CASE REPORT

Type 2 Diabetes Mellitus with HbJ trait: A management conundrum

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HbA1c, haemoglobinopathy, HbJ trait

Abstract

Optimal glycaemic control is crucial in patients with diabetes mellitus (DM) to avoid episodes of hypoglycaemia and both micro- and macrovascular complications. Diabetic control relies mainly on the evaluation of haemoglobin A1c (HbA1c), which is unfortunately unreliable in patients with haemoglobinopathies. This case report describes a patient with type 2 DM and haemoglobin J (HbJ) trait, which resulted in erratic HbA1c values throughout her follow-up. Other approaches, such as self-blood glucose monitoring, are needed to evaluate glycaemic control instead of relying on HbA1c alone to guide the management DM in these patients.

Introduction

Haemoglobinopathies are common in many parts of the world. There are over 900 described Haemoglobin (Hb) variants, and at least 43% of all possible single-point mutations have been identified.1 Several studies detail the impact of silent haemoglobinopathy variants on haemoglobin A1c (HbA1c) values; for example, Hb Camden, Hb Austin, and Hb N-Baltimore lead to false elevation of HbA1c values.2 If an HbA1c result does not correlate with a patient’s clinical condition, haemoglobinopathies and conditions affecting the lifespan of red blood cells must be considered as potential causes.3

Case Presentation

A 63-year-old woman presented to our local clinic in 2011 with fever and cough for 1 week, and she was treated for mild community-acquired pneumonia. At that time, her random capillary blood sugar (CBS) was 9.8 mmol/L. She otherwise had no symptoms of hyperglycaemia prior to the visit. Further investigations showed a fasting blood glucose of 10.7 mmol/L and an HbA1c of 37.3%; a diagnosis of type 2 diabetes mellitus (DM) was made based on these findings. The patient was started on metformin 500 mg BD. Due to the abnormally high HbA1c, a full blood picture (FBP) and Hb analysis were ordered. The FBP showed red blood cells (RBCs) containing stomatovalocytes and normal white blood cells (WBCs) and platelet morphology, which was suggestive of hereditary stomatocytosis. The patient’s Hb was 129 g/L, MCV 93.3 fl, and MCH 31.3 pg. The results of her Hb analysis using the capillary-CE/HPLC method showed 68.2% HbA, 1.9% HbA2, 0.7% Hb constant spring, and 29.2% HbJ, which was consistent with a possible HbJ trait. Other investigations at diagnosis noted renal impairment, with an EGFR of 41 mL/min/1.73 m² and 2+ urine albumin. The fasting lipid profile showed a total cholesterol of 4.8 mmol/L, triglycerides 1.7 mmol/L, HDL 0.82 mmol/L, and LDL 3.2 mmol/L.

Her diabetic medication was optimised with gliclazide 80 mg BD, and simvastatin 10 mg ON was added to address the elevated LDL levels. Perindopril 4 mg OD was also added for renal impairment and proteinuria. Throughout her follow-up, HbA1c levels were always erratic and mostly did not correspond with the random blood glucose readings (Table 1). The patient was adherent to all her medications and diet. The patient was also informed of the use of HbA1c in the monitoring of her illness and the difficulties that the doctor faced due to the haemoglobinopathy. She was instructed to perform self-blood glucose monitoring ( SMBG); however, she was unable to do so due to financial constraints. Most of the time, the clinician relied on CBS results instead of HbA1c when evaluating the treatment, as CBS was believed to more accurately represent the patient’s blood glucose control.

Despite acceptable CBS values during the initial years of treatment, the patient’s diabetic control became uncontrolled and she developed further diabetic complications. Unfortunately, 5 years after diagnosis, her renal...
function deteriorated from chronic kidney disease stage 3B to stage 4. She also developed bilateral eye cataracts as a complication of her uncontrolled diabetes.

Table 1. Summary of the patient’s HbA1c and blood glucose readings

<table>
<thead>
<tr>
<th>Year</th>
<th>Range of capillary blood glucose (mmol/L)</th>
<th>HbA1c (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>2012</td>
<td>9.8–10.7 (fasting)</td>
<td>37.3</td>
</tr>
<tr>
<td>2013</td>
<td>6.7–8.3 (fasting)</td>
<td>Invalid result</td>
</tr>
<tr>
<td>2014</td>
<td>6.0–12.0 (random)</td>
<td>6.6</td>
</tr>
<tr>
<td>2015</td>
<td>6.4–7.2 (random)</td>
<td>Invalid result, repeated x3</td>
</tr>
<tr>
<td>2016</td>
<td>6.1–7.9 (random)</td>
<td>5.0</td>
</tr>
<tr>
<td>2017</td>
<td>5.7 (fasting)</td>
<td>26.8 (July)</td>
</tr>
<tr>
<td></td>
<td>6.3–10.7 (random)</td>
<td>33.4 (September)</td>
</tr>
<tr>
<td>2018</td>
<td>7.2 (fasting)</td>
<td>Not available</td>
</tr>
<tr>
<td></td>
<td>9.5–21.5 (random)</td>
<td></td>
</tr>
<tr>
<td>2019</td>
<td>8.3–9.4 (fasting)</td>
<td>29.7 (April)</td>
</tr>
<tr>
<td></td>
<td>7.5–13.8 (random)</td>
<td>34.3 (May)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>33.6 (July)</td>
</tr>
<tr>
<td>2020</td>
<td>8.8–12.5 (fasting)</td>
<td>7.7</td>
</tr>
<tr>
<td></td>
<td>11.0–24.6 (random)</td>
<td></td>
</tr>
</tbody>
</table>

Discussion
The HbJ-α mutation is an alpha-chain variant found in a heterozygous state that presents a normal haematological picture.4 The HbJ variant is uncommon in white racial groups, and the majority of the variants are present in individuals of Asian or Southeast Asian descent.5 HbJ has various properties and functions and has a variable effect on HbA1c levels. HbJ Capetown (α2 92Gln β2), the most common variant of Hb J, causes erroneously elevated levels of HbA1c, as does HbJ Valencia; in contrast, HbJ Baltimore and HbJ Meerut result in falsely low HbA1c values.7 To our knowledge, no HbJ variants have been reported to cause both abnormally high and abnormally low HbA1c estimation.

This case highlights two important points for discussion regarding HbA1c measurement in HbJ trait cases and DM management. First, the role of HbA1c in the diagnosis of DM must be discussed. HbA1c is highly sensitive to fluctuations in blood glucose levels, as a slight increase of 25–32 mg/dL in average blood glucose levels corresponds to a 1% change in HbA1c.4 High HbA1c levels may mislead clinicians in terms of diagnosis. A patient with the HbJ trait can be diagnosed with DM due to falsely elevated HbA1c levels and may subsequently be started on antidiabetic drugs; this can be dangerous, as the patients is at a high risk of hypoglycaemia. Therefore, a thorough history of hyperglycaemia symptoms is particularly important before making a diagnosis in these patients. It is important to not rely solely on high HbA1c to diagnose DM in patients with haemoglobinopathies.

Second, the role of HbA1c in monitoring glycaemic control must be discussed. HbA1c most accurately indicates the previous 2–3 months of glycaemic control, and it has been unequivocally demonstrated that HbA1c can predict the risk of long-term microvascular and macrovascular complications in the general population. However, some haemoglobinopathies that are clinically silent can cause biochemical aberrations that can interfere with HbA1c assays. Haemoglobin variants, such as HbS, HbC, and HbE are known to affect HbA1c assays.9 When the HbA1c reading is inaccurate, it affects the glucose monitoring, which leads to either overtreatment or suboptimal treatment.

The four most common methods of measuring HbA1c are affinity column immunoassay, ion-exchange high-performance liquid chromatography (HPLC), boronate affinity HPLC, and enzymatic assay.10 In cases of haemoglobinopathy, boronate affinity HPLC is the recommended method to measure HbA1c, as it can more precisely estimate HbA1c levels than other measurement methods.1 Another alternative for monitoring glucose control is fructosamine level. Fructosamine is a measurement of the average blood glucose concentration over the past 2–3 weeks, and the value is unaffected by the presence of a haemoglobinopathy because it is dependent on protein glycation.1 Unfortunately, fructosamine was of limited value in this patient as this investigation was not provided by the clinic she attended; it is performed only at a larger healthcare centres, which leads to higher costs and delayed return of results, by which time the results have reduced value. In the absence
of other reliable methods of measuring glucose control, a correlation between clinical findings, SMBG, and HbA1c needs to be considered before reaching conclusions regarding the glycaemic control of the patient.

The presence of a haemoglobinopathy in this patient has made the management of her diabetes particularly challenging. Despite her adherence to treatment and diet, her glucose control deteriorated over the years, resulting in the emergence of diabetic complications. The main reason for her poor glucose control was failure to appropriately optimise the medications due to suboptimal glucose monitoring; this was due to inaccurate HbA1c readings and the lack of SMBG. It is recommended that, for diabetic patients with haemoglobinopathies, a reliable method for HbA1c assay must be used and supplemented with SMBG. It is especially important for primary care providers to properly educate patients about the complexity of their condition and the importance of their active participation in the management of their illness, thus ensuring patient-centred care.

**Conclusion**

It is important to remember that there are many Hb variants that can interfere with routine laboratory tests. Abnormally high or low HbA1c levels in diabetic patients should prompt further investigation for haemoglobinopathies, and other methods of blood glucose monitoring should be considered.

**Acknowledgements**

None.

**Conflicts of interest**

The authors report no conflicts of interest.

**Patients’ consent for the use of images and content for publication**

Verbal consent was obtained from the patient. No consent form was signed.

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**What is new in this case report compared to the previous literature?**

- Rather than highlighting a new phenomenon in the literature, this case highlighted that many primary care providers might not be aware that, in the presence of haemoglobinopathy, HbA1c should be measured using ion-exchange high-performance liquid chromatography (HPLC). In addition, there is a need for other blood glucose monitoring methods for these patients.

**What is the implication to patients?**

- Abnormally high or low HbA1c in a patient with diabetes should alert the clinician of the presence of a haemoglobinopathy.
- In the presence of a haemoglobinopathy, HbA1c should be measured using ion-exchange high-performance liquid chromatography (HPLC).
- HbA1c readings in a patient with haemoglobinopathy should be correlated with other blood glucose parameters, and other methods of monitoring (e.g., fructosamine) should be considered.
- In the presence of a haemoglobinopathy, SMBG is required to guide insulin titration and help guide decision-making in the overall management of diabetes.

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**References**


