Erroneous Diabetes Diagnosis: A Case of HbA_{1c} Interference

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A 66-year-old Caucasian female was referred for specialist follow-up of her treatment-refractory type 2 diabetes. The diagnosis was made based on two consecutive HbA_{1c} results >6.5% (48 mmol/mol) in accordance with the Canadian Diabetes Association and the American Diabetes Association guidelines (1,2). Fasting glucose was normal and hyperglycemic symptoms were absent at diagnosis. The patient's hematological indices were normal and she was unaware of any family history of hemoglobinopathy. Her glycemic control proved difficult to manage, with persistently elevated HbA_{1c} (10.8–11.2% [95–99 mmol/mol]) despite treatment with metformin and, eventually, insulin glargine. Further, with treatment, the patient began to experience symptoms of episodic hypoglycemia.

A fasting glucose of 84.6 mg/dL (4.8 mmol/L) obtained at the same time as an HbA_{1c} of 11.2% (99 mmol/mol) triggered suspicion of interference. As all of the HbA_{1c} results were obtained by high-performance liquid chromatography (HPLC) (Bio-Rad VARIANT II TURBO 2.0), the analysis was repeated by immunoassay (DCA 2000+, Siemens Healthcare Diagnostics), which showed a normal result of 5.2% (33 mmol/mol).

The ordering physician was contacted and treatment withheld. The patient's blood glucose remained within normal limits with cessation of hypoglycemic symptoms. Hemoglobinopathy investigation revealed the presence of the α-globin chain mutant hemoglobin (Hb) Wayne. Carriers of one affected α-globin gene ($\alpha\alpha/\alpha\alpha^{Wayne}$) are clinically normal with unremarkable hematological indices (3). Hb Wayne was previously reported to interfere with Bio-Rad VARIANT II HPLC HbA_{1c} measurements (4). Hb Wayne results from a frameshift mutation in the *HBA2* gene (HBA2:c.420del) and exists as two isoforms, Hb Wayne I Asn and Hb Wayne II Asp. Each isoform comprises ~6–9% of total Hb and has different chromatographic properties on the Bio-Rad VARIANT II TURBO 2.0. Hb Wayne I coelutes with HbA_{1c}, whereas Hb Wayne II coelutes with fetal Hb (HbF). Because the immunoassay uses antibodies recognizing the structure of the β-N-terminal glycated amino acid, the measurement of HbA_{1c} is more accurate.

Both HbA_{1c} methodologies are certified by the NGSP as traceable to the Diabetes Control and Complications Trial (DCCT) as required by the recent "Guidelines and Recommendations for Laboratory Analysis in the Diagnosis and Management of Diabetes Mellitus" (5). All samples with HbF >15%, HbA_{1c} results <4% (20 mmol/mol) or >12% (108 mmol/mol) are verified by repeat testing and visual inspection of the chromatogram and evaluated for clinical concordance. However, HbA_{1c} results from patients with Hb Wayne trait do not meet these criteria for further review.

Clinical practice guidelines recommend repeat testing by the same method to confirm a diagnosis of type 2 diabetes in asymptomatic patients. This approach led to diabetes misdiagnosis in this patient despite the availability of additional laboratory tests, such as fasting glucose. With this case, we aim to highlight that despite the usefulness of practice guidelines, their limitations must be recognized and sound clinical judgment should prevail. Like all laboratory tests, HbA_{1c} measurement is subject to interferences, and results must be interpreted within the clinical context.

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