CONCISE REPORT

Glycosylated Hemoglobins (GHb): An Index of Red Cell Survival

By Simon Panzer, Gerhard Kronik, Klaus Lechner, Peter Bettelheim, Erich Neumann, and Robert Dudczak

Levels of glycosylated hemoglobins (GHb) are significantly (p < 0.0005) lower in patients with hemolytic anemia (n = 20; mean = 3.9% ± 0.1% SD GHb of total Hb) compared to patients with nonhemolytic anemia (n = 16; mean = 7.0% ± 0.7% GHb) and normal controls (n = 30; mean = 6.7% ± 0.7% GHb). A curvilinear correlation between GHb and red cell survival is demonstrable (n = 20; r² = 0.88; p < 0.001). Determination of GHb may be useful as a screening test for hemolytic anemia and for the evaluation of the degree of hemolysis, provided that diabetes mellitus can be excluded.

Glycosylated Hemoglobins (GHb) are formed through progressive glycosylation of Hb β-chains in proportion to blood glucose concentration. Determination of GHb has therefore been successfully used for monitoring diabetic patients. Since values of GHb not only depend on the blood glucose level but also on red cell lifespan, we were prompted to study the possibility of using this parameter as a measure of red cell survival in nondiabetic patients with various forms of anemia.

MATERIALS AND METHODS

Patients

Patients who took part in this study were being investigated for suspected hemolytic disease, and fully informed consent was obtained from each subject. Patients with hemolytic anemia (HA, n = 20; sex ratio 1:1; age 13–81 yr) carried the following diagnoses: immune hemolytic anemia due to warm antibodies (n = 14), immune hemolytic anemia due to cold antibodies (n = 2), and hereditary spherocytosis (n = 4; 2 of them before and after splenectomy). Hemoglobin (Hb) was 10.0 ± 2.4 g/dl, packed cell volume (PCV) 30.5 ± 7.0%, red blood cell count (RBC) 2.9 ± 0.9 x 10¹²/liter, reticulocyte count 7.3 ± 9.5%. Patients with nonhemolytic anemia (NHA, n = 20; sex ratio 1:1; age 15–76 yr) had the following diagnoses: myeloproliferative diseases (n = 11), acute lymphoblastic leukemia (n = 3), iron deficiency anemia (n = 3), chronic lymphocytic leukemia (n = 2), Hodgkin’s disease (n = 1). Hemoglobin in this group was 8.5 ± 1.8 g/dl, PCV 28.0 ± 5.7%, RBC 2.85 ± 0.5 x 10¹¹/liter, reticulocyte count 0.83 ± 11.2%. Healthy subjects (n = 30; sex ratio 1:1; age 14–75 yr) served as controls. None of the subjects had been transfused in the 3 wk before the study and all were in a hematologic steady state during the investigation. Patients with overt diabetes mellitus or abnormal oral glucose tolerance tests were excluded from the study.

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RESULTS

GHb Concentrations in Patients With HA and NHA

GHb was significantly (p < 0.0005) decreased in patients with HA (3.9% ± 0.1% GHb of total Hb), but was within the normal range in patients with NHA (7.0% ± 0.7% GHb). In normal controls, GHb was 6.7% ± 0.7% GHb, range 6.0%–8.0% GHb (Fig. 1).

Relation Between GHb Levels and Red Cell Survival

A curvilinear correlation between GHb levels and red cell survival was found (r² = 0.88; p < 0.001; Fig. 2). Sums of squares residuals were higher in the monoeponential model as compared to the linear regression with logarithmic abscissa. The level of saturation was 6.5% GHb. All patients with T50-RBC survival of less than 30 days had decreased levels of GHb.

Rise of GHb in Patients With Hereditary Spherocytosis After Splenectomy

In two patients with hereditary spherocytosis who underwent splenectomy, hematologic remission was
Fig. 1. Concentrations of GHb in healthy controls compared to patients with hemolytic and nonhemolytic anemia.

**DISCUSSION**

It is known that GHb formation depends on mean blood glucose concentration and red cell lifespan. The former is the reason that this parameter is successfully used for monitoring diabetic patients, assuming normal red cell survival. Studies have shown that GHb levels reflect diabetic control within the preceding 4–8 wk. In a few cases of hemolytic anemia, low levels of GHb were reported, indicating that shortened red cell lifespan decreases glycosylation of hemoglobin. Our study shows that patients with anemia due to considerable red cell destruction have low GHb values, while GHb is invariably normal in patients with nonhemolytic anemia. Likewise, even elevated GHb concentrations were reported in iron deficiency anemia. Moreover, we demonstrated a significant correlation between GHb and Cr-tagged red cell survival, indicating that GHb values reflect accurately the severity of in vivo hemolysis. Evaluating the relation between GHb levels and red cell survival, the sums of squares residuals were higher in the monoexponential model as compared to the linear regression with loga-

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**Fig. 2.** Correlation between Cr-tagged red cell survival and GHb in patients with anemia. Open symbols represent patients with nonhemolytic anemia (n = 10); closed symbols represent patients with hemolytic anemia (n = 10); triangular symbols correspond to stable (diaryzed) GHb levels. The broken line shows the linear regression with logarithmic abscissa; the dotted line the monoexponential model (equation in parenthesis); the hatched area indicates the normal range.

**Fig. 3.** Hematologic recovery and delayed rise of GHb in two patients with hereditary spherocytosis after splenectomy. One week after splenectomy, both patients had normal Hb values; GHb rose towards the normal range not before 4 wk. (Open symbols, patient 1; closed symbols, patient 2; the hatched area indicates the normal range.)
rhythmic abscissa, indicating a better fit for the latter curve. Noteworthy, the level of saturation was 6.5% GHB, about the mean GHB level obtained in healthy subjects.

Except for 7 patients, we did not remove the reversible aldimine form before GHB determination. In the normal red cell lifespan, we observed a reduction of GHB of less than 10% due to the reversible aldimine component, while higher levels of the labile precursor were observed in reduced red cell lifespan. Thus, the difference of GHB between HA and NHA would be considerably higher after dialyzation of hemolysates. Avoiding the time consuming procedure of dialyzation allows rapid GHB measurements in a routine use, however.

In diabetics, GHB levels do not reflect actual blood glucose concentrations, but rather the mean blood glucose values during the preceding 4–8 wk. It may be assumed that actual GHB levels in patients with HA are representative for the degree of hemolysis within the preceding weeks. This conclusion is supported by our observation that after successful splenectomy in two patients with hereditary spherocytosis, GHB values rose gradually within 4 wk towards the normal range, while hematologic recovery was already complete 1 wk after operation. We conclude from the presented data, provided that diabetes mellitus and posthemorrhagic anemia can be excluded, that determination of GHB may serve as a rapid and simple screening test that is reliable as an indicator of hemolysis and may make labeled erythrocyte survival studies unnecessary in many patients. Furthermore, it may be useful for monitoring therapy in patients with HA.

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