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Too Good to Be True: The Clinical Deception of Low HbA1c– Case Series

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ABSTRACT

Background: Glycated hemoglobin (HbA1c) is widely used for the diagnosis and monitoring of diabetes mellitus, as it reflects average glycemic status over the preceding 2–3 months. However, HbA1c interpretation is based on assumptions of normal hemoglobin structure and erythrocyte lifespan. Violation of these assumptions can lead to falsely low HbA1c values, resulting in misinterpretation of glycemic control and inappropriate clinical management. This study aims to highlight the clinical and laboratory causes of discordantly low HbA1c values and to emphasize the role of root cause analysis (RCA) and alternative glycemic markers in accurate patient assessment.

Methods: This case series includes three patients who presented with clinical or biochemical evidence of dysglycemia but had spuriously low HbA1c values measured by high-performance liquid chromatography (HPLC). A systematic RCA was performed, including review of chromatograms, hematological parameters, and relevant clinical history. Fructosamine was used as an alternative marker of glycemic control in all cases.

Results: The causes of falsely low HbA1c included severe iron deficiency anemia, hemoglobinopathy with recent blood transfusion, and end-stage renal disease on dialysis. In all cases, HbA1c values were discordant with blood glucose levels. Fructosamine measurements provided a more accurate reflection of glycemic status and guided appropriate clinical management.

Conclusion: Falsely low HbA1c values can mask poor glycemic control and pose significant risks to patient care. A structured laboratory root cause analysis, combined with the use of alternative glycemic markers such as fructosamine, is essential for accurate interpretation. Awareness of HbA1c limitations and close collaboration between clinicians and laboratory professionals are critical to prevent clinical mismanagement.

Key-words: Blood glucose concentrations, Chromatogram analysis, Glycated Haemoglobin (HbA1c), Hemoglobinopathy, Hematological parameters

INTRODUCTION

Glycated Haemoglobin (HbA1c) has become the essential foundation of contemporary diabetes management. A well-established means of assessing average blood glucose concentrations over the past 2–3 months.

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HbA1c is universally accepted by the most important international organisations for diabetes care as one of the key tests used for the diagnosis of diabetes, and for monitoring to achieve target glucose control. Also, determining whether a person has an increased risk of long-term microvascular complications related to excessive glucose levels [1]. The clinical utility of HbA1c derives from a clear understanding of the underlying biochemical principle, that is, non-enzymatic glycation of the β-chain of adult haemoglobin (HbA) that is directly proportional to the ambient glucose concentration during the normal life span of red blood cells (RBC) [2].

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The validity of HbA1c as a «retrospective index» for glycemia is based on several critical and unstated physiological assumptions. These include that the normal lifespan of erythrocytes is 120 days. The structure of the molecule itself is normal, and there are no significant variants or deviations from established characteristics [3]. Finally, there are no underlying clinical conditions or interfering substances that adversely impact the glycation of HbA or the measurement of HbA1c. Any violation of these previous examples will negatively affect the accuracy and reliability of HbA1c measurements in a patient and can result in a significant discrepancy between the laboratory result and the true state of glycemia for that patient. An example of how HbA1c can be falsely high is found in patients with iron-deficient states who may have significant, continued high glycated HbA levels [4].

A more subtle clinical problem exists with patients with uncontrolled diabetes who have a falsely low HbA1c reading. Falsely low HbA1c readings can mislead healthcare providers into believing their patients are doing well regarding glycemic control and therefore may under-treat a patient with hyperglycaemia, thus increasing their chance of developing acute complications due to hyperglycaemia and accelerating their development of long-term complications associated with a history of hyperglycaemia [5].

A response to these potential diagnostic errors can only occur through a systematic and proactive approach to HbA1c testing by clinical laboratories. A discrepancy in a patient's HbA1c measurement should never be reported in isolation, but should trigger an investigation initiated by the laboratory. So, emphasising the need for a formal Root Cause Analysis (RCA) to include analytical verification/validation of the measurement process, chromatographic review of the HbA1c specimen, and clinical correlation with the patient's history and other laboratory test results [6]. In addition, they highlight the important role of other glycaemic markers, such as fructosamine, as valuable diagnostic adjuncts in cases where the HbA1c measurement is invalid. The use of three complex cases illustrates a practical framework for uncovering the causes of falsely low HbA1c readings and ultimately will help preserve patient safety through the accurate interpretation of lab results.

Methodology

Three patients exhibited clear signs of dysglycemia with HbA1c testing by HPLC, yielding low values with controlled Internal and External Quality Control (meeting required standards). The stability of the results obtained via HPLC was not in question. A structured Root Cause Analysis (RCA) of the pre-analytical factors and chromatographic data was completed for each of the patients. Due to the limitation of HbA1c, fructosamine is an alternative marker of glycemic index. Fructosamine, which reflects average glucose over the preceding 2-3 weeks, was measured in addition to HbA1c.

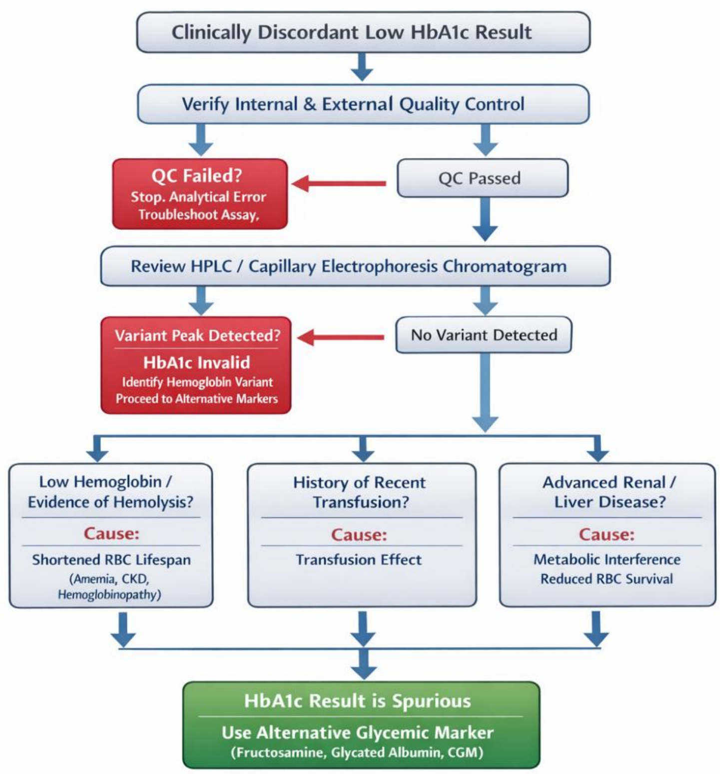

Fig. 1: A stepwise laboratory Algorithm for investigating discordantly Low HbA1c values

CASE PRESENTATIONS

CASE 1: Severe Iron Deficiency Anaemia

A 53-year-old male was referred to our hospital for borderline elevation of a random blood glucose level with markedly low HbA1c 2.3%. The haemoglobin showed no significant variant on the HPLC chromatogram no significant variant. Patient's results from a Reticulocyte Count Assay showed severe iron deficiency anaemia with a haemoglobin of 7.5 g/dL. The spuriously low HbA1c can be explained by relative short life of red blood cells (RBC), allowing less time in order for haemoglobin to become glycosylated. The level of

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fructosamine was increased at 253.3 µmol/L (Ref: 151-300 µmol/L). Fructosamine and glucose levels at the same time period correlate to provide an accurate representation of the patient's current glycemic status.

CASE 2: Thalassemia with Recent Transfusion

A 32-year-old female with Type 2 Diabetes Mellitus has an elevated blood glucose level but an undetectable HbA1c (0%). Hemoglobin was found to be at 9.3 g/dl. When tested for hemoglobin using HPLC, it was found that there was a large peak of fetal hemoglobin (HbF). Patient had a medical history of a recent blood transfusion, which caused variant interference in the HPLC test as well as slowing of the red blood cell's ability to circulate. At the same time, the fructosamine level was 401 µmol/L, higher than normal. This correlates with poor control of her blood sugar level. This discordance prompts appropriate therapy based on fructosamine results rather than HbA1c results.

CASE 3: End-Stage Renal Disease on Dialysis

A 42-year-old male parent with stage 5 chronic kidney disease (CKD) who is receiving long-term haemodialysis with an HbA1c level of 2.5% with a random blood glucose value within the reference range. A high-performance liquid chromatography (HPLC) assay did not demonstrate any abnormal variants. The reference centre (RCA) report attributes that falsely low HbA1c value to the combined effects of reduced red blood cell (RBC) survival time resulting from chronic kidney disease and the presence of carbamylated hemoglobin due to uraemia. Fructosamine concentration is 195.27 µmol/l and is consistent with the measured glucose levels. This accurately provides a clear measure of average glycemic control over time.

DISCUSSION

Through these three cases, we have provided examples of three categories that account for a discordantly low HbA1c value: abnormalities in RBC (Red Blood Cell) kinetics, structural variations of hemoglobin, and interference from other disease processes.

The first case illustrates how RBC survival dramatically impacts HbA1c. In patients with severe iron deficiency anaemia, the lifespan of erythrocytes can be reduced to between 60 and 70 days [6]. As a result, significantly less time is available for glycation of hemoglobin, leading to a falsely low HbA1c and an inaccurate estimate of average plasma glucose. This principle applies to any condition that increases RBC turnover, such as haemolytic anaemia, hemoglobinopathies (e.g., sickle cell disease with an erythrocyte lifespan frequently <20 days), splenomegaly, and chronic renal failure [4,7,8]. Therefore, clinicians need to have a heightened index of suspicion for hematologic disorders when they encounter an unexpectedly low HbA1c value, particularly in patients who also have anaemia.

The second case illustrates the complexity created by hemoglobin variants, which are becoming increasingly common in multi-ethnic populations. The current gold-standard assay for HbA1c measurement is HPLC; however, some hemoglobin variants (e.g., higher than usual amounts of fetal hemoglobin, or HbF, in patients with thalassemia syndromes) can interfere with this assay [9]. The additional complexity of a recent blood transfusion can lead to a heterogeneous population of RBCs (with different age and glycation histories) contributing to the overall HbA1c result. The HbA1c value is unreadable when the preceding situation takes place. The fructosamine blood value is an excellent alternative as it is not impacted by the hemoglobin composition and age of red blood cells, and thus provides an accurate representation of how poorly this patient's glycemic control is controlled, which will lead to different treatment options [10]. The third case of CKD and associated ESKD exposes a complex pathophysiological process. Uremic toxicity and erythropoietin deficiency resulting in the diminished RBC lifespan, due to uremic toxicity and erythropoietin deficiency, are significant factors in creating this disorder [11]. Another way that RBCs in patients with uraemia experience damage/decreased lifespan is through carbamylation, in which the isocyanic acid formed from urea binds non-enzymatically to hemoglobin. Although modern HPLC analytical methods exist to separate cHb from normal HbA1c, large quantities of cHb can still elute or interfere with normal HbA1c measurements. Still, more importantly, carbamylation may also change the kinetic process used to determine how HbA1c is produced [3,12]. Consequently, HbA1c cannot be routinely applied in patients with advanced CKD, so HbA1c should be routinely complemented with other markers such as fructosamines or glycated albumin to monitor glycemic control [13].

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The consistent and systematic application of an RCA protocol, such as that described in these respective cases, is necessary. The first step involves ensuring that the results produced by the testing laboratory methodology are valid results using a quality control procedure consistent with laboratory guidelines [14]. The next step is to examine the HPLC chromatogram and to determine if there are specific variants on this chromatogram, such as cHb or HbA1c. Finally, it is crucial to correlate all clinical and hemogram parameters (e.g., hemoglobin, RBC indices, history of transfusion, renal/liver function) to identify specific pathological/biological characteristics that may be contributing to the discrepancies. This systematic method allows the testing laboratory to be more than a vendor of results. To become an active member of the overall healthcare team, including but not limited to the testing laboratory.

When the laboratory provides an HbA1c value that appears too good to be true, the healthcare provider must view this finding as a significant alarm, and not an assurance that the patient has normal glycemic control. This value represents a breakdown of the biological basis of measurement inherent in this measurement methodology. A specific, organized, and methodical investigation involving the testing laboratory and clinician will be required to determine what is causing the abnormal difference between the two measurements. In our methodology, consistent with the findings of others in similar scenarios, fructosamines are consistently adequate action surrogate markers that can be used to progress with patient care. Therefore, without question, fostering an understanding of the limitations of the HbA1c and encouraging algorithms for investigating discrepancies between the HbA1c and other markers is essential in establishing accurate and individualized diabetes management for all patient types.

CONCLUSIONS

Values of HbA1c that seem suspiciously ideal should undergo a thorough investigation immediately by performing a structured laboratory-root cause analysis carefully designed to identify the actual cause(s) of an erroneously ideal HbA1c result, whether haematologically, biochemically, or analytically based. If there is no valid HbA1c laboratory result available for a patient, clinicians will need to ascertain their patients' glycemia status using an alternative laboratory marker like fructosamine; therefore, alternative laboratory markers will also provide the measure of glycemia needed to manage the patient appropriately within a safe range. Clinicians and laboratory professionals will require solid collaboration with respect to the interpretation of HbA1c values in light of all other clinical and laboratory data available for a particular patient.

CONTRIBUTION OF AUTHORS

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