Decreased HbA$_{1c}$ Levels Due to Sulfonamide-Induced Hemolysis in Two IDDM Patients

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Regular measurement of HbA$_{1c}$ (percentage) is an essential component of modern diabetes care. Factors that affect the life span of erythrocytes will also influence HbA$_{1c}$ results. In this study, we describe two patients with IDDM, whose regularly determined HbA$_{1c}$ values were considerably decreased with the concomitant use of two related sulfonamide drugs, sulfasalazine and dapsone. The fall in HbA$_{1c}$ results is explained by increased erythrocyte turnover as a product of drug-induced hemolysis. Fructosamine concentrations are not affected by hemolysis and reflected glycemic control better. We conclude that under conditions of persistent subclinical hemolysis, as occurs during the use of sulfonamides, HbA$_{1c}$ is not a reliable indicator of glycemic control.

R egular evaluation of the percentage of HbA$_{1c}$ is an important and effective component of diabetes care (1). Most laboratory assays used to determine HbA$_{1c}$ are influenced by disturbances in the hemoglobin structure (2,3). Factors that affect the life span of erythrocytes also affect HbA$_{1c}$ levels. In this study, we describe in detail the significant influence of chronic hemolysis that is induced by sulfonamides on HbA$_{1c}$ levels in two IDDM patients.

Case 1
A female, born in 1938 and diagnosed with IDDM in 1970, was fairly well regulated on various insulin regimens, including pump therapy. HbA$_{1c}$ values were 7.5–8.0%. High-performance liquid chromatography, DIA-MAT, Bio-Rad, Veenendaal, The Netherlands, reference value, 4.8–6.0%. Since 1973, she suffered from seropositive rheumatoid arthritis (RA), for which she was treated in 1980 with 1,000 mg b.i.d. sulfasalazine, with good clinical results. However, at routine controls, her HbA$_{1c}$ concentration decreased to 4.3–5.0%, while daily glucose profiles measured by self-monitoring showed unchanged values, mainly between 5 and 14 mmol/l. Furthermore, serum fructosamine remained clearly above normal at ~380 μmol/l (colorimetric test with nitroblue tetrazolium, a commercially available kit from Roche NV, Mijdrecht, The Netherlands; normal value, <280 μmol/l). In 1992, when the sulfasalazine treatment was discontinued, HbA$_{1c}$ rose subsequently to 7.5–9.0%. In 1994, sulfasalazine was re-instituted. Weekly laboratory evaluations again showed that the HbA$_{1c}$ concentra-

<table>
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<th>7.2</th>
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<td>fructosamine</td>
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<td>396</td>
<td>376</td>
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**Figure 1**—Illustration of the course of haptoglobin levels (g/l, left y-axis) and HbA$_{1c}$ levels (%) at 3-month intervals (right y-axis) in case 1. Laboratory values for hemoglobin and fructosamine determined at specific time points are indicated across the top of the graph; the use of sulfasalazine is indicated across the bottom.

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IDDM, insulin-dependent diabetes mellitus; RA, rheumatoid arthritis.
Decrease of HbA₁c levels by sulfonylamides

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<td>396</td>
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Haptoglobin (g/l)

![Graph showing HbA₁c levels over time with dashed line indicating dapsone and trimethoprim administration.]

Figure 2—Illustration of the course of haptoglobin levels (g/l, y-axis, right y-axis) and HbA₁c levels (%) over time (months, x-axis) for case 2. Laboratory values for LDH, hemoglobin, fructosamine, and reticulocytes determined at specific time points are indicated across the top of the graph; the use of dapsone is indicated across the bottom. The large arrow refers to the day of kidney transplantation; the smaller arrows refer to the day that dapsone medication was discontinued.

Case 2
A female, born in 1948 and diagnosed with IDDM in 1970, developed progressive renal failure due to diabetic nephropathy since 1990. Metabolic control was only moderate (HbA₁c values, 8.8–10%), despite an intensive (multiple injection) treatment. Because of end-stage renal disease, she underwent a successful renal transplant from her HLA-identical sister in March 1995. The patient was treated routinely with prednisone, cyclosporin, and famotidine and, in addition, 100 mg dapsone and 200 mg trimethoprim, both once daily for Pneumocystis carinii prophylaxis (she was allergic to the usual prophylaxis of cotrimoxazol). Based on self-performed blood glucose measurements, her diabetes was still moderately-to-poorly regulated during this period, but her HbA₁c levels decreased to as low as 2.8% and remained around 3–4% in the months thereafter. Fructosamine values clearly remained above normal. Further laboratory investigations revealed elevated lactate dehydrogenase (LDH) levels and reticulocyte counts and very low levels of haptoglobin, despite a fairly normal hemoglobin count, all consistent with hemolysis. After discontinuation of dapsone and trimethoprim, the HbA₁c increased 3 months later to 10.3%, but fructosamine results remained unchanged (Fig. 2).

Summary
We have described two IDDM patients, who were in stable metabolic control. During the simultaneous use of sulfonylamides, HbA₁c grossly decreased. The data strongly suggest that the fall in HbA₁c was related to persistent low-grade hemolysis. As a consequence, the average age of the red blood cells is considerably shortened; because the glycation of proteins is essentially an aging process, the lower mean age of erythrocytes results in a low HbA₁c. In these two cases, the concurrent use of sulfonylamides almost certainly induced hemolysis, which is a well-known side effect of these drugs (4–6). Apparently, HbA₁c is quite a sensitive indicator of hemolysis, since the changes of HbA₁c in our patients closely paralleled the changes of haptoglobin. Thus, under the clinical conditions of decreased erythrocyte survival and increased bone marrow maturation of red blood cells (such as persistent hemolysis), HbA₁c levels are not a reliable index of glycomic control. Note that the interferences described in this study were not caused by errors in the HbA₁c assay; virtually every laboratory method measures for "falsely low" values. Erythrocyte life span has no influence on the fructosamine assay, which therefore could be used as an alternative under these conditions, despite some disadvantages of this method in general use (2,7). In conclusion, drugs like sulfonylamides can induce hemolysis and thereby falsely lower HbA₁c values. This clinical situation may occur more often than expected and deserves more attention.

References