

Reticulocyte indices rapidly reflect an increase in iron availability for erythropoiesis

An increase in blood hemoglobin content following iron supplementation can confirm a diagnosis of iron deficiency, but the long delay in response is a major drawback and makes this approach inappropriate for routine clinical use. We evaluated the ability of red blood cell and reticulocyte indices to reflect the increase in iron availability for erythropoiesis. We found that the reticulocyte hemoglobin content and, in particular, the percentage of hypochromic reticulocytes rapidly reflect the response of erythropoiesis to iron medication in iron-deficient subjects.

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A total of 310 female students were screened for anemia (Hb < 125 g/L) using the HemoCue blood hemoglobin system (HemoCue AB, Ångelholm, Sweden) in routine health checks when entering Kuopio University. In the case of anemia, a venous blood sample was taken and iron deficiency was defined as a transferrin receptor (TfR) concentration above 2.4 mg/L (IDeA TfR-IT assay (Orion Diagnostica, Espoo, Finland).^{1,2} A complete blood cell count including measurement of red blood cells and reticulocyte parameters and hemoglobin concentration was done with an Advia 120 Hematology System (Bayer Diagnostics Co., Tarrytown, NY, USA).³ A total of 14 students (4.5%) were defined as iron-deficient and 8 of them were given oral iron supplementation (200 mg of elemental iron daily in two doses in the form of ferrous sulfate, Obsidan Schwarz Pharma, Verman) and the same laboratory tests for evaluation of iron status were repeated on days 2, 7, 14, 21 and 28 after the start of treatment.

Reference ranges for the percentage of hypochromic red blood cells (%HYPOm), percentage of hypochromic reticulocytes (%HYPOr) and the content of hemoglobin in reticulocytes

(CHR) were produced by measuring these parameters in a population of healthy females (n = 57, aged between 19 and 50). Hematologic diseases, C-reactive protein value >10 mg/L, TfR value > 2.4 mg/L and ferritin value < 10 µg/L were criteria for exclusion from the reference population. The reference ranges (the central 95% of the distribution of the recorded values in the healthy population) for %HYPOm, %HYPOr and CHR were 0.1–3.4%, 3.7–43.5% and 28.8–34.5 pg, respectively, which agreed well with previously published values.^{4–6} Before the start of oral iron medication the mean %HYPOm and %HYPOr values in the iron-deficient subjects (n = 8) were 21.0% and 60.0%, respectively (Table 1). The %HYPOr values fell remarkably rapidly after the start of iron medication and a considerable decrease was evident within seven days as the mean %HYPOr (± SD) decreased from 60±19.8% to 21±8.3% (Figure 1). A comparable response was observed in the CHR which increased fairly fast and returned to within the normal range in the week after starting iron supplementation. In contrast, the %HYPOm responded very slowly to the iron medication and values within the normal range were not reached until after one month of therapy. Hb and ferritin values increased slowly during the iron treatment and both parameters returned close to the lower limits of the reference ranges after two weeks. Plasma TfR concentration declined in the course of the iron treatment and was within the reference range by one month in most cases (Table 1). However, as this response is so slow it is only of very limited use when judging the effectiveness of iron medication.

Thus far, %HYPOm and CHR have been regarded as the most useful cellular indices in the assessment of iron status, and the %HYPOm has been widely adopted in clinical practice guidelines concerning iron supplementation during erythropoietin treatment. They have also been suggested to be useful in the diagnosis of iron-deficiency anemia.^{3,4,7–10} Besides aiding the diagnosis of a depletion of iron stores, red blood cell and reticulocyte parameters could potentially be helpful in monitoring the response of erythropoiesis to iron supplementation. However, in the follow-up of iron-deficient subjects treated with oral iron medication the response of %HYPOm was very slow

Table 1. Laboratory values reflecting iron status before and after a 28-day course of oral iron medication in 8 young females with iron deficiency anemia.

| Index | Before medication Mean±SD | Day 2 Mean±SD | Day 7 Mean±SD | Day 14 Mean±SD | Day 28 Mean±SD |
|-----------------|------------------------------|------------------|-------------------------|-------------------------|-------------------------|
| Hb (g/L) | 109±11.0 | 109±10.5 | 113±6.6 | 119±4.4 ^a | 128±4.8 |
| TfR (mg/L) | 4.1±1.65 | 3.8±1.41 | 3.3±1.23 ^a | 3.1±1.05 ^b | 2.3±0.67 ^b |
| Ferritin (mg/L) | 5.2±7.41 | 16.2±21.14 | 16.1±10.87 ^a | 16.6±7.79 ^b | 21.8±10.07 ^c |
| MCV (fL) | 76.7±7.93 | 78.1±7.86 | 78.6±6.72 | 78.4±5.87 | 81.6±4.82 ^a |
| CHR (pg) | 26.9±3.39 | 27.6±3.22 | 31.1±2.56 ^b | 31.4±1.99 ^c | 32.5±1.53 ^c |
| %HYPOm | 21.0±19.01 | 19.5±12.90 | 19.0±12.20 | 13.9±13.98 ^a | 10.7±11.88 ^b |
| %HYPOr | 60.0±19.77 | 56.4±21.08 | 20.8±8.30 ^c | 13.7±6.94 ^c | 7.4±4.16 ^c |

The statistical significances are based on Student's t-test for paired data (^a = p<0.05; ^b = p < 0.01; ^c = p < 0.001).

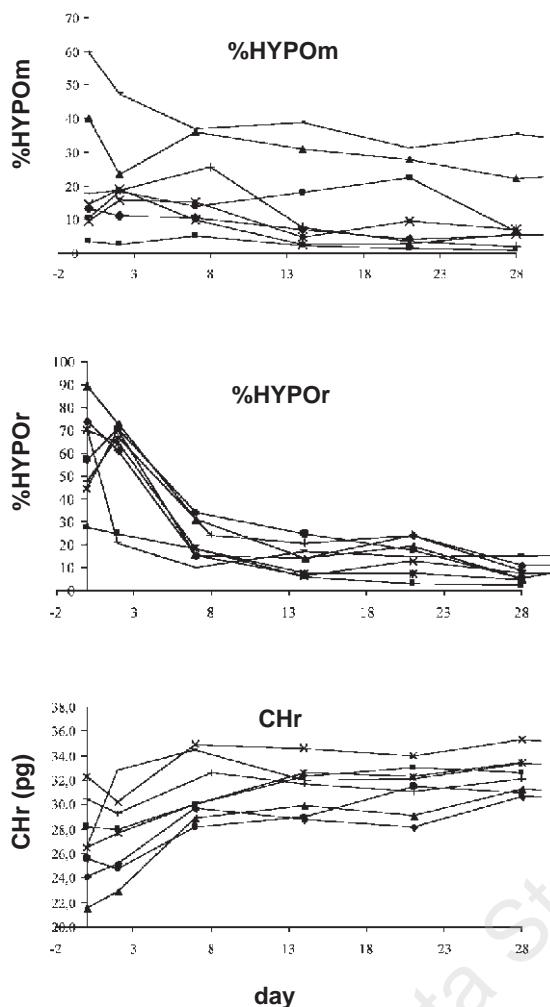


Figure 1. Figure 1. The responses of %HYPOM (top), %HYPOr (middle), and CHr (below) to oral iron medication in each of the iron deficient subjects (n=8). The samples were analysed on days 2, 7, 14, 21 and 28 after the start of iron medication.

and comparable to that of hemoglobin whereas the increase in CHr, and the fast decrease of %HYPOr could be observed already after 5 to 7 days. This suggests that CHr and particularly %HYPOr rapidly reflect increased iron availability for erythropoiesis and could be useful for monitoring the effectiveness of oral iron medication.

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Combined therapy with desferrioxamine and deferiprone in thalassemic patients: effect on urinary iron excretion

Desferrioxamine B mesylate (DFO) and deferiprone (1,2-dimethyl-3-hydroxypyrid-4-one) (DFP) have been used for the treatment of hemosiderosis in patients with thalassemia major.¹ Preliminary studies have suggested that chelation is enhanced by the simultaneous administration of DFO and DFP.²⁻⁶ In this study we evaluated the urinary iron excretion (UIE) of patients during treatment with DFO or DFP or the two drugs simultaneously.

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Sixty patients (32 females) with transfusion-dependent β -thalassemia major, aged 16 -37.7 years (mean: 24 ± 4.5), were included in the study. Their ferritin levels ranged between 512 and 9359 $\mu\text{g/L}$ (mean: 3118 ± 1861). Nine patients were splenectomized. Eleven had anti-hepatitis C antibodies. All patients had been on regular chelation therapy with either DFO