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CASE REPORT

Falsely decreased HbA1c in a type 2 diabetic patient treated with dapsone

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Glycated hemoglobin A1c (HbA1c) is an important indicator of glycemic control. The current recommendation for glycemic control based on HbA1c values has been widely accepted. However, HbA1c values depend on the lifespan of erythrocytes and the assay methods used. Here, we report the case of a patient with type 2 diabetes with unusual falling of HbA1c due to interference from dapsone treatment for leukocytoclastic vasculitis. He was a 52-year-old man, who was diagnosed with type 2 diabetes mellitus 5 years previously and who had been treated in our hospital in the past 3 years. Glycemia was controlled by sulfonylurea and metformin. During the 3-years follow-up period, HbA1c dropped significantly during the addition of dapsone treatment, although plasma glucose levels remained stable. HbA1c levels were raised after discontinuation of dapsone. With rechallenge of dapsone usage, HbA1c decreased again. We conclude that dapsone may be the cause of artificially low HbA1c. Other measurements to monitor glycemic control should be considered when dapsone is used for the treatment of concurrent disorders, such as autoimmune disease and pneumocystis jiroveci pneumonia.

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Introduction

Dapsone (4,4'-diaminodiphenylsulfone, a synthetic sulfone) is an old drug used to treat leprosy and malaria. For its anti-

inflammatory action, dapsone has become one of the major treatments for autoimmune and allergic disorders.^{1–3} In post-transplanted or human immunodeficiency virus-infected patients, dapsone is an alternative drug for prophylaxis of pneumocystis jiroveci pneumonia. In this report, we describe a fall in glycated hemoglobin A1c (HbA1c) readings when a diabetic patient received dapsone treatment. We also discuss the possible mechanisms of artificially low HbA1c when a diabetic patient is co-treated with dapsone.

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Case report

This male patient, born in 1956, was diagnosed with type 2 diabetes mellitus in 2003 and treated with sulfonylurea and metformin from then onwards. He visited our hospital in July 2005 for examination of purpura over the lower limbs. Skin biopsy showed leukocytoclastic vasculitis, for which dapson 100 mg per day was prescribed from December 2005. He tolerated dapson well except his hemoglobin levels decreased from 14.3 g/dL to 12.3 g/dL in half a year. Hematologic assessment showed a mean corpuscular volume (MCV) of 106.5 fL; reticulocytes 2.92%; and reticulocyte production index 1.62 in June 2006. For macrocytic anemia and reticulocytosis, the patient received dapson-induced hemolysis. He was transferred to our diabetic clinic for further diabetic care in June 2006. Examination showed no nephropathy, retinopathy, neuropathy, or abnormal ankle brachial index. The initial fasting plasma glucose was 144 mg/dL, postprandial plasma glucose 141 mg/dL, and HbA1c 4.4% (collected in a fluoride-EDTA-containing tube; assay method used: high-performance liquid chromatography, Primus CLC385, Kansas city, USA, reference range: 3.8–6.0%). The estimated average glucose⁴ derived from HbA1c was 79.58 mg/dL (Fig. 1). The patient did not report any hypoglycemic symptoms. He was treated with oral metformin 850 mg and modified-release gliclazide 30 mg per day from July 2006.

In September 2006, cutaneous vasculitis improved and dapson was discontinued. The HbA1c increased to 6.2% 3-months later without any change of oral antidiabetic agents or lifestyle. He did not complain of any hyperglycemic symptoms, such as polyuria, polydipsia or weight loss. The oral antidiabetic agents were changed to glimepiride 2 mg and metformin 850 mg per day in December 2006. The HbA1c ranged from 5.7 to 7.6%, fasting plasma

glucose 112 to 103 mg/dL, and postprandial plasma glucose 109 to 117 mg/dL in the following 6 months.

New purpura lesions recurred and dapson was then restarted in August 2007. Three months later, the patient's HbA1c level was reported to as low as 4.1% when the fasting plasma glucose was 123 mg/dL and 2-hr postprandial plasma glucose 110 mg/dL. The estimated average glucose derived from HbA1c was 70.97 mg/dL. Antidiabetic treatment was adjusted to only metformin 850 mg per day from then on. Fasting glycemia was elevated to 158 mg/dL and postprandial glycemia to 154 mg/dL; however, we observed that HbA1c remained low at around 4.2% to 5.5%. Hemoglobin electrophoresis was checked and results showed no elevated hemoglobin H, hemoglobin A2 or hemoglobin F. From February 2009, dapson was discontinued again because of short supply. We found that HbA1c increased to 6.2% 2-months later when fasting glycemia was 132 mg/dL and postprandial glycemia 137 mg/dL. The patient's hemogram results also recovered: hemoglobin increased from 10.3 to 13.3 g/dL, MCV from 105.4 to 96.9 fL, and reticulocyte percentage from 2.55 to 0.74% in 3 months.

Discussion

This patient received dapson to treat cutaneous condition of leukoclastic vasculitis with a good response but did not achieve complete remission. During a period of over 3 years, we observed an abrupt reduction of HbA1c during two courses of dapson treatment for recurrent cutaneous lesions. His HbA1c increased to 7.6% after the first course of dapson treatment. Similar changes in the HbA1c were also observed during the second course of dapson treatment (Fig. 1). In the literature, low HbA1c induced by dapson has been reported in one study of NOD mice⁵ and six case

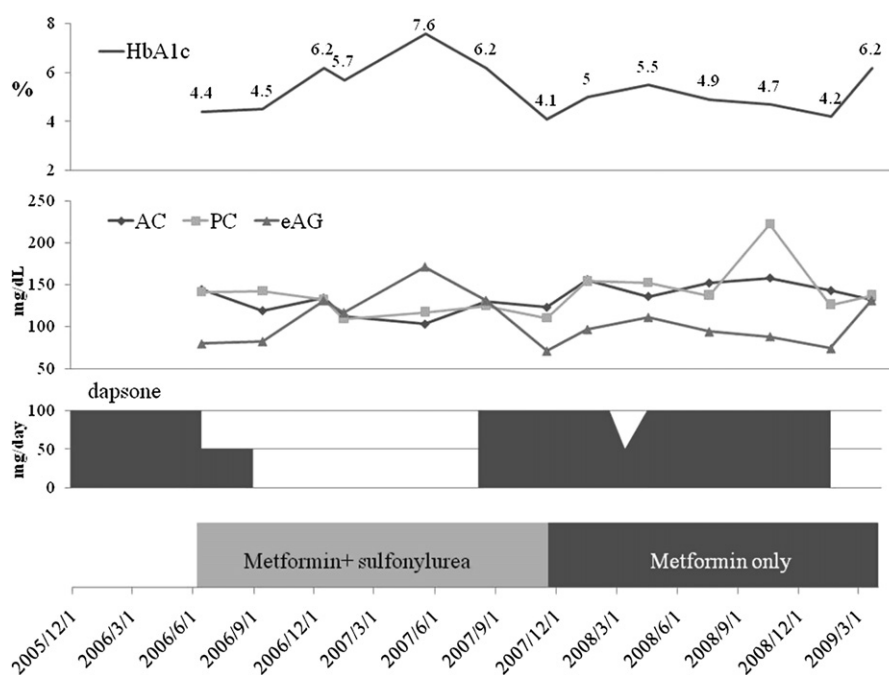


Figure 1 Interference of HbA1c readings in a patient receiving dapson treatment. AC: fasting plasma glucose; PC: postprandial plasma glucose; eAG: estimated average glucose value = $(\text{HbA1c} \times 28.7) - 46.7$ mg/dL⁴.

reports in humans.^{6–11} To our knowledge, this is the first case showing recurrent low HbA1c after repeated administration of dapsone.

HbA1 is a negative hemoglobin and can be detected by cation-exchange chromatography, which was first reported by Allen in 1958.¹² HbA1 can be further divided into different components, including HbA1a, HbA1b and HbA1c. HbA1c was formed by non-enzymatic condensation of glucose with the N-terminal valine residues of the β -chains of hemoglobin. Initially, glucose condensates bind hemoglobin to form an unstable Schiff base. After Amadori rearrangement, the labile Schiff base switches into a stable ketoamine (1-deoxy, 1-aminofructose). Glucose condensates also bind to the NH₂-terminal valine of the α -chain and certain epsilon amino groups of the lysine residues on the α - and β -chains.¹³ HbA1c values depend on erythrocyte lifespan and the assay methods used. Some conditions, such as kidney disease, erythropoietin injection,¹⁴ hemolytic anemia,¹⁵ hemoglobinopathy,¹⁶ or chronic lymphocytic leukemia¹⁷ can affect HbA1c measurements. This patient had macrocytic anemia. Although metformin may decrease intestinal absorption of vitamin B12 and folic acid, it rarely causes anemia. Besides, the MCV was around 102.1–109.8 fL, which was not large enough to reach the criteria of megaloblastic anemia. Non-megaloblastic causes were considered, including hemolytic anemia, hemorrhage, alcohol, hypothyroidism, and bone marrow disorders.¹⁸ This patient didn't have any symptom of bleeding or hypothyroidism. Also, his reticulocyte percentage increased during administration of dapsone and decreased after discontinuation of dapsone. Dapsone may reduce the survival life of erythrocytes and aged erythrocytes are susceptible to hemolysis.¹⁹ Metformin-induced hemolysis has also been reported,²⁰ but this case received metformin continuously and the dosage did not change. After discontinuation of dapsone, hemoglobin increased and reticulocyte decreased remarkably. Therefore, dapsone-induced hemolysis was the most likely cause of his anemia and low HbA1c.

There are many methods for measurement of HbA1c. These methods are mostly based on either cation differences (such as in cation-exchange chromatography, electrophoresis, and isoelectric focusing) or structural differences (such as in affinity chromatography and immunoassay).²¹ Our hospital uses Primus CLC 385 to quantify HbA1c. The HbA1c results indirectly come from the measurement of total glycated hemoglobin by the boronate affinity method. Elevated fetal hemoglobin would artificially lower HbA1c on Primus CLC 385.²² However, a hemoglobin variant is probably not the cause of low HbA1c in this patient because HbA1c raised and fell several times. The hemoglobin electrophoresis also revealed no elevated hemoglobin H, hemoglobin A2 or hemoglobin F.

Since the lifespan of erythrocyte is 120 days, we can use HbA1c to predict the average plasma glucose in the previous 3 months.¹³ In this case, we saw the patient's estimated average glucose calculated by HbA1c was much lower than fasting plasma glucose and 2-hour postprandial glucose during dapsone therapy (Fig. 1). In addition to dapsone-induced hemolysis, another explanation is dapsone-induced oxygen stress. Hydroxylamine, a dapsone metabolite, reacts with oxyhemoglobin (Fe²⁺) to form methemoglobin (Fe³⁺). The process of methemoglobin

formation depletes reduced glutathione, then generates reactive oxygen species and impairs antioxidant defenses.²³ In one study in non-insulin-dependent diabetic patients, HbA1c levels were significantly negatively correlated with scavenging capacity of oxygen radicals.²⁴ HbA1c production is also decreased under oxygen tension.²⁵

This case report has some limitations. First, fructosamine was unavailable and so was not used for appropriate monitoring of glycemic control. Previous reports have shown that fructosamine is not changed under conditions of hemolysis and dapsone treatment.^{7,11} Second, we did not check haptoglobin, lactate dehydrogenase, or serum unconjugated bilirubin to make the definite diagnosis of hemolytic anemia. However, dapsone-induced hemolysis should be suspected by macrocytic anemia and reticulocytosis during dapsone treatment.

In conclusion, dapsone is commonly used in diabetic patients who have autoimmune disease or who are immunocompromised. Doctors should be aware that HbA1c levels can be misread as indicating good glycemic control when in fact they are due to dapsone interference. Other tests, such as blood glucose, urine glucose, glycated serum protein, and fructosamine are alternatives to monitor glycemic control in patients treated with dapsone.

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