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CASE REPORT

Discordantly high glycated hemoglobin might assist in diagnosing α-thalassemia, but not diabetes: A case report

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ABSTRACT
Glycated hemoglobin (HbA1c) is an important method for monitoring blood glucose and diagnosing diabetes. High-performance liquid chromatography is more commonly used in the laboratory for the detection of HbA1c. Although HbA1c detected by high-performance liquid chromatography is susceptible to abnormal hemoglobin, there are few reports that it is affected by α-thalassemia. Previous reports have generally concluded that α-thalassemia does not affect or lower HbA1c. Here, we report a case of discordantly high HbA1c inconsistent with fasting blood glucose. Finally, the patient was diagnosed with α-thalassemia and insulin resistance. α-Thalassemia might lead to a discordantly high HbA1c result, which could be attributed to elevated hemoglobin H. In this case, glycated albumin might accurately reflect the real average level of blood glucose. When finding discordant HbA1c, patients should be advised to undergo thalassemia and hemoglobinopathy screening by diabetologists/endocrinologists or primary care physicians to avoid a missed diagnosis of hematopathy.

INTRODUCTION
Glycated hemoglobin (HbA1c) is an important method for monitoring blood glucose. Since 2010, the American Diabetes Association has listed HbA1c as a diagnostic criterion for diabetes[1]. There are many methods for the detection of HbA1c, and high-pressure liquid chromatography (HPLC) is more commonly used in the laboratory[2]. Although HbA1c detected by HPLC is susceptible to abnormal hemoglobin, there are few reports that it is affected by α-thalassemia, and previous reports have generally concluded that α-thalassemia does not affect or lower HbA1c [3].

Here, we report a case of discordantly high HbA1c inconsistent with fasting blood glucose. Finally, the patient was diagnosed with α-thalassemia and insulin resistance. Discordantly high HbA1c might assist in diagnosing α-thalassemia, but not diabetes in some cases.

CASE REPORT
A 57-year-old Chinese man presented with HbA1c 12.7% (normal range 3.9–6.1) by ion exchange HPLC (TOSOH HLC-723G11, Tosoh Corporation, Shunan, Yamaguchi, Japan) in a health examination. There was no obvious abnormality in the chromatogram (Figure 1). However, fasting blood glucose was 84.06 mg/dL (normal range 70.2–106.2). HbA1c was tested repeatedly, and the value was still significantly elevated. He had no complaints or past medical history. Other results were as follows: red blood cell count 6.8 × 10^{12}/L (normal range 4.3–5.8), hemoglobin (Hb) 135 g/L (normal range 130–175 g/L), mean corpuscular volume 72 fL (normal range 82–100 fL), mean corpuscular hemoglobin 20 pg (normal range 27–34 pg), mean corpuscular hemoglobin concentration 278 g/L (normal range 316–354), total bilirubin 58.7 μmol/L (normal range 5.5–28.8 μmol/L), direct bilirubin 14.7 μmol/L (normal range <8.8 μmol/L) and indirect bilirubin 44 μmol/L (normal range <20 μmol/L). Further tests were ordered by the primary care physician. The oral glucose tolerance test and insulin release test results were as follows: fasting plasma glucose 90.72 mg/dL (normal range 70.2–106.2 mg/dL), 0.5 h plasma glucose 183.24 mg/dL (normal range 93.6–154.8 mg/dL), 1 h plasma glucose 219.96 mg/dL (normal range 109.8–180 mg/dL), 2 h plasma glucose 127.62 mg/dL (normal range 59.4–140.4 mg/dL), 3 h plasma glucose 77.76 mg/dL (normal range 50.4–120.6 mg/dL), fasting insulin 13.8 μU/mL (normal range 1.5–15.0 μU/mL), 0.5 h insulin 84.9 μU/mL (normal range 20–

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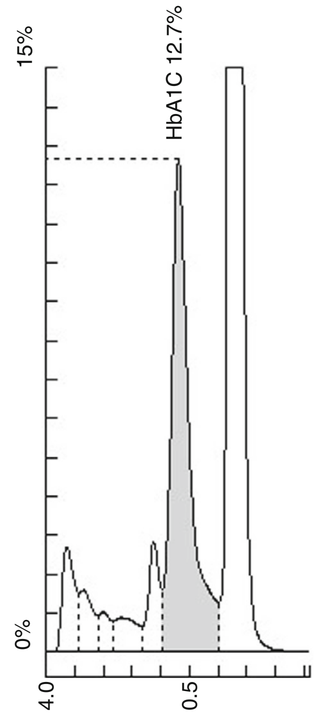

Figure 1 | High-pressure liquid chromatography chromatogram of glycated hemoglobin (HbA1c).

120 μU/mL), 1 h insulin 232 μU/mL (normal range 15–110 μU/mL), 2 h insulin 151 μU/mL (normal range 3.0–60.0 μU/mL), 3 h insulin 38.5 μU/mL (normal range 1.5–10.0 μU/mL), homeostatic model assessment for insulin resistance 3.09 and Matsuda insulin sensitivity index 59.34. Glycated albumin (GA) was 9.02% (Lucica GA-L, enzymatic assay kit, Asahi Kasei Pharma Corporation, Chiyoda, Tokyo, Japan; normal range 9–14), glucose-6-phosphate dehydrogenase was 4,360 U/L (normal range >1,300 U/L) and haptoglobin was <58.30 mg/L (normal range 500–2,200 mg/L). The laboratory results of the patient are shown in Table 1. Hemoglobin electrophoresis showed that hemoglobin A accounted for 80.4% (normal range 96–97.6), hemoglobin A2 accounted for 0.7% (normal range 2.4–3.2), hemoglobin H accounted for 17.7% (normal range 0) and abnormal Hb Bart's accounted for 1.2% (Figure 2). α-Thalassemia gene tests showed α-thalassemia gene deletion, and the genotype was --(SEA)/–α3.7.

DISCUSSION

Discordantly high HbA1c was found in a health checkup, which was inconsistent with fasting blood glucose levels. Further examination showed abnormal hemoglobin. The patient was diagnosed with α-thalassemia. The oral glucose tolerance test and insulin release tests suggested insulin resistance.

The accuracy of HbA1c in patients with thalassemia is method dependent. Popular methods for the determination of HbA1c include ion exchange HPLC, boronate affinity chromatography, immunoturbidimetry and capillary electrophoresis[2,4]. HbA1c can be accurately measured using appropriate

Table 1 | Laboratory results of the patient

Factors	Results	Reference range
HbA1c (%)	12.7	3.9–6.1
Fasting blood glucose (mg/dL)	84.06	70.2–106.2
Red blood cell count ($\times 10^{12}$/L)	6.8	4.3–5.8
Hb (g/L)	135	130–175
MCV (fL)	72	82–100
MCH (pg)	20	27–34
MCHC (g/L)	278	316–354
Total bilirubin (μmol/L)	58.7	5.5–28.8
Direct bilirubin (μmol/L)	14.7	<8.8
Indirect bilirubin (μmol/L)	44	<20
Fasting plasma glucose in OGTT (mg/dL)	90.72	70.2–106.2
0.5 h plasma glucose (mg/dL)	183.24	93.6–154.8
1 h plasma glucose (mg/dL)	219.96	109.8–180
2 h plasma glucose (mg/dL)	127.62	59.4–140.4
3 h plasma glucose (mg/dL)	77.76	50.4–120.6
Fasting insulin (μU/mL)	13.8	1.5–15.0
0.5 h insulin (μU/mL)	84.9	20–120
1 h insulin (μU/mL)	232	15–110
2 h insulin (μU/mL)	151	3.0–60.0
3 h insulin (μU/mL)	38.5	1.5–10.0
HOMA-IR	3.09	–
Matsuda-ISI	59.34	–
Glycosylated albumin (%)	9.02	9–14
Glucose-6-phosphate dehydrogenase (U/L)	4,360	>1,300
Haptoglobin (mg/L)	<58.30	500–2,200

Hb, hemoglobin; HbA1c, glycated hemoglobin; HOMA-IR, homeostatic model assessment for insulin resistance; Matsuda ISI, Matsuda insulin sensitivity index; MCH, mean corpuscular hemoglobin; MCHC, mean corpuscular hemoglobin concentration; MCV, mean corpuscular volume; OGTT, oral glucose tolerance test.

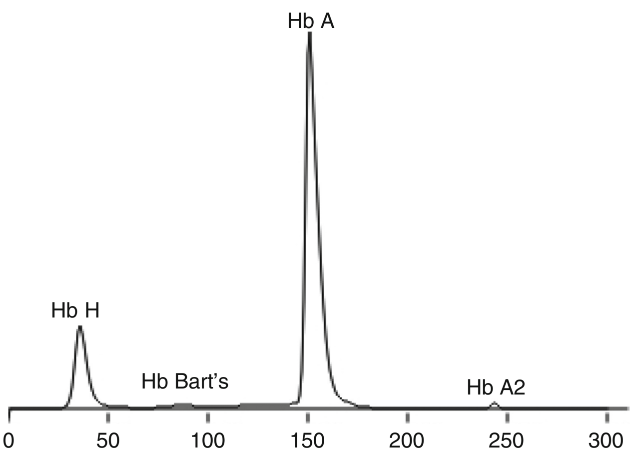

Figure 2 | Chromatogram of hemoglobin (Hb) electrophoresis.

methods in most patients with abnormal hemoglobin[2]. However, if the hemoglobin variation affects the glycosylation ability of hemoglobin or the turnover of red blood cells is abnormal, no matter what method is used, accurate HbA1c cannot be obtained[2]. In areas with a high incidence of thalassemia, boronate affinity chromatography and immunoturbidimetry should be used with caution[2]. Capillary electrophoresis has a good ability to identify abnormal hemoglobin[4], but there are also some exceptions[5]. HbA1c by ion exchange HPLC is susceptible to abnormal hemoglobin[3,6]. Although visual inspection and manual review of chromatograms might always assist the interpretation of HbA1c[2], it is not appropriate all the time. There were no abnormal peaks in the chromatogram in this patient. Previous studies have suggested that the type of α-thalassemia (--(SEA)/–α3.7) lowers HbA1c, which is due to the increase in red blood cell turnover and the complete separation of Hb H and HbA1c on chromatogram[3]. The determination of HbA1c in previous studies was made by the Bio-Rad Variant™ II Turbo Analyzer and is different from that in the present study[3]. We speculate that the discordantly high HbA1c is caused by the co-elution of Hb H and HbA1c in the HPLC chromatogram. In this case, other methods, such as capillary electrophoresis, might be considered to obtain accurate HbA1c results.

In addition to using other detection methods for HbA1c, GA is also an alternative choice[7]. GA is another commonly used indicator to evaluate the average blood glucose level at 2–3 weeks[8], which has been shown to be unaffected by abnormal hemoglobin[9]. In regions with a high prevalence of thalassemia, the role of GA must be emphasized in diabetes screening and blood glucose control evaluation[7]. However, there are a few notes when using GA. The method of GA determination is not standardized, and the reference value range varies among laboratories [7]. The detection method for GA should be confirmed to be accurate. In addition, GA is not suitable for patients complicated with abnormal albumin metabolism, such as nephrotic syndrome and cirrhosis[8]. In this case, blood glucose self-monitoring and dynamic blood glucose monitoring are better options[10].

The patient had no symptoms, and hemoglobin was normal, but an increased red blood cell count, small cells with low pigmentation and high bilirubin showed some clues. Discordance of high HbA1c inconsistent with fasting blood glucose also provides important evidence for the diagnosis of α-thalassemia. When HbA1c is inconsistent with blood glucose, patients should be advised to undergo thalassemia and hemoglobinopathy screening by diabetologists/endocrinologists or primary care physicians to avoid a missed diagnosis of hematopathy.

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DISCLOSURE

The authors declare no conflict of interest.
Approval of the research protocol: N/A.
Informed consent: The study was carried out with the consent of the patient.
Registry and the registration no. of the study/trial: N/A.
Animal studies: N/A

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