Falsely low HbA1c value due to a rare variant of hemoglobin J-Baltimore

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ABSTRACT

HbA1c values are heavily relied on to assess glycemic control. Hemoglobin variants may interfere with measurements of HbA1c resulting in falsely low values. We present the first report of a rare variant of Hb in a patient with type 2 diabetes, which lead to a falsely low HbA1c.

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1. Case report

A 55-year-old Caucasian man with a 10-year history of type 2 diabetes was referred to the diabetes clinic due to a recent deterioration of his glycemic control. He was not symptomatic; he had occasional nocturia but had no polydipsia or weight loss. He denied symptoms related to hypoglycemia. Home blood glucose monitoring (HBGM) showed values between 8.0 and 12.0 mmol/l (114 and 216 mg/dl). His 14- and 30-day average from his blood glucose meter was 9.0 mmol/l (162 mg/dl).

His past medical history consisted of hypertension, hyperlipidemia and chronic back pain. His medications were metformin 1 g twice daily, gliclazide 160 mg twice daily, rosiglitazone 8 mg once daily, simvastatin 40 mg at night, and perindopril 2 mg twice daily. There was no significant family history. He smoked 10 cigarettes a day with minimal alcohol intake.

On examination he had no evidence of jaundice, clubbing or pallor. His body mass index was 41 kg/m². His pulse was regular at 78 bpm with a blood pressure of 156/82 mmHg. Otherwise examination was unremarkable. He had normal visual acuity and background diabetic retinopathy on dilated fundoscopy. His urinalysis showed a trace of protein with leucocytes.

His Hb was 14.2 g/dl (13.5–18), MCV 91fl (80–100), WBC $10.8 \times 10^9 l^{-1}$ (4–11). Renal function was normal. Clinic HbA1c was 5.9% (DCCT, UKPDS aligned), his random plasma glucose was 11.3 mmol/l (204 mg/dl) and his urine albumin/creatinine ratio was 1.3 (0–2.5).

Because of the discrepancy between his clinic HbA1c and his HBGM values, further information regarding his previous glycemic control was obtained from his general practitioner. This showed several previous HbA1c values between 4.9 and 6.3% (DCCT, UKPDS aligned). During this period labora-
tory fasting plasma glucose values were measured between 10.4 and 19.4 mmol/l (188 and 350 mg/dl). This discrepancy between his HBGM values and his laboratory HbA1c prompted further investigation.

The first sample was analysed using cation exchange high-performance liquid chromatography (HPLC). As a result of the discrepancy, a discussion with our consultant clinical pathologist led to the sample being analysed using an affinity HPLC method which uses an affinity gel. This method detects glucose bound to Hb, and the type of the Hb does not affect separation in this method [9]. This method gave an HbA1c value of 8.6%, more consistent with his measured fasting glucose, and his HBGM 14-and 30-day averages.

Due to the discrepancy between his HbA1c and HBGM measurements a hemoglobinopathy was suspected. He had a normal Hb electrophoresis. Further testing was done looking for other Hb variants, which revealed that he had a relatively rare ‘hemoglobin J-Baltimore’, which explained the falsely low HbA1c results.

2. Discussion

HbA1c (hemoglobin glycated at the N-terminal valine of the β-chain) remains the gold standard for monitoring glycemic control in people with diabetes mellitus [5]. Two large, prospective, randomised clinical trials have demonstrated a strong relationship between hyperglycemia and the development of microvascular complications in type 1 and type 2 diabetes [16,18]. Glycated hemoglobin (GHb) is formed in vivo by a reaction between glucose and the N-terminal region of Hb α or β chains. The irreversible non-enzymatic reaction between glucose and HbA, the main type of Hb in normal adults, occurs over 3 months (the life span of the erythrocyte) [12]. The resulting molecule is a stable GHb containing primarily glycated N-terminal chains, and the total amounts depend directly on the average glucose concentration over the 3 months before measurement. Genetic variants may alter glucose binding, resulting in discordant HbA1c and home blood glucose test values [13].

Several methods exist for measuring HbA1c values. These include gel electrophoresis and iso-electric focusing [8,14]. Low pressure and high performance, ion-exchange liquid chromatography, immunooassay, affinity chromatography and calorimetric procedures are also used [4,6,11,15,17].

HbA1C values are influenced by red cell survival. Thus, falsely high values in relation to a mean blood glucose values can be obtained when red cell turnover is low, resulting in a disproportionate number of older red cells. This problem can occur in patients with iron deficiency anemia, and in patients following splenectomy. On the other hand, rapid red cell turnover leads to a greater proportion of younger red cells and falsely low HbA1c values. Examples include patients with hemolysis and those treated for iron, vitamin B12, or folate deficiency [10].

Bry et al. have previously reviewed how hemoglobinopathies may interfere with GHb analysis, independent of their effects on erythrocyte survival [3]. Influence on GHb analysis by HbF, HbS, HbC and other abnormal forms of Hb has been reported [13]. Results may be falsely raised or lower, depending on the particular method used to measure HbA1c and the type of hemoglobinopathy. For example Hb variants that cannot be separated from HbA will produce spuriously increased or decreased results by ion-exchange HPLC.

With respect to J-Baltimore hemoglobin, Baglioni and Weatherall first described this variant in 1963 in a black American family [2]. Only a few cases have been reported in the literature since [1,7,19]. Because the change in amino acid structure is minimally different from HbA this variant does not produce a separate peak on cation exchange HPLC, which is the method used to analyse our patient’s HbA1c at first.

In summary, we have used this case of a rare hemoglobinopathy to highlight the importance of looking at home blood glucose measurements and correlating them with the HbA1c. In addition, we believe that this is the first case of a spuriously low HbA1c reported with this particular variant. Clinicians should be alerted when faced with discordant HbA1c and HBGM values. They should also be aware of the factors which would lead to falsely low HbA1c measurements and when necessary to liaise with their local clinical biochemistry department when an abnormal Hb variant is suspected. This should enable the use of alternative methodologies to provide an accurate HbA1c value.

Conflict of interest

We declare we have no conflicts of interest. Dr. Dhatariya acts as the guarantor for this paper.

REFERENCES