Drug-Induced Falsely Low A1C: Report of a Case Series From a Diabetes Clinic

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Introduction

A1C is a universally used blood test to assess glycemic control during the previous 2–3 months in patients with diabetes (1). It is used to monitor long-term glycemic control and assess patients' response to therapy and is a quality-assessment tool for diabetes care in the United Kingdom and throughout the world (2). Hence, it is important that any condition that can affect the true value of A1C be considered in clinical practice.

We report here a case series of patients attending our adult secondary care diabetes clinic, all of whom were noted to have considerably lower A1C levels than what would be expected from their daily blood glucose monitoring results. The cause for the falsely low A1C in each case was found to be drug-induced hemolysis, most commonly due to sulfasalazine use. When A1C is inaccurate, fructosamine levels can be another way of monitoring average glycemic control, particularly in patients taking drugs that cause drug-induced hemolysis (1,3).

Background

In some patients, A1C can be falsely low. Any condition that shortens the life span of red blood cells, and therefore the length of time hemoglobin is exposed to glucose in the bloodstream, can falsely lower A1C. Examples include hemolytic anemias, hemoglobinopathies, splenomegaly, blood loss, blood transfusions, chronic liver or kidney disease, and some drugs (4,5).

Drugs that cause subtle hemolysis without anemia may interfere with the accuracy of A1C measurement (6). Reported examples of such drugs include dapsone, sulfasalazine, ribavirin, and antiretroviral drugs (4). There are few data from randomized, controlled studies on the subject of drug-induced hemolysis causing falsely low A1C levels; thus, there is little information about the prevalence of this phenomenon.

There are, however, several case reports. The first, reported in 1979 from Kesson et al. (6), described a case of dapsone-induced hemolysis causing a falsely low A1C. The patient had type 1 diabetes and was taking dapsone for dermatitis herpatiformis. His A1C was normal despite high blood glucose levels. His reticulocyte count was raised, but there was no evidence of significant hemolysis causing anemia or jaundice.

Tack et al. (7) in 1996 and Albright et al. (8) in 2002 also reported drug-induced hemolysis falsely lowering A1C. Tack et al. reported the cases of two patients with type 1 diabetes, one of whom received dapsone and the other sulfasalazine. Albright et al. reported the case of a 35-year-old patient with type 1 diabetes who was taking dapsone for necrobiosis lipoidica. All of these patients had low A1C despite high blood glucose and fructosamine levels. In the case reported by Albright et al., a reduction in the dose of dapsone resulted in the return of A1C to an appropriate level. Again, in each of these cases,

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hemolysis was subclinical with no anemia or jaundice.

Polgreen et al. (9) in 2003 reported on four patients with HIV and diabetes. Two of the patients were taking dapsone as prophylaxis for *Pneumocystis carinii* infection, one was taking ribavirin, and one was taking trimethoprim-sulfamethoxazide. In all of these cases, A1C was found to be inaccurately low in comparison to blood glucose levels.

Finally, Robertson et al. (10) in 2008 reported an additional cause of falsely low A1C in a patient with type 2 diabetes and chronic hepatitis who was taking ribavirin. When the ribavirin was stopped, the patient's A1C returned to an appropriate level.

Design and Methods

We undertook a retrospective case note review of all patients attending our adult diabetes clinic between 2010 and 2015 to compare laboratory A1C measurements with daily blood glucose monitoring data. We looked in detail at specific cases in which there was a significant mismatch in these two parameters. In such cases, we extended our analysis back to the earliest available records and investigated the cause of the inconsistency. We report here a series of cases in which the inconsistency between blood glucose data and A1C was caused by drug-induced hemolysis. We also examined values of an alternative biomarker, fructosamine, in these patients.

A1C levels were measured by ion exchange high-pressure liquid chromatography using a Tosoh G8 analyser (Tosoh Bioscience, Tokyo, Japan). Fructosamine samples were sent to Sandwell General Hospital, in West Midlands, U.K., for analysis. Fructosamine levels were measured by a colorimetric method, which is based on the ability of fructosamine to reduce nitroblue tetrazolium to formazan at an alkaline pH (11).

The relationship between A1C and fructosamine can be expressed as a linear regression analysis (Eq. 1)

$$\text{A1C (\%)} = 0.017 \times \text{fructosamine (}\mu\text{mol/L)} - 1.61$$

EQ 1.

(12,13). For each of our patients, we used the fructosamine level to calculate the predicted A1C (i.e., the A1C expected given the fructosamine level) and compared it to the measured A1C value.

Case Series Presentation

Case 1

Patient 1, a 57-year-old man with type 1 diabetes diagnosed in 1982, was under regular review at our diabetes clinic. He was diagnosed at the age of 22 years, and his current treatment included insulin glargine 56–58 units nightly, insulin aspart with meals, and metformin 1,000 mg twice daily. His medical history included celiac disease, dermatitis herpetiformis, and obesity.

The patient's A1C tests, taken at his primary care provider's clinic, were consistent with good glycemic control. Between March 2010 and May 2015, his A1C levels were always <6.0%. Despite blood glucose readings of 145–270 mg/dL on his glucose meter, his A1C was suspiciously low at 4.9–5.4% and occasionally as low as 4.5%.

The patient was taking dapsone 150 mg twice daily for dermatitis herpetiformis, a skin condition related to celiac disease. Therefore, the possibility of dapsone-induced hemolysis leading to falsely low A1C was considered.

In January 2011, a fructosamine level was checked along with his usual A1C test. The patient's A1C again was suspiciously low at 5.0%; however, his fructosamine level was elevated at 389 µmol/L (reference range 200–285 µmol/L). This fructosamine level correlates to an A1C level of 8.2%, which would have been more consistent with his daily blood glucose readings.

The patient discontinued dapsone in May 2015. His A1C taken 1 month later in June 2015 was 9.4%. This was in keeping with his daily blood glucose values at the time of 180–270 mg/dL. Interestingly, the patient developed falsely low A1C levels again when dapsone was reintroduced in March 2016. His A1C was reported as 5.0% and 4.2% in June 2016 and August 2016, respectively, despite little change in his daily blood glucose monitoring levels (Figure 1).

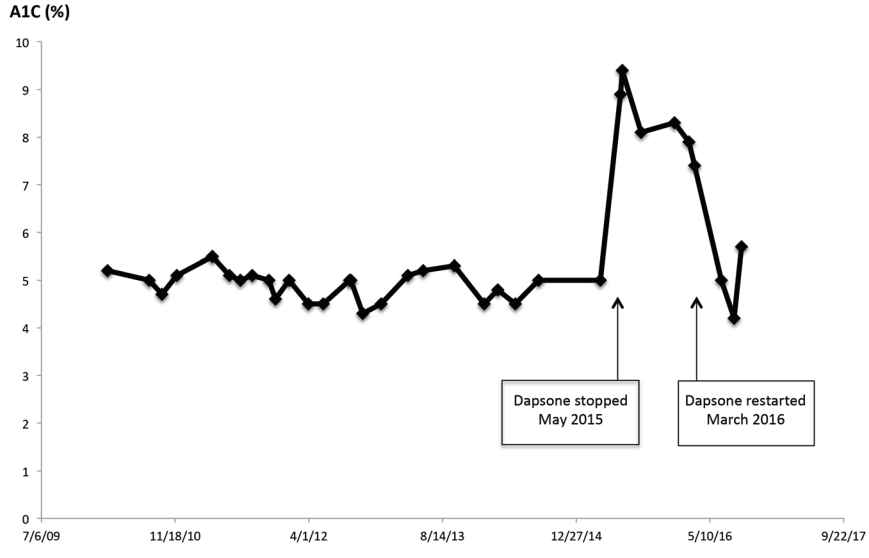

FIGURE 1. Case 1 patient's A1C over time. Arrows indicate discontinuation and recommencement of dapsone.

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TABLE 1. Demographics, Measured and Predicted A1C, Daily Blood Glucose, Fructosamine Levels, and Drug Causing Falsely Low A1C FOR Patients 1–5

	Age (years)	Sex	Type of Diabetes	Daily Blood Glucose (mg/dL)	Measured A1C (%)	Fructosamine (µmol/L)	A1C Predicted From Fructosamine (%)	Drug Causing Falsely Low A1C	A1C After Withdrawal of Drug (%)
Patient 1	57	M	Type 1	144–180	5.0	389	8.2	Dapsone	9.4
Patient 2	67	F	Type 1	180–270	6.1	491	10.0	Sulfasalazine	N/A
Patient 3	62	M	Type 2	72–126	4.3	229	5.5	Sulfasalazine	6.7
Patient 4	77	M	Type 2	90–234	4.3	385	8.1	Sulfasalazine	N/A
Patient 5	67	F	Type 2	198–252	6.6	440	9.1	Sulfasalazine	N/A

After this case, we undertook a retrospective review to look for similar cases in our clinic cohort.

Case 2

Patient 2 was a 67-year-old woman with type 1 diabetes who was prescribed sulfasalazine for Crohn's disease. Her capillary blood glucose levels ranged from 180 to 270 mg/dL, but her A1C was low at 6.1%. Her fructosamine level was elevated at 491 µmol/L.

Case 3

Patient 3 was a 62-year-old man with type 2 diabetes and ankylosing spondylitis, for which he received sulfasalazine. His capillary blood glucose recordings were between 72 and 145 mg/dL. However, his A1C was lower than expected at 4.9%, and his fructosamine level was 229 µmol/L. When he stopped taking sulfasalazine in May 2015, his A1C rose to 6.7% despite no change in his capillary blood glucose readings.

Case 4

Patient 4 was a 77-year-old man with type 2 diabetes and psoriatic arthritis, for which he was given sulfasalazine. His capillary blood glucose measurements were 90–234 mg/dL, but his A1C was low at 4.3%. A simultaneous fructosamine level was high at 385 µmol/L.

Case 5

Patient 5 was a 67-year-old woman with type 2 diabetes and undifferentiated connective tissue disease who was taking sulfasalazine. Her capillary blood glucose measurements were between 198 and 252 mg/dL. Her A1C was lower than expected at 7.2%, but her fructosamine level was elevated at 440 µmol/L.

Patient demographics and details of these five cases are summarized in Table 1.

We did not formally test for hemolysis in case 1, but the patient's hemoglobin, bilirubin, and liver function tests were normal. The patient in case 4 had the most extensive testing for hemolysis. His bilirubin, liver function tests, and hemoglobin level were normal. His blood film showed target cells. His lactate dehydrogenase was normal (344 U/L), as was haptoglobin (150 mg/dL) and immunoglobulins. His direct Coombs test was negative. In case 2, the patient was found to have a marginally raised reticulocyte count at 3.5%. These findings would fit with previous case reports of drug-induced hemolysis, which reported that hemolysis is usually subclinical (7,8).

Question

Should an alternative measure of average glycemic control be used instead of A1C in patients for whom there is the possibility of drug-induced hemolysis (e.g., those taking sulfasalazine)?

Commentary

Glycated hemoglobin is a measure of long-term glycemic control (1). It is formed by the nonenzymatic permanent linkage of glucose in the bloodstream to hemoglobin within red blood cells, forming HbA_{1a}, HbA_{1b}, and HbA_{1c} (A1C), the latter of which is the most abundant and measured through blood testing (3). The concentration of glucose within the blood and the time for which the hemoglobin is exposed to the glucose, are directly proportional to degree of A1C formation (1). A1C estimation from average blood glucose values has already been described in the literature (Table 2) (14). The life span of an average red blood cell is 120 days; therefore, A1C provides a measure of the average blood glucose level over the preceding 90–120 days (1,3). Any condition that shortens the life span of red blood cells thus shortens the length of time hemoglobin is exposed to circulating blood glucose; hemolysis will therefore falsely lower A1C levels (3,5).

A1C testing has a significant role in diabetes management. It gives an average indication of glycemic control and therefore avoids the day-to-day variation apparent through blood glucose monitoring (5). A1C has been shown in several clinical trials

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TABLE 2. Relationship Between Average Blood Glucose and A1C (14)

Average Blood Glucose (mg/dL)	A1C (%)
97	5
126	6
155	7
184	8
213	9
241	10
268	11
297	12

(e.g., the U.K. Prospective Diabetes Study and the Diabetes Control and Complication Trial) to be a strong predictor of the risk of developing the microvascular complications of diabetes (1). It is a quantitative and reliable measure and forms the basis of glycemic control targets in national and international guidelines (2,15). A1C also has a role in the diagnosis of diabetes. A diagnosis can be made if a person's A1C is ≥6.5% with symptoms of diabetes (2,16).

Fructosamine is similar to A1C in that it can be used as a measure of mid-term glycemic control (1). However, instead of measuring glycated hemoglobin, it is a measure of glycated protein in the blood, 80% of which is albumin (1). The higher the blood glucose level is, the more glycated proteins there are, and therefore the higher the fructosamine level will be. The normal value range for fructosamine is 200–285 µmol/L (11). However, the level can be altered by changes to serum albumin concentration (e.g., during acute illness or with liver disease) (3). Fructosamine reflects glycemic control over a period of 14–21 days, which is the half-life of albumin (1).

Fructosamine has not been used or studied to the same extent as A1C, and there remains little evidence that fructosamine levels correlate with the risk of developing diabetes complications (3).

In the past few years, there has been interest in measuring glycated albumin, both for its role in the pathogenesis of diabetes complications and for use as a robust biomarker for monitoring glycemia (17). Fructosamine measurement involves quantification of all serum glycated proteins and is affected by total protein levels, uric acid concentrations, and other factors (17). Recent studies have confirmed that glycated albumin has a correlation with microvascular complications similar to that of A1C (17). Fructosamine levels are often checked when A1C results do not correlate with daily blood glucose levels, especially if there is the possibility of drug-induced haemolysis.

In our index case (patient 1), the patient had hemolysis induced by the drug dapsone, which he was taking for dermatitis herpetiformis. However, we found sulfasalazine to be the drug that most frequently caused drug-induced hemolysis in our diabetes clinic population. Dapsone is a synthetic sulphone that is used to treat autoimmune and allergic disorders because of its anti-inflammatory properties. It is well known to cause hemolysis through its metabolites, which can increase oxidative stress, cause methemoglobinemia, reduce red cell survival, and precipitate hemolytic anemia; this may be marked in patients with glucose 6 phosphate dehydrogenase (G6PD) deficiency (18). Sulfasalazine is an aminosalicylate and an anti-inflammatory agent used in chronic inflammatory illnesses such as inflammatory bowel disease and rheumatoid arthritis. It is known to cause hemolysis through immune-mediated mechanisms, and it can also precipitate hemolytic anemia in G6PD-deficient individuals (19). None of our patients developed anemia, and they were not tested for G6PD deficiency.

Clinical Pearls

- A1C and fructosamine are both measures of mid- to long-term glycemic control.
- A1C may be falsely low when medical conditions or drugs cause hemolysis, which shortens the life span of red blood cells.
- Fructosamine levels should be considered as an alternative to A1C in patients for whom A1C appears consistently lower than blood glucose readings would suggest and for whom there is an identifiable cause or high suspicion of hemolysis.

Conclusion

This case series demonstrates that A1C values may be falsely low in a significant number of patients attending a diabetes clinic given that sulfasalazine and dapsone are commonly used drugs. In our experience, sulfasalazine was the most common cause of anomalous A1C results. Larger studies are needed to determine whether A1C is reliable in the majority of patients taking sulfasalazine or whether another measure such as fructosamine would be more appropriate in such patients.

Author Contributions

K.M. researched data and wrote, reviewed, and edited the manuscript. B.M. reviewed and edited the manuscript. B.M. is the guarantor for this work and, as such, had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Duality of Interest

No potential conflicts of interest relevant to this article were reported.

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