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Clinica Chimica Acta 355 (2005) 83–89

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Soluble transferrin receptor concentration is not superior to log ferritin for evaluating erythropoiesis in adolescents with iron deficiency anemia

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Received 6 October 2004; received in revised form 14 December 2004; accepted 15 December 2004

Abstract

Background: This study investigated the associations of soluble transferrin receptor (sTfR), log ferritin, the ratio of sTfR to log ferritin (sTfR-F index), and the log of the ratio of sTfR to ferritin [log(sTfR/F)] vs. reticulocyte production during iron deficiency.
Methods: Fluorescent intensity of reticulocytes, immature reticulocyte fraction (IRF), reticulocyte maturity index (RMI), sTfR, and serum ferritin were measured in 149 adolescents.
Results: There were no significant differences in reticulocyte parameters between the iron deficiency anemia (IDA) subjects with sTfR≥4.9 mg/l and those with sTfR<4.9 mg/l. However, IDA subjects with log ferritin <0.73 μg/l exhibited significantly higher mean values for IRF and RMI, compared to those with log ferritin ≥0.73 μg/l (2.75±1.36% vs. 1.45±1.01%, $p<0.05$; 2.76±1.31% vs. 1.46±1.09%, $p<0.05$). In the non-IDA group, reticulocytes averaged 0.97±0.31% in subjects with sTfR≥2.1 mg/l, which were significantly above the values in those with sTfR<2.1 mg/l (0.72±0.16%, $p=0.005$), but no significant differences were observed in reticulocyte parameters between the subjects with log ferritin ≥1.35 μg/l and those with log ferritin <1.35 μg/l. Correlation coefficients of log ferritin vs. RMI ($r=-0.41$) were higher than those of sTfR, sTfR-F index, and log(sTfR/F) vs. RMI ($r=0.24$, $r=0.30$, and $r=0.28$, respectively) in IDA subjects.
Conclusion: Reticulocytopoiesis is more closely associated with log ferritin value than with sTfR concentrations in IDA patients, although sTfR significantly reflects erythropoietic activity in non-IDA subjects.

Keywords: Erythropoiesis; Body iron status; Soluble transferrin receptor; Log ferritin

1. Introduction

Iron deficiency is one of the most common single nutritional deficiencies, especially among infants,

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doi:10.1016/j.cccn.2004.12.010

young children, and adolescents [1]. Iron transport in the blood is carried out by transferrin, which facilitates cellular iron uptake through its interaction with a specific membrane receptor, the transferrin receptor (TfR). Soluble TfR (sTfR) is a truncated monomer of the tissue receptor and measurement of sTfR has been used as a diagnostic tool for the evaluation of total body iron status [2,3]. The sTfR level does not appear to be influenced by the acute phase response and has been reported to have low biological variability [4]. The sTfR originates mostly from erythroblasts and to a lesser extent from reticulocytes. In a healthy adult, approximately 80% of TfRs are in the erythroid precursors in bone marrow [5].

Effective erythropoiesis can be monitored by measurement of reticulocytes. Flow cytometric analysis enables evaluating maturation of reticulocytes by quantitating the fraction of reticulocytes within low-, middle-, and high-fluorescence intensity regions (LFR, MFR, and HFR, respectively) [6]. Reticulocyte fluorescence intensity is directly proportional to the amount of intracellular RNA. Immature reticulocyte fraction (IRF), the sum of MFR and HFR, which corresponds to young reticulocytes released prematurely, is a useful parameter to evaluate erythropoietic activity in anemia. The reticulocyte maturity index (RMI) is calculated from the proportion of reticulocyte subpopulations and can be used as an early and sensitive predictor of erythropoiesis [7].

Because erythroid precursors and circulating reticulocytes shed their TfR into the blood during maturation, sTfR is a useful marker to monitor erythropoiesis [8]. However, there have been few studies that have closely examined associations between sTfR and RMI for evaluating reticulocytopoiesis according to body iron status. In the present study, we investigated which index among sTfR, log ferritin, the ratio of sTfR to log ferritin (sTfR-F index), and the log of the ratio of sTfR to ferritin [log(sTfR/F)] most accurately reflects reticulocyte production in subjects with or without iron deficiency anemia (IDA).

2. Methods

A total of 149 adolescents (36 males and 113 females) aged 15–17 years (mean 16.1 years) were investigated by measurements of hemogram, immature reticulocyte fractions, sTfR, and serum ferritin. The study population consisted of 73 IDA subjects and 76 apparently healthy non-anemic controls. This study was explained to, and was approved by, both parents and directors at each educational center, and only volunteers were included in the study population. The study was approved by the Committee of Ethics of the Inha University Hospital, and informed consent was obtained from all subjects. Seven subjects who had a previous history of iron or vitamin supplementation (n=5) or recent infections (n=2) were excluded from this study, because in inflammation, erythropoiesis may be blunted by inhibitory cytokines. No one had a history of bleeding, hemolysis, or renal insufficiency or had taken any medication. Non-anemic subjects with normal serum iron (≥50 μg/dl) and ferritin levels (≥12 μg/l) were classified as healthy controls. When the subjects showing a decreased serum ferritin concentration (<12 μg/l) and a decreased serum iron level (<50 μg/dl) and also had a decreased hemoglobin level (<12 g/dl), we considered them to have IDA.

The healthy control (n=76) and IDA subjects (n=73) were each divided sequentially into 2 groups (Tables 2 and 3) based first on the mean sTfR concentration and then based on the mean log ferritin concentration applicable to each group and shown in Table 1. We further stratified the IDA adolescent subjects into 2 groups based on those with a sTfR concentration <20th percentile (1.8 mg/l) or >80th percentile (7.5 mg/l) sTfR value of all subjects in this group. We defined the IDA subgroup with sTfR values >7.5 mg/l as having “frank IDA”. Log ferritin, sTfR-F index, and log(sTfR/F) were defined as the logarithmic values for serum ferritin concentrations, the ratio of sTfR level to log ferritin, and the log of the ratio of sTfR concentration to serum ferritin level, respectively.

After the subjects had fasted >12 h, venous blood was drawn into an iron-free evacuated tube. Complete blood cell counts were measured with EDTA-anticoagulated blood using an electronic counter (SE 9000, Sysmex, Kobe, Japan). Reticulocytes and their subpopulations were analyzed by flow cytometry (R-3000; Sysmex). Reticulocytes were classified into 3 categories by the fluorescence intensity of auramine O staining. RMI was calculated using the equation: