Glycosylated haemoglobin in rheumatoid arthritis

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SUMMARY Shortened red cell survival has a role in the anaemia of rheumatoid arthritis (RA), but direct measurement of it is difficult. Glycosylated haemoglobin (HbA₁) provides an index of red cell life span in normoglycaemic patients, because glycosylation depends on both the concentration of blood glucose and the duration of erythrocyte survival. HbA₁ was significantly lower in 30 patients with RA ($5.6 \pm 0.7\%$, mean $\pm$ SD) than in 15 healthy controls ($7.3 \pm 0.7\%$) and 14 patients with osteoarthritis ($7.4 \pm 0.7\%$, $p < 0.001$). HbA₁ was depressed less in active RA than during remission, which is consistent with diminished red cell production in active RA. These data on HbA₁ confirm that shortened red cell survival is common in RA, and point to diminished red cell production in active disease. Determination of HbA₁ should prove to be of clinical value in the assessment of normoglycaemic patients with RA but is an inadequate index of glucose homeostasis in diabetics with RA.

The anaemia of rheumatoid arthritis (RA) has been attributed to diminished red cell production and shortening of red blood cell (RBC) survival.¹⁻³ HbA₁ content of erythrocytes is a function of the rate and duration of glycosylation, which in turn are dependent on the concentration of glucose and the duration of erythrocyte survival.⁴ Thus in normoglycaemic patients HbA₁ reflects the average age of circulating RBC.

In this study we have measured HbA₁ in normoglycaemic patients with RA.

Patients and methods

HbA₁ was measured in 30 nondiabetic patients with RA, 14 patients with osteoarthritis (OA), and 15 healthy controls. Patients with glycosuria or a non-fasting midmorning blood glucose of >6 mmol/l were excluded. The RA patients were 7 males and 23 females, ages 21-79 (mean 57 years), with mid-morning blood glucose of 4.0 ± 0.7 mmol/l (mean $\pm$ SD). Nineteen patients had active RA as judged by the presence of 2 or 3 of the following features: active synovitis (17 patients) elevated erythrocyte sedimentation rate (ESR >30 mm in first hour; 15 patients), and anaemia (Hb <11.5 g/dl; 10 patients). Therapy

for RA included nonsteroidal anti-inflammatory drugs (NSAID) in all patients, gold in 16, D-penicillamine in 6, and azathioprine in 2. The patients with OA were 5 males and 9 females ages 18-82 (mean 59 years), with a mean midmorning blood glucose of 4.4 ± 0.7 mmol/l. All were receiving NSAID therapy similar to that of the RA patients. Heparinised blood samples for HbA₁ determination were stored at 4°C for up to 3 days. HbA₁ was measured as the proportion of total haemoglobin by chromatographic separation at 22.5°C on a Biorex microcolumn (Isolab Ltd., Akron, Ohio, USA). Statistical significance was assessed by Student's *t* and χ^2 tests.

Results

HbA₁ was significantly lower in patients with RA ($5.6 \pm 0.7\%$, mean $\pm$ SD) than in patients with OA ($7.4 \pm 0.7\%$) and controls ($7.3 \pm 0.7\%$, $p < 0.001$). In active RA, HbA₁ was depressed less ($5.9 \pm 0.6\%$) than in patients in remission ($5.1 \pm 0.6\%$, $p < 0.005$). Thus HbA₁ was within the normal range ($5.9-8.7\%$) in 11 of 19 patients with active RA but only 2 of 11 patients with inactive disease ($p < 0.04$, Fig. 1). Furthermore, HbA₁ correlated directly with ESR ($r = 0.5$, $p < 0.006$, Fig. 2) and inversely with haemoglobin concentration ($r = 0.41$, $p < 0.002$, Fig. 3). There was no correlation with age, sex, or therapy. In particular, HbA₁ was similar whether or not patients

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Fig. 1 Glycosylated haemoglobin (HbA_{1c}) in 15 healthy controls, 30 patients with rheumatoid arthritis (RA), and 14 patients with osteoarthritis (OA).

Fig. 2 Correlation of HbA_{1c} with erythrocyte sedimentation rate.

Fig. 3 Inverse correlation of HbA_{1c} with haemoglobin concentration.

were receiving gold thiomalate therapy ($5.7 \pm 0.6\%$ and $5.5 \pm 0.8\%$ respectively).

Discussion

Shortened RBC survival has been demonstrated by radioactive chromium and ferrokinetic studies in small numbers of patients with RA.^{2,3} By contrast the measurement of HbA_{1c} is a far simpler approach, since in the absence of prolonged hypoglycaemia low HbA_{1c} indicates a younger population of circulating RBC. Levels of HbA_{1c} similar to those described here have been reported in chronic renal failure,⁵ during venesection in haemochromatosis,^{6,7} and with the rise in haemoglobin concentration during iron therapy for iron deficiency anaemia.⁸ Still lower levels of HbA_{1c} occur in haemolytic anaemia.⁹

The low HbA_{1c} in RA found in this study suggests increased RBC destruction, since there was no evidence of hypoglycaemia or recent rise in haemoglobin concentration. Any occult gastrointestinal blood loss caused by NSAID therapy was insufficient to depress HbA_{1c} in the patients with osteoarthritis and is therefore unlikely to be a factor responsible for the low HbA_{1c} in RA. Thus the low HbA_{1c} suggests increased haemolysis.

The smaller reduction in HbA_{1c} found in patients with active RA may be related to a decrease in RBC production (so that fewer young cells circulate)⁸ or to impaired splenic clearance of older erythrocytes. Indeed, clearance of heat damaged RBC has been shown to be significantly lower in patients with active RA than in those with inactive disease.¹⁰ However, diminished RBC production is the more likely explanation of the phenomenon, since HbA_{1c} was inversely correlated with haemoglobin concentration in our patients.

In view of the abnormalities discussed above HbA_{1c} is probably an inadequate index of glucose homeostasis in rheumatoid patients.

Our data on HbA_{1c} confirm that shortened RBC survival is common in RA. Furthermore the data indicate that bone marrow depression may be as important as haemolysis in the pathogenesis of anaemia in active RA. In contrast to radiotracer techniques and bone marrow studies HbA_{1c} determination is simple and suitable for any euglycaemic patients. In patients with RA, HbA_{1c} levels in the normal range suggest bone marrow depression, which is generally a result of disease activity.

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