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FASELY DECREASED HBA$_{1c}$ IN A TYPE 2 DIABETIC PATIENT TREATED WITH DAPSONE

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Abstract

Objective—To discuss a case of a falsely low hemogloin A$_{1c}$ (HbA$_{1c}$) in a transplant patient treated with dapsone and its implications. HbA$_{1c}$ is widely used as a measure of glycemic control in diabetic patients. With the increasing transplant population, it is important to be mindful of medications used in this population that can affect HbA$_{1c}$ and to use other measures of glycemic control to guide treatment decisions.

Methods—We present details of the case and review the relevant literature.

Results—A 61-year-old patient received a liver transplant in 2012 and subsequently was noted to have a falling HbA$_{1c}$ despite evidence of hyperglycemia based on finger-stick glucose and fructosamine measurements. Review of the medical records revealed that the discordance between HbA$_{1c}$ and fingerstick glucose levels developed after initiation of dapsone therapy. Dapsone may lead to a falsely low HbA$_{1c}$ via several mechanisms. Upon cessation of dapsone therapy, the patient's HbA$_{1c}$ returned to pre-dapsone levels.

Conclusion—It is important to be aware of medications commonly used in transplant patients that may lead to a falsely low HbA$_{1c}$ level so that incorrect treatment decisions are not made. Fructosamine correlates with HbA$_{1c}$ and can be used as a measure of glycemic control in transplant patients when HbA$_{1c}$ cannot be used.

CASE REPORT

A 61-year-old Chinese woman underwent a liver transplant in November 2012 for cirrhosis secondary to hepatitis C. Her past medical history was notable for portopulmonary hypertension, leukocytoclastic vasculitis, hyperlipidemia, and type 2 diabetes mellitus (T2DM). She was diagnosed with T2DM several years prior to transplant and was managed with glyburide alone. Her diabetic control varied due to her liver disease, and her hemoglobin A$_{1c}$ (HbA$_{1c}$) level was generally between 6.5 and 8.0%. In patients with cirrhosis, glycemic control is frequently unsatisfactory for several reasons, including

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DISCLOSURE

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impaired glucose homeostasis and impaired glucagon catabolism, which is accompanied by an increased risk of hypoglycemia due to decreased hepatic insulin extraction and decreased hepatic glycogen stores (1,2). In addition, treatment of diabetes in patients with cirrhosis is complex for several reasons, including malnutrition, impaired ability to metabolize certain oral antidiabetic drugs, hepatotoxicity of certain oral antidiabetic drugs, and the risk of hypoglycemia (1,2).

Following her transplant, the patient required insulin for several months to achieve glycemic control. Her fingerstick glucose levels were closely monitored to assist with insulin titration, as her immunosuppressant regimen (including prednisone) was often changed. Once her prednisone was tapered to a maintenance dose of 5 mg, she was able to transition off insulin to metformin and glyburide. On this regimen, the patient reported fasting glucose levels of 120 to 160 mg/dL, yet her HbA_{1c} decreased from 7.1 to 4.9%. Her metformin and glyburide doses were being reduced based on HbA_{1c} results approximately every 6 weeks. Glyburide was stopped based on an HbA_{1c} of 4.3%; however, the patient was reporting fasting glucose levels of 160 to 184 mg/dL and pre-dinner glucose levels of 270 to 285 mg/dL. It became increasingly apparent that there was a discordance between her fingerstick glucoses and HbA_{1c} levels. Repeat testing showed a fructosamine level of 470 μmol/L (range, 190 to 270 μmol/L), fasting glucose level of 140 mg/dL, and HbA_{1c} of 4.2% (Table 1).

An endocrinology eConsult was ordered. Review of the medical records revealed that the patient was started on dapsone 6 months earlier. Prior to dapsone, the patient's HbA_{1c} on insulin alone was 7.1%. One month after initiation of dapsone, her HbA_{1c} was 4.9% on metformin and glyburide. It was felt that the falsely low HbA_{1c} was due to hemolysis induced by dapsone therapy. Dapsone was stopped.

Literature Search

A systematic review of the literature was performed. The terms "dapsone and hemoglobin A_{1c}" were entered into PubMed to search for relevant articles. Twelve articles were returned in the search results. All 12 articles and their references were reviewed.

DISCUSSION

Measurement of HbA_{1c} was incorporated into clinical practice in the 1980s after studies demonstrated that it correlates with blood glucose measurements (3,4). Today, it is used as an indicator of glycemic control and as a diagnostic test for diabetes mellitus (4). HbA_{1c} is formed by nonenzymatic condensation of glucose with the N-terminal valine residue of the β chains of hemoglobin (4,5). Therefore, HbA_{1c} reflects the glucose level an erythrocyte has been exposed to during its lifespan and is a measure of glycemic control over the last 3 months, with the immediately preceding 30 days contributing 50% to the HbA_{1c} (4). These measurements help guide treatment decisions. However, HbA_{1c} values depend both on erythrocyte lifespan and assay methods (5). Therefore, conditions and medications that affect red blood cell turnover and erythrocyte lifespan lead to false measurements of HbA_{1c} (6). Dapsone can lead to a falsely low HbA_{1c} (4).

In our patient, there was a dramatic decrease in HbA_{1c} after dapsone was started (despite evidence of hyperglycemia based on fingerstick glucose levels) (Table1). Of note, the patient was not experiencing any hypoglycemia during this time, but the doses of her diabetes medications were being reduced based on the HbA_{1c}. Six months later, a large discrepancy was noted between HbA_{1c} and fructosamine (Table 1). The accuracy of the HbA_{1c} was questioned, and it was thought that the dapsone was causing a falsely low HbA_{1c}. After cessation of the medication, her HbA_{1c} returned to pre-dapsone values, and furthermore, her HbA_{1c} values now correlated with fructosamine (Table 1). In addition, based on the score calculated using the Naranjo algorithm (7), this was a probable adverse drug reaction.

There are several case reports of falsely low HbA_{1c} levels in patients on dapsone, including reports of patients infected with the human immunodeficiency virus (8,9), patients with autoimmune and skin conditions (5,10–14), transplant patients (15), and patients on dapsone therapy for other reasons, such as necrobiosis lipoidica and leprosy (12,16–18).

Dapsone leads to a falsely low HbA_{1c} via 3 mechanisms. One of the mechanisms by which dapsone can cause a misleadingly low HbA_{1c} is by inducing hemolysis. While we do not have measures of hemolysis in our patient, her hemoglobin dropped about 1 g/dL from baseline after initiation of dapsone, and 1 month after cessation of the drug, her hemoglobin increased by about 2 g/dL and has remained at this level, suggesting that the dapsone was inducing hemolysis. In addition, prior case reports demonstrated that patients on dapsone have elevated reticulocyte counts and elevated lactate dehydrogenase levels, which are indicative of hemolysis (5,9,11,12,14,17,18). Hemolysis does not always result in anemia (9), although most patients on dapsone do experience a 1 to 2 g/dL reduction in hemoglobin (5,8,12). Therefore, hemolysis can lead to a misleadingly low HbA_{1c} by reducing erythrocyte lifespan. Second, dapsone promotes the oxidation of hemoglobin to methemoglobin, which interferes with the high-performance liquid chromatography assay used to measure HbA_{1c}, since it will not spike in the correct HbA_{1c} location and hence, will give a falsely low value (4,8,12–14,16). In addition, diminished activity of nicotinamide adenine dinucleotide-methemoglobin reductase leads to decreased breakdown of methemoglobin and further affects the HbA_{1c} measurement (13). Finally, dapsone is thought to reduce erythrocyte survival independent of its hemolytic effect (4,13).

Given the multiple mechanisms by which dapsone leads to a falsely low HbA_{1c}, another measure of glycemic control is necessary in patients taking this medication. Fructosamine measures glycated serum proteins and therefore can serve as an alternative measure of glycemic control over a 2- to 3-week period (9,13,14). However, because fructosamine measures glycosylation of serum albumin, it is less reliable in patients with hypoalbuminemia (9,13).

Dapsone is being increasingly used for prophylaxis against *Pneumocystis jiroveci* pneumonia in the growing transplant population, especially when patients are unable to tolerate trimethoprim-sulfamethoxazole (19). Our patient was on dapsone for this reason. A falsely low HbA_{1c} in a transplant patient on dapsone has been demonstrated (15). Therefore, providers should be attentive to possible falsely low HbA_{1c} values and should be careful

when using it for glycemic monitoring in the setting of dapsone use. In this case, use of the falsely low HbA_{1c} to guide therapy led to a medical error and inappropriate adjustments in the patient's therapy. However, Tharavanij et al (20) demonstrated that fructosamine correlates with HbA_{1c} in islet transplant patients and therefore can be used to evaluate glycemic control in transplant patients. When our patient was on dapsone, fructosamine should have been used to monitor her glycemic control.

Case Follow-up

As noted above, the patient had a dramatic decrease in her HbA_{1c} after initiation of dapsone therapy despite evidence of hyperglycemia by fingerstick glucoses and fructosamine. Use of the HbA_{1c} to guide therapy led to incorrect treatment decisions. Her HbA_{1c} returned to predapsone levels after cessation of therapy and became consistent with fructosamine and fingerstick glucoses levels. Currently, she is doing well on oral agents and very-low-dose insulin glargine.

CONCLUSION

This case illustrates the fact that the HbA_{1c} measurement may be falsely low when certain medications—such as dapsone—are being used. With the growing transplant population, it is critical to be mindful of instances when the HbA_{1c} may be falsely low in this population so that incorrect treatment decisions are not made. In settings where HbA_{1c} cannot be used, fructosamine serves as a good alternative. Therefore, in transplant patients receiving dapsone, we recommend following fructosamine levels.

Abbreviation

HbA_{1c}	hemoglobin A_{1c}

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Table 1

Summary of Patient Data: Medications and Laboratory Values

	Months 0–40	Months 42–44	Month 45	Month 47	Month 48	Month 49	Month 50	Month 52[a]	Month 54	Month 56	Month 62
Key medications	Glyburide	Insulin	Insulin	Glyburide and dapsone started March 2013	Glyburide and metformin, dapsone	Glyburide and metformin, dapsone	Glyburide and metformin, dapsone	Metformin, dapsone (glyburide stopped for <1 week)	Glyburide and metformin, NO dapsone	Glyburide and metformin, septra SS, NO dapsone	Glyburide and metformin, insulin, septra SS, NO dapsone
Fructosamine (range, 190–270 μmol/L)								407		392	
Glucose (range, 70–99 mg/dL)			120–150 (fasting)	80–140 (fasting)	100–160 (fasting)	120–150 (fasting) and 200 (pre-dinner)	120–150 (fasting) and 200 (pre-dinner)	166–184 (fasting) and 271–285 (pre-dinner)		110–140 (fasting) and 160–200 (pre-dinner)	110–154 (fasting)
Hemoglobin A_{1c} (range, 4.3–5.6%)	7.0–8.3		7.1	4.9	4.8	5.2	4.6	4.2	6.8	7.8	7.0

[a] Dapsone was stopped *after* month 52 and has not been restarted since.