Higher concentrations of serum transferrin receptor in children than in adults[1,2]

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ABSTRACT

Background: The serum transferrin receptor (TfR) concentration in adults is suggested to provide a sensitive measure of iron depletion and together with the serum ferritin concentration to indicate the entire range of iron status, from iron deficiency to iron overload. However, little is known about TfR concentrations in children.

Objective: Our objective was to compare serum TfR and ferritin concentrations and their ratios in children and adults and look for correlations between TfR concentrations and other measures of iron status.

Design: Our study groups were healthy 1-y-old infants (n = 36), 11–12-y-old prepubertal boys (n = 35), and 20–39-y-old men (n = 40).

Results: TfR concentrations were higher in infants ($\bar{x}$; 95% reference interval: 7.8 mg/L; 4.5, 11.1) than in prepubertal boys (7.0 mg/L; 4.7, 9.2) and higher in prepubertal boys than in men (5.8 mg/L; 3.1, 8.5). Geometric mean TfR-ferritin ratios were higher in infants (316; 95% reference interval: 94, 1059) than in prepubertal boys (219; 78, 614) and higher in prepubertal boys than in men (72; 23, 223). By multiple linear regression analysis, the best predictors of TfR concentration were serum iron (P = 0.004) and log serum ferritin (P < 0.0001), both being inverse correlations (R^2 = 0.32). Mean corpuscular volume, blood hemoglobin, transferrin iron saturation, transferrin, and even age seemed to not have an influence on the TfR concentration and erythropoiesis was not a determinant of TfR concentration.

Conclusions: Low serum ferritin and iron concentrations, even within the normal physiologic range, result in high TfR concentrations. The lower the iron stores, the stronger the influence of ferritin on TfR. A high TfR concentration in children, especially in infants, is a response to physiologically low iron stores. Age-specific reference concentrations for TfR are needed. *Am J Clin Nutr* 1999;69:256–60.

KEY WORDS Transferrin receptor, ferritin, iron, mean corpuscular volume, hemoglobin, transferrin, iron status, children, infants, age

INTRODUCTION

Iron deficiency is the most common nutritional deficiency in the world, children being one of the major high-risk groups. Cell-surface transferrin receptors (TfRs) carry iron into the cells, but a truncated form of the receptor is also present in soluble form in the circulation (1). The concentration of circulating TfR has been suggested to provide an accurate and sensitive measure of iron depletion and of iron deficiency at the tissue level in those with depleted iron stores (2). Serum TfR and ferritin together have been suggested to depict the entire range of iron status (2–5). The diagnostic use of serum TfR in children is problematic because *1*) in adults, serum TfR rises not only when iron is deficient, but also when erythropoiesis is hyperplastic; *2*) knowledge of the physiologic concentration of serum TfR in children is poor; and *3*) a lack of standardization of serum TfR assays invalidates comparisons of results obtained with different methods.

To further understand iron physiology in childhood, we compared serum TfR and ferritin concentrations and their ratios in healthy children and adults. By selecting a heterogeneous group of subjects with known dissimilar physiologic iron statuses and laboratory measures of iron status, we were also able to analyze correlations between serum TfR concentrations and other measures of iron status.

SUBJECTS AND METHODS

Subjects

We studied 3 groups of healthy subjects: 1-y-old infants, 11–12-y-old prepubertal boys, and 20–39-y-old men. Thirty-six (12 boys and 24 girls) healthy 1-y-old infants with no history of chronic disease and born at term were recruited from child health centers in the city of Malmö, Sweden (6, 7). The infants had been fed according to Swedish guidelines for infant feeding during the first year of life and had not had feeding problems. Fifty percent of the children were breast-fed at 6 mo of age, 19% were breast-

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Received October 17, 1997.

Accepted for publication July 17, 1998.

fed at 9 mo of age, and 8% were breast-fed at 11 mo of age. Supplementary foods were introduced at 3–6 mo of age. All but 3 of the children were given a Swedish iron-fortified follow-up formula with meals. A trained technician at the pediatric laboratory of the University Hospital of Malmö took the blood samples by finger puncture.

We selected blood samples from the 35 prepubertal boys of 60 healthy boys aged 11–12 y from a study of iron metabolism in Helsinki (8). Only prepubertal boys were selected because their growth rate is low and their iron intake is abundant, which should make iron deficiency unlikely. Those selected had testicular volumes ≤2 mL and had Tanner's pubertal and genital stages of PH1 and G1 (8, 9). A trained nurse at the pediatric laboratory of Helsinki University Central Hospital took the blood samples by venipuncture.

Samples from the men were taken from 40 voluntary, nonremunerated blood donors at the Finnish Red Cross Blood Transfusion Service, Helsinki. To ensure that they were healthy, the donors were selected according to the guidelines of the Council of Europe (10). They were also selected so as to be evenly distributed over the following age groups: 20–24 y (n = 9), 25–29 y (n = 10), 30–34 y (n = 11), and 35–39 y (n = 10). The minimum time elapsed from a previous blood donation was 2 y and the donors had not used iron supplements for >1 mo during the preceding year. Their blood hemoglobin concentration was ≥135 g/L, as measured with a HemoCue photometer (Angelholm, Sweden) in a skin puncture blood sample drawn before the donation. To avoid unnecessary venipunctures, blood samples for the other tests were drawn immediately after blood donation through the same venipuncture site.

Written consent was obtained from the parents of the infants and prepubertal boys. The portion of the study applying to the infants was approved by the Ethical Committee, University of Lund, Sweden. The portion of the study applying to the prepubertal boys was approved by school authorities, those responsible for school health care, and the Ethics Committee of the Hospital for Children and Adolescents, University of Helsinki. Samples from blood donors were taken with the approval of the Ethical Committee of the Finnish Red Cross Blood Transfusion Service, Helsinki.

Laboratory measurements

All blood samples were taken between 0830 and 1400. Blood was collected into EDTA-containing tubes for automated blood cell analysis. Blood hemoglobin and red blood cell mean corpuscular volume (MCV) were determined by using a model T890, JT3, or STKS analyzer (Coulter Electronics Limited, Luton, United Kingdom). The analyzers were calibrated and controlled with the S-Cal standard and the 4C and 5C cell controls (Coulter Electronics Limited).

Serum was separated immediately and frozen at −20°C until analyzed. Serum TfR was measured with an enzyme-linked immunosorbent assay (TfR; Ramco Laboratories, Inc, Houston). In our laboratory, the mean (±SD) ratio between measured and expected values in diluted samples (n = 38) was 0.98 ± 0.11, the intraassay CVs were 5–7% at normal or high concentrations and 13–16% at low concentrations, and the interassay CVs were 6–9% at normal or high concentrations and 13–16% at low concentrations.

Serum ferritin was measured with the ACS:180 by using the ACS Ferritin chemiluminometric immunoassay (Ciba Corning Diagnostics Corp, Medfield, MA). The assay was calibrated with the WHO IRP 80/602 standard (WHO, Geneva). Serum iron was measured with a model 911 automatic analyzer (Hitachi Ltd, Mito, Japan) by using a colorimetric method without deproteinization (Kit 1010 Iron; Orion Diagnostica, Espoo, Finland) and serum transferrin with a model 911 automatic analyzer by using an immunoturbidimetric method with use of anti-human transferrin (catalog no. 67758; Orion Diagnostica). Serum transferrin iron saturation was calculated with the following formula: transferrin saturation (%) = 3.825 × serum iron (μmol/L)/serum transferrin (g/L).

Statistical analyses

Serum ferritin concentrations in all age groups and serum TfR-ferritin ratios in the prepubertal boys had skewed distributions ($P < 0.005$; skewness: 1.40–1.47). Distributions of the TfR-ferritin ratios in infants and men were not skewed (skewness: 0.70 and 0.60, respectively). However, the ferritin concentrations and TfR-ferritin ratios of all age groups were analyzed after logarithmic transformation. The 95% reference intervals for TfR and ferritin concentrations and for TfR-ferritin ratios were set by calculating the mean ± 1.96 SD. All iron-status variables for the different age groups were compared with the Bonferroni test (11). In addition, serum TfR and ferritin concentrations and TfR-ferritin ratios for the different age groups were compared by calculating CIs for the differences in the means (12). For the variables analyzed after logarithmic transformation, differences are given in linear scale as the means and CIs of the ratios of the values. Student's t test was used to analyze differences between the sexes within the group of infants. Simple correlations were evaluated by linear regression analysis. Multiple linear regression analysis with the stepwise minimal R^2 improvement method was used to evaluate associations between serum TfR concentrations and other laboratory measurements (11).

Data from the study by Anttila et al (13) were reanalyzed to obtain distributions of serum TfR-ferritin ratios in the pubertal boys before and after they took iron supplements. We found that the distributions were skewed (1.52 and 2.36, respectively; $P < 0.001$). The upper limits of the 95% reference intervals for the TfR-ferritin ratios were determined after logarithmic transformation.

RESULTS

Our 3 groups of subjects had normal blood hemoglobin concentrations, MCVs, serum iron and transferrin concentrations, and serum transferrin saturations for their ages (**Table 1**). There were no sex-related differences in serum TfR or ferritin concentrations in the infants. The serum TfR and ferritin concentrations and serum TfR-ferritin ratios of our subjects are reported in Table 1. Serum TfR concentrations were higher in the infants than in the prepubertal boys and higher in the prepubertal boys than in the men, the means being 7.8 mg/L (95% reference interval: 4.5, 11.1) in the infants, 7.0 mg/L (95% reference interval: 4.7, 9.2) in the prepubertal boys, and 5.8 mg/L (95% reference interval: 3.1, 8.5) in the men. The difference between infants and boys was 0.8 mg/L (95% CI: 0.1, 1.5) and the difference between boys and men was 1.2 mg/L (95% CI: 0.6, 1.7). No age-related difference was observed in the men. Serum ferritin concentrations were lower in the infants than in the prepubertal boys and lower in the prepubertal boys than in the men, the geometric means being 24 μg/L (95% reference interval: 9, 62) in the infants, 31 μg/L (95% reference interval: 12, 79) in the prepu-

TABLE 1
Results of laboratory tests reflecting the iron status of the study populations

	Infants, age 1 y (n = 36)	Prepubertal boys, age 11–12 y (n = 35)	Men, age 20–39 y (n = 40)
Blood hemoglobin (g/L)[1]	119 (106–128)	129 (120–143)[2]	149 (130–166)[2,3]
Mean corpuscular volume (fL)[1]	77 (72–85)	85 (81–93)[2]	90 (83–100)[2,3]
Serum iron (μmol/L)[1]	10.1 (3.5–21.2)	16.1 (5.3–23.6)[2]	18.1 (2.5–30.0)[2]
Serum transferrin (g/L)[1]	2.8 (1.9–3.3)	2.9 (2.3–3.3)	2.5 (1.6–3.1)[3,4]
Serum transferrin saturation (%)[1]	14 (5–42)	23 (8–32)[5]	31 (4–47)[2,6]
Serum TfR (mg/L)[7]	7.8 (4.5–11.1)	7.0 (4.7–9.2)[5]	5.8 (3.1–8.5)[2,6]
Serum ferritin (μg/L)[8]	24 (9–62)	31 (12–79)	79 (30–208)[2,3]
Serum TfR-ferritin ratio[8]	316 (94–1059)	219 (78–614)[5]	72 (23–223)[2,3]

[1] Median (range).
[2,4,5] Significantly different from infants (Bonferroni test): [2] $P < 0.001$, [4] $P < 0.01$, [5] $P < 0.05$.
[3,6] Significantly different from prepubertal boys (Bonferroni test): [3] $P < 0.001$, [6] $P < 0.01$.
[7] Mean (95% reference interval).
[8] Geometric mean (95% reference interval).

bertal boys, and 79 μg/L (95% reference interval: 30, 208) in the men. There was a 1.3-fold difference between the infants and boys (95% CI: 1.04- to 1.6-fold) and a 2.5-fold difference between the boys and men (95% CI: 2.0- to 3.1-fold). The difference between the ferritin concentrations of the infants and of the prepubertal boys was, however, not significant when tested with the Bonferroni test for multiple comparisons. Again, in the men, no age-related difference was observed. Serum TfR-ferritin ratios were higher in the infants than in the prepubertal boys and higher in the prepubertal boys than in the men, the geometric means being 316 (95% reference interval: 94, 1059) in the infants, 219 (95% reference interval: 78, 614) in the prepubertal boys, and 72 (95% reference interval: 23, 223) in the men. There was a 1.4-fold difference between infants and boys (95% CI: 1.1- to 1.9-fold) and a 3.0-fold difference between boys and men (95% CI: 2.4- to 3.9-fold).

When we analyzed the age groups separately, we found an inverse correlation between serum TfR and log ferritin concentrations ($r = -0.50$, $P = 0.002$) and between serum TfR concentrations and MCVs ($r = -0.40$, $P = 0.02$) in the infants, but not in the other age groups. Unexpectedly, in the prepubertal boys, although not in the other age groups, serum TfR concentrations correlated directly with blood hemoglobin concentrations ($r = 0.39$, $P = 0.02$). We found no correlations between serum TfR, on the one hand, and serum iron, transferrin, or transferrin iron saturation, on the other hand, within any of the age groups.

When we analyzed all subjects together we found that serum TfR concentrations correlated inversely with log ferritin, MCV, blood hemoglobin, serum iron, and transferrin iron saturation and directly with serum transferrin. The correlation with log ferritin was strongest (**Figure 1**). In multiple linear regression analysis with serum TfR concentration as the dependent variable and the other above-mentioned indexes and age as the independent variables, the best predictors of serum TfR concentration were log serum ferritin and serum iron (**Table 2**).

DISCUSSION

The ratio of serum TfR to serum ferritin concentration has been introduced as a sensitive index covering the entire range of iron status (2–5, 13). Recently, Punnonen et al (14) showed that the ratio of TfR to log ferritin was a superior index for identifying iron depletion in a group of patients with the anemia of chronic disease, or iron deficiency anemia, or both. Skikne et al (2) suggested that a TfR-ferritin ratio >500 indicates depleted iron stores in adults. We calculated in healthy pubertal boys that the upper limit of the 95% reference interval of the TfR-ferritin ratio was 1023 before iron medication and 529 after it (13). The respective upper limits of the 95% reference intervals in our study were 1059 for the 1-y-old infants, 614 for the prepubertal boys, and 223 for the men. If a value of 8.5 mg TfR/L, which is the upper limit of the reference values determined by Flowers et al (15) for adults, were used as the cutoff value for iron deficiency in all 3 of our age groups, 33% of the infants, 9% of the boys, and 3% of the men would have been considered iron deficient. None of the infants or men, but 3% of the boys, had ferritin concentrations below a cutoff value of 12 μg/L, which is used often as the criterion for iron deficiency in adults. Twenty-five percent of the infants, 6% of the boys, and 0% of the men had values above the TfR-ferritin ratio cutoff value of 500 used by Skikne et al (2) to indicate depleted iron stores in adults. Consequently, it is obvious that the same cutoff values cannot be used for both adults and children. Present knowledge did not allow us to determine the cutoff values for iron deficiency in the different age groups.

One of the goals of this study was to compare the concentrations of TfR in children and adults. We selected healthy 1-y-old

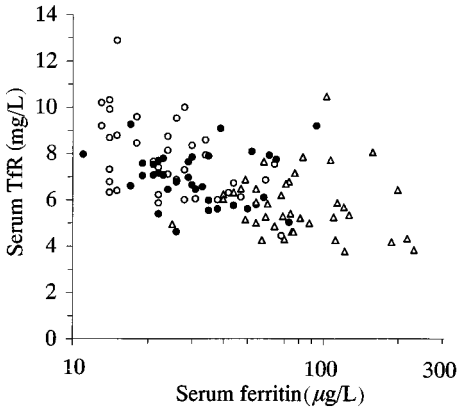

FIGURE 1. Comparison between serum ferritin and transferrin receptor (TfR) concentrations in 1-y-old infants (○), 11–12-y-old prepubertal boys (●), and 20–39-y-old men (△). For all subjects, $r = -0.52$ and $P < 0.0001$.

TABLE 2
Multiple linear regression analysis of serum transferrin receptor concentrations (mg/L)[1]

Independent variable[2]	Parameter estimate	95% CI of estimate	*P*
Intercept	11.7	10.3, 13.1	—
Log serum ferritin (μg/L)	−1.06	−1.43, –0.69	<0.0001
Serum iron (μmol/L)	−0.066	−0.110, −0.022	0.004

[1] R^2 of the model = 0.32.
[2] Best model for serum TfR concentrations. When added to this model, none of the other variables (mean corpuscular volume, blood hemoglobin, transferrin iron saturation, transferrin, or age) was significant, and so they did not improve the model.

infants, prepubertal boys, and men, whose physiologic iron statuses are known to be dissimilar. One-year-old infants are known to have low iron stores. In contrast, the growth rate of boys just before puberty is low and their iron intake abundant, resulting in moderate iron stores. Finally, the iron stores of healthy men aged 20–39 y are known to be large. Our subjects were normal, healthy representatives of a population in which iron deficiency is rare. Therefore, we considered the iron statuses of our subjects normal for their ages.

This is the first time that physiologic concentrations of serum TfR in healthy children and adults were measured by the same method in the same study and thus could be compared. We found higher concentrations in children than in adults and higher concentrations in infants than in prepubertal boys. Indirect data from an earlier study suggested that serum TfR concentrations might be higher in children. Anttila et al (8) found mean (±SEM) serum TfR concentrations of 6.9 ± 0.14, 7.2 ± 0.16, and 7.2 ± 0.15 mg/L in 11.7-, 12.6-, and 13.6-y-old boys with a method used earlier for obtaining reference values ($\bar{x}$ ± SD) of 5.63 ± 1.42 mg/L for adults (15). Singhal et al (16), using the same method (15), reported mean (±SD) serum TfR concentrations of 5.9 ± 1.7 and 7.2 ± 1.8 mg/L in 8-y-old boys and girls. Using a method giving much lower concentrations, Bergström et al (17) reported mean (±SD) serum TfR concentrations of 2.96 ± 0.93 and 2.74 ± 1.01 mg/L in 14-y-old boys and girls, respectively, and of 2.35 ± 0.53 and 2.27 ± 0.67 mg/L in 17-y-old boys and girls, respectively. The reference values for adults given by the manufacturer of the method, 1.54 ± 0.43 mg/L, are even lower. Using the same method, Lönnerdal et al (18) reported concentrations of ≈3 mg/L for 6-mo-old babies.

On the basis of our present data and those cited earlier, it seems that serum TfR concentrations really are higher in children than in adults. TfR concentrations in the circulation depend on the total amount of cells with transferrin receptors in the body (19, 20), which depends mainly on erythropoietic activity. The concentration is also dependent on the density of receptors on individual cells, which increases in iron deficiency (21). Consequently, we speculate that there are 3 alternative explanations for the different circulating TfR concentrations seen at different ages: differences in iron status, differences in the rate of erythropoiesis, or some unknown physiologic mechanism.

The ages of the subjects in our study groups were selected in a way that resulted in a wide physiologic variation of iron stores. This enabled us to analyze correlations between serum TfR and other variables. In multiple linear regression analysis, we observed the best predictors of serum TfR concentration to be log serum ferritin and serum iron. Both variables correlated inversely with serum TfR. The result seems biologically reasonable: serum ferritin reflects the amount of iron stores, whereas serum iron measures the momentary iron status of the circulating blood and has a wide short-term variation. Correlations between serum TfR and the other variables studied, even age, seemed to be secondary because they lost significance in models that included log serum ferritin and serum iron. The different circulating TfR concentrations seen at different ages thus seemed to be the result of normal age-specific physiologic variation in iron stores and in serum iron concentrations.

In a study of adults undergoing repeated phlebotomies, Skikne et al (2) reported a rise in serum TfR concentration only when iron stores were depleted. We, however, observed a close-to-linear relation between log-transformed serum ferritin concentrations and serum TfR concentrations over the whole physiologic range (Figure 1). There is actually no discrepancy between these 2 findings. On a linear scale, the slow phase before the accelerating rise can give the impression that a rise occurs only when iron stores are depleted. This is obviously not the case in infants, in whom normal physiologic iron stores are accompanied by a high serum TfR concentration. In agreement with our results, when Anttila et al (8) gave iron medication to healthy pubertal boys who were iron sufficient on the basis of accepted reference values of traditional laboratory tests for iron status, they observed both a rise in serum ferritin concentrations and a fall in serum TfR concentrations. These responses to iron supplementation indicated that the 2 indexes were inversely correlated even when iron status was sufficient.

The blood volume per kilogram should be fairly constant (75–77 mL/kg; $\bar{x}$: 76 mL/kg) in healthy subjects aged 1–40 y (22); however, during this time period, hematocrit rises. An average hematocrit of 0.36 has been reported for 1-y-old children, 0.41 for 11–12-y-old boys, and 0.45 for men (22). If there were no changes in body weight, the rate of formation of new red blood cells, per kilogram body weight, would be 0.36 × 76 mL, 0.41 × 76 mL, and 0.45 × 76 mL per 120 d in these age groups. In other words, the rate of formation of new red blood cells per kg body weight would be directly proportional to hematocrit values. During the time period when all circulating red blood cells are replaced by a new generation, ie, over 120 d, 12-mo-old children have an average weight gain of 10% and 11–12-y-old boys have an average weight gain of 3% (23, 24). This brings about a corresponding proportional rise in the need for new red blood cells during this period compared with a situation in which no growth is occurring. It can be calculated that, even with the effect of growth taken into account, the actual formation of new red blood cells per kg body weight is greatest in men and least in infants. Consequently, if the major factor influencing serum TfR concentrations in these age groups had been erythropoiesis, serum TfR concentrations would have been lower in the children than in the adults.

Many laboratory measurements, such as hemoglobin and MCV, have age-dependent reference values, although the physiologic reasons for the age-dependency are not always obvious (25). In addition to iron status, as discussed above, there may be some other as yet unknown, physiologic mechanisms that influence serum TfR concentrations. Unexpectedly, we observed a direct correlation between serum TfR and blood hemoglobin in the prepubertal boys. We have no explanation for this and consider it a coincidence.

In conclusion, our data indicate that low serum ferritin and iron concentrations, even within the normal physiologic range, result in high TfR concentrations. The lower the iron stores, the stronger the influence of ferritin on TfR. However, the rate of

increase in TfR concentrations increases when iron stores get very low. The other variables we studied—MCV, blood hemoglobin, transferrin iron saturation, transferrin, and even age—did not seem to have an independent influence on serum TfR concentrations. The age-specific physiologic variation in the rate of erythropoiesis did not explain the differences seen in serum TfR concentrations either. The association between serum TfR concentrations and iron stores is similar at all ages. The higher serum TfR concentration in the children, especially in the infants, than in the adults was a response to physiologically lower iron stores. This does not mean that these healthy children were iron deficient or that they would benefit from iron therapy. Our results indicate the necessity of age-specific reference values for serum TfR concentrations.

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