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 erythrocytopoiesis 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.

Regular 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 1958 and diagnosed with IDDM in 1970, was fairly well regulated on various insulin regimens, including pump therapy (HbA_{1c} values ~7.5–8.0% [high-performance liquid chromatography, DIA-MAT, Bio-Rad, Veenendaal, The Netherlands; reference value, 4.8–6.3%]). Since 1973, she suffered from seropositive rheumatoid arthritis (RA), for which she was treated in 1990 with 1,000 mg b.i.d. sulfasalazine, with good clinical results. However, at routine controls, her HbA_{1c} concentration decreased to 4.5–5.0%, 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 nitrobluetetrazolium, 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 reinstituted. Weekly laboratory evaluations again showed that the HbA_{1c} concentra-

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hemoglobin	8.1	7.1	7.2	7.2 mmol/l
fructosamine	394	396	376	408 μmol/l

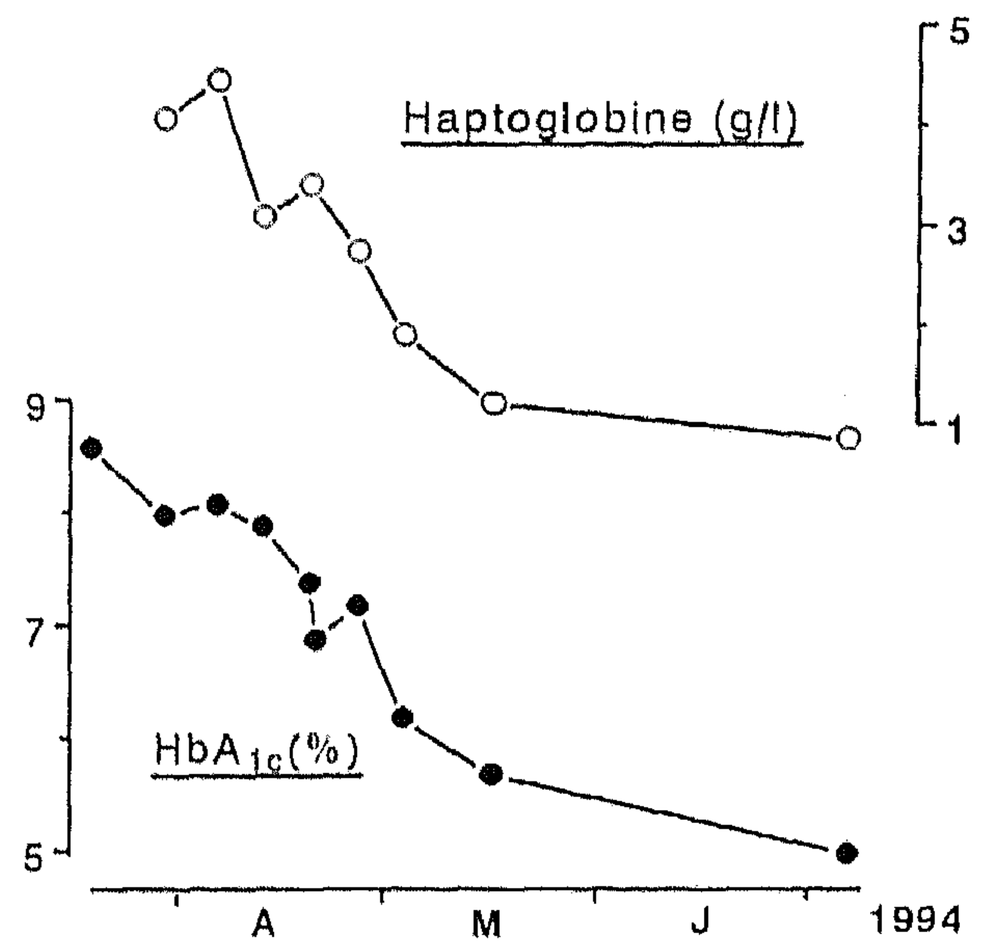

Figure 1—*Illustration of the course of haptoglobin levels (g/l, ○, right y-axis) and HbA_{1c} levels (%, ●, left y-axis) over time (months, x-axis) for case 1. Laboratory values for hemoglobin and fructosamine determined at specific time points are indicated across the top of the graph; the use of sulfasalazine is indicated across the bottom.*

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LDH, lactate dehydrogenase; RA, rheumatoid arthritis.

LDH	557		486	281	242	U/l
hemoglobin	6.6		7.2	8.4		mmol/l
fructosamine		352	358	379	396	μmol/l
reticulocytes	53	52	46	3		%

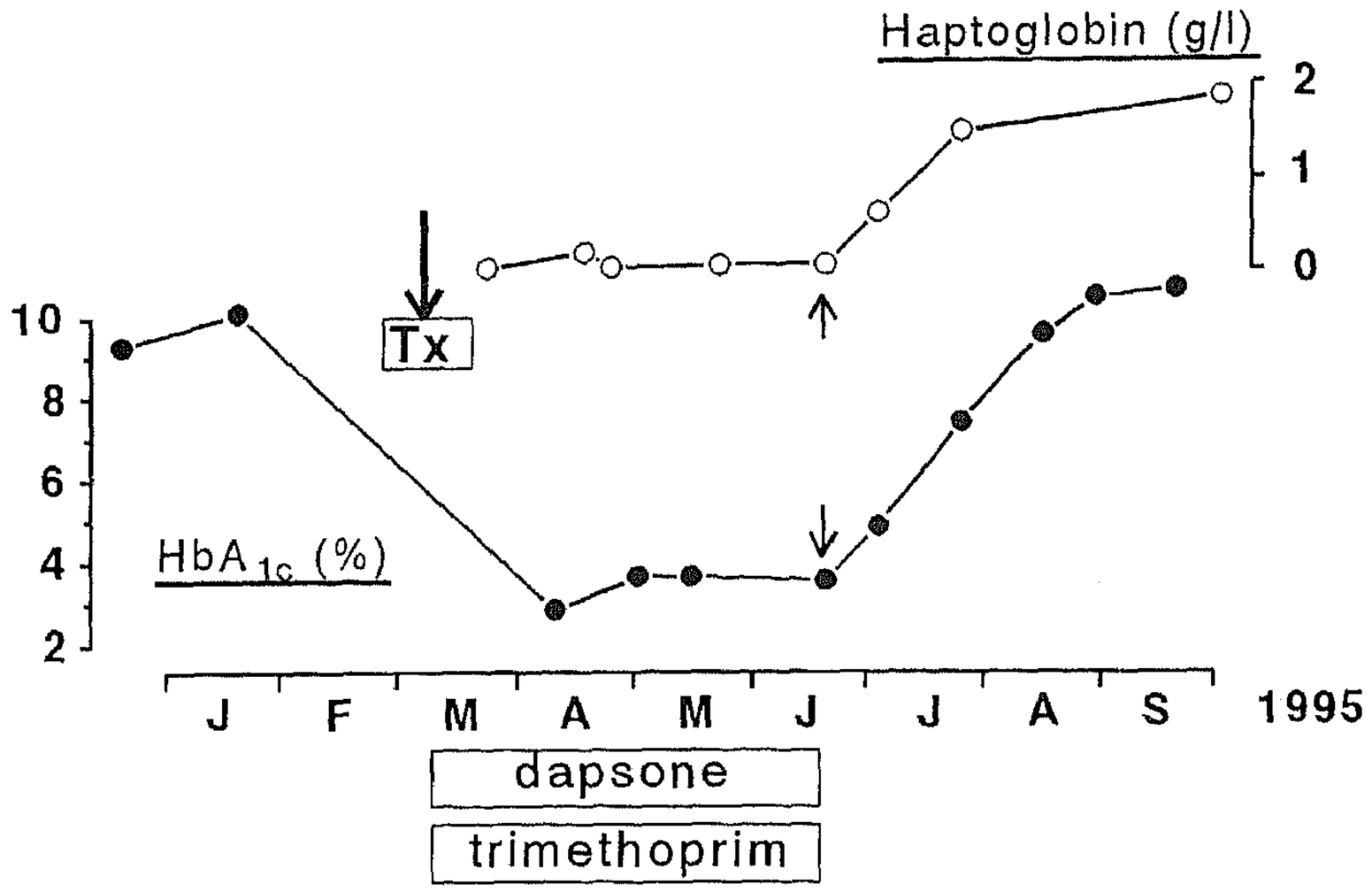

Figure 2—*Illustration of the course of haptoglobin levels (g/l, ○, right y-axis) and HbA_{1c} levels (%, ●, left y-axis) over time (months, x-axis) for case 2. Laboratory values for LDH, hemoglobin, fructosamine, and reticulocytes determined at specific time points are indicated across the top of the 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.*

tion decreased gradually within some weeks, while serum fructosamine remained unchanged (Fig. 1). Sulfasalazine induced a clear decrease in haptoglobin and a small decrease in hemoglobin, while reticulocyte count increased to 36‰, all consistent with chronic hemolysis.

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 (HbA_{1c} 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 HbA_{1c} 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 HbA_{1c} 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 sulfonamides, HbA_{1c} grossly decreased. The data strongly suggest that the fall in HbA_{1c} 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 HbA_{1c}. In these two cases, the concurrent use of sulfonamides almost certainly induced hemolysis, which is a well-known side effect of these drugs (4–6). Apparently, HbA_{1c} is quite a sensitive indicator of hemolysis, since the changes of HbA_{1c} 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), HbA_{1c} levels are not a reliable index of glycemic control. Note that the interferences described in this study were not caused by errors in the HbA_{1c} 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 sulfonamides can induce hemolysis and thereby falsely lower HbA_{1c} values. This clinical situation may occur more often than expected and deserves more attention.

References

1. Larsen ML, Horer M, Mogensen EF: Effect of long-term monitoring of glycosylated hemoglobin levels in insulin-dependent diabetes mellitus. *N Engl J Med* 323:1021–1025, 1990
2. Goldstein DE, Little RR, Lorenz, RA, Malone JI, Nathan D, Peterson CM: Technical review: test of glycemia in diabetes. *Diabetes Care* 18:896–909, 1995
3. Eberentz-Lhomme C, Ducrocq R, Intrator S, Elion J, Nunez E, Assan R: Haemoglobinopathies: a pitfall in assessment of glycosylated haemoglobin HbA_1. *Diabetologia* 27:596–598, 1984
4. Hoigné R, Malinverni R, Somntag R: Sulfonamides, other folic acid antagonists and miscellaneous antibacterial drugs. In *Meyler's Side Effects of Drugs*. 12th ed. Dukes MNG, Ed. Amsterdam, Elsevier, 1992, p. 718–719
5. van Hees PAM, van Elferen LW, van Rossum JM, van Tongeren JHM: Hemolysis during salicylazosulfapyridine therapy. *Am J Gastroenterol* 70:501–505, 1979
6. DeGowin RL: A review of the therapeutic and hemolytic effects of dapsone. *Arch Intern Med* 120:242–248, 1967
7. Smart LM, Howie AF, Young RJ, Walker SW, Clarke BF, Smith AF: Comparison of fructosamine with glycosylated hemoglobin and plasma proteins as measures of glycemic control. *Diabetes Care* 11:433–436, 1988