikilocytosis, and microcytosis supported an underlying hemoglobinopathy.

This patient's falsely low HbA1C was due to irregular haemoglobin fractions and decreased red blood cell lifespan interfering with HbA1C estimation by HPLC. Variance in the HbA1C readings may have been worsened by coexisting iron deficiency anemia.

Table 1 Initial Laboratory Investigations

Parameters	Results	Reference range
Haemoglobin	10.3	12-17 gm/dL
RBC count	4.29	4.30- 5.60 million
PCV	29.6	38 -48 %
MCV	69	80-100 fL
MCH	24	27-34 pg
MCHC	34.8	31-37 g/dL
RDW	14.2	12.10- 14.00
TLC	14470	4000-11000 /µL
Iron, Total	20.90	70-180 ug/dL
% saturation (%TSAT), serum	10.46	25-50 %

In this case a markedly low HbA1c of 4.6% was observed despite established type 2 diabetes mellitus requiring insulin therapy. HPLC analysis showed inappropriate haemoglobin fractions corresponding with a compound heterozygous hemoglobinopathy, probably the HbS/β-thalassemia trait, and considerably reduced HbA with markedly high HbA2 and increased HbF.



Peak table - ID: 9095902

Peak	R.time	Height	Area	Area %
Unknown	0.15	1386	3746	0.3
A1a	0.23	2599	9872	0.9
A1b	0.32	880	3813	0.3
F	0.46	4175	24652	2.3
A1c	0.82	365	4166	4.3
P3	1.48	6077	31032	2.8
A0	1.73	17102	88886	8.1
A2	3.13	12916	308026	31.8 *
S-Window	4.20	118807	619161	56.6
Total Area:	1093354			

Concentration:	%
F	2.3
A1c	4.3
A2	31.8 *

Figure 1 HPLC-variant Analysis

3. Discussion

The HbA1c value of patients with have to be carefully assessed since abnormal red blood cell dynamics and analytical interference can both provide incorrect outcome [2,3]. The pateint in this current case has noticeably low HbA1c value of 4.6%, even though they had T2DM and insulin therapy. A compound heterozygous HbA hemoglobinopathy, most likely the HbS/β-thalassemia phenotype [6,7], was shown by HPLC analysis as having unsuitable hemoglobin fractions that were significantly reduced with noticeably elevated HbA2 and increased HbF.

Patients with haemoglobinpathies typically have associated haematological problems, even though some HbA1c assay methods may not be influenced directly by haemoglobin variations. In this patient peripheral smear and iron investigations revealed microcytic hypochromic anemia with iron and folate deficiencies, which has been related to decreased erythrocyte survival and quicker red cell turnover. HbA1c levels are lowered as a result of haemoglobin's reduced exposure to glucose [5]. Whereas liver disease, renal failure, or substantial blood loss may have an effect on HbA1c, these factors were irrelevant in this case. This present case indicates how hemoglobinopathies, especially those associated with sickle cell compound heterozygous forms and β-thalassemia, can result in a substantial discrepancy between HbA1c and actual glycaemic status, requiring the use of alternative glycaemic indices like fructosamine, glycated albumin, CGM [9,10].

Limitations

Molecular genetic analysis could not be performed in this patient due to financial constraints, as the patient was unwilling to undergo further testing. Therefore, definitive molecular confirmation to distinguish between β-thalassemia, sickle cell anemia, or a compound heterozygous state could not be established. Nevertheless, the hemoglobin fraction pattern on HPLC—characterized by markedly reduced HbA, significantly elevated HbA_2, increased HbF, and the presence of HbS-related peaks—along with supportive peripheral smear findings, strongly suggests an underlying hemoglobinopathy within the sickle cell–β-thalassemia spectrum. Despite the absence of molecular confirmation, the observed hemoglobin abnormalities were sufficient to explain the discordance between HbA1c values and the patient's true glycemic status.

Abbreviations

- HPLC- High-performance liquid chromatography
- T2DM - Type 2 Diabetes Mellitus
- HbF - Fetal haemoglobin
- HbA_2 - Haemoglobin A_2
- HbA - Haemoglobin A

- CGM – Continuous Glucose Monitor

4. Conclusion

This case demonstrates a clinically important discordance between HbA1c values and true glycaemic status in a patient with type 2 diabetes mellitus, attributable to an underlying hemoglobinopathy. Despite requiring insulin therapy, the patient exhibited a spuriously low HbA1c of 4.6%. Hemoglobin fraction analysis by HPLC revealed markedly reduced HbA with significantly elevated HbA_2 and increased HbF, along with abnormal hemoglobin fractions suggestive of a compound heterozygous hemoglobinopathy involving β-thalassemia and a sickle cell–related variant. Supporting evidence from peripheral smear findings and red cell indices further strengthened this diagnosis. Molecular genetic analysis was advised by the pathology team to definitively differentiate between β-thalassemia and sickle cell anemia; however, it could not be performed due to financial constraints. Nonetheless, the combined clinical, hematological, and chromatographic findings provide strong indirect evidence for the coexistence of these hemoglobinopathies.

This case highlights the need for cautious interpretation of HbA1c in patients with suspected hemoglobinopathies and emphasizes the importance of alternative glycaemic assessment methods, like glycaemic variability should be considered in good glycaemic control.

Compliance with ethical standards

Acknowledgments

Authors would like to extend their sincere gratitude to the Physician of General Medicine Department and institution for their kind support in this Case Report.

Disclosure of conflict of interest

No conflict of interest to be disclosed.

Statement of ethical approval

The present research work does not involve any studies performed on animals or human subjects by any of the authors. The study was based on retrospective laboratory data analysis of HbA1c discordance in hemoglobinopathies, with no direct patient intervention or experimentation.

Statement of informed consent

The authors certify that they have obtained consent from the patient in this case report, and their details will be kept confidential with due diligence.

References

[1] Bry L, Chen PC, Sacks DB. Effects of hemoglobin variants and chemically modified derivatives on assays for glycohemoglobin. Clin Chem. 2001;47(2):153-63.

[2] Radin MS. Pitfalls in hemoglobin A1c measurement: when results may be misleading. J Gen Intern Med. 2014;29(2):388-94.

[3] Little RR, Roberts WL. A review of variant hemoglobins interfering with hemoglobin A1c measurement. J Diabetes Sci Technol. 2009;3(3):446-51.

[4] English E, Idris I, Smith G, Dhatariya K, Kilpatrick ES, John WG. The effect of anaemia and abnormalities of erythrocyte indices on HbA1c analysis: a systematic review. Diabetologia. 2015;58(7):1409-21.

[5] Cohen RM, Franco RS, Khera PK, Smith EP, Lindsell CJ, Ciraolo PJ, et al. Red cell life span heterogeneity in hematologically normal people is sufficient to alter HbA1c. Blood. 2008;112(10):4284-91.

[6] Lacy ME, Wellenius GA, Sumner AE, Correa A, Carnethon MR, Liem RI, et al. Association of sickle cell trait with hemoglobin A1c in African Americans. JAMA. 2017;317(5):507-15.

[7] Bain BJ. Haemoglobinopathy diagnosis. 2nd ed. Oxford: Blackwell Publishing; 2006.

[8] National Glycohemoglobin Standardization Program. Factors that interfere with HbA1c test results. Available from: NGSP Official Website

[9] Parrinello CM, Selvin E. Beyond HbA1c and glucose: the role of nontraditional glycemic markers in diabetes diagnosis, prognosis, and management. Curr Diab Rep. 2014;14(11):548.

[10] American Diabetes Association. Glycemic targets: Standards of Medical Care in Diabetes. Diabetes Care. 2023;46(Suppl 1):S97-S110.