Usefulness of serum transferrin receptor and serum ferritin in diagnosis of iron deficiency in infancy[1,2]

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ABSTRACT

Background: The serum transferrin receptor (TfR) and the ratio of TfR to serum ferritin (TfR:SF) have been shown to be useful as early indicators of iron deficiency.

Objective: The objective of this study was to evaluate the performance of TfR and TfR:SF in the assessment of iron deficiency in infants and to analyze age-related changes in both variables.

Design: A total of 716 blood samples obtained from 515 healthy infants aged 8–15 mo were studied.

Results: In 144 samples in which all other laboratory indicators of iron status were within the reference range, the median and 95% CI for TfR and TfR:SF were 8.5 mg/L (95% CI: 5.9, 13.5) and 497 (95% CI: 134, 975), respectively. TfR and TfR:SF were significantly correlated with the other laboratory indicators of iron status. Furthermore, as the severity of iron deficiency progressed, there was a gradual increase in mean TfR concentration ($P < 0.00001$; analysis of variance). The sensitivity of TfR > 13.5 mg/L and TfR:SF > 975 in the diagnosis of iron deficiency was 23.6% and 68.4%, respectively. The specificity was 98.3% and 63.3% for TfR and TfR:SF, respectively. The sensitivity and specificity of SF < 10 μg/L were 63.7% and 60.8%, respectively. Receiver operator characteristic analysis showed that TfR and TfR:SF were more accurate than was SF alone in the diagnosis of iron deficiency.

Conclusions: TfR and TfR:SF showed age-related changes; TfR and TfR:SF appear to be better diagnostic tests for iron deficiency in infants than SF. *Am J Clin Nutr* 2000;72:1191–5.

KEY WORDS Transferrin receptor, serum ferritin, ratio of transferrin receptor to ferritin, iron deficiency, infants

INTRODUCTION

Iron deficiency continues to be one of the most prevalent nutritional deficiencies throughout the world. In the undeveloped world, infants are especially susceptible because of the high amounts of iron required for their growth coupled with a diet low in bioavailable iron.

The diagnosis of iron deficiency is based primarily on laboratory measurements. However, the tests used commonly have limitations due to their poor sensitivity or specificity, or because they are modified by conditions other than iron deficiency (1). The practice of using a battery of assays improves the precision of defining iron nutrition in a population (1); however, 2 pitfalls continue to confound this issue: the difficulty in accurately detecting mild iron deficiency and the identification of inflammation as a cause of changes in laboratory test results that are not due to iron deficiency. The serum transferrin receptor (TfR) assay has shown promise in the clarification of these pitfalls thus far because it is not influenced by acute or chronic inflammatory conditions (2, 3) and seems to be able to detect mild iron deficiency (4). However, its usefulness in the evaluation of iron status in infancy has not been fully evaluated.

In the diagnosis of iron deficiency, age-related variations in laboratory measurements must also be considered. Changes have been described for hemoglobin, mean corpuscular volume (MCV), serum iron, total-iron-binding capacity (TIBC), transferrin saturation (Sat), free erythrocyte protoporphyrin (FEP), and serum ferritin (SF) (1).

The determination of accurate reference values is pivotal to the adequate interpretation of population data and for the analysis of individual cases. Our aim was to assess whether TfR has developmental changes during infancy and to determine its usefulness in the diagnosis of iron deficiency during this period of the life cycle.

SUBJECTS AND METHODS

Five hundred fifteen healthy, well-nourished infants aged 4–15 mo and of both sexes were studied. They were part of a cohort study designed to measure the effectiveness of an iron-fortified cereal in the prevention of iron deficiency anemia (5). The subjects belonged to a low- and low-middle-income group living in urban Santiago, Chile, and receiving their routine pediatric care in a Ministry of Health outpatient clinic. All the infants selected for the study weighed >3000 g at birth to ensure that neonatal iron stores were not compromised by premature delivery. Thus, any abnormalities in iron metabolism that were observed later in infancy would have been postnatal in origin. The infants were tested for iron status at ages 8, 12, and 15 mo. Infants with hemoglobin <105 g/L were excluded and treated.

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TABLE 1
Correlation of serum transferrin receptor (TfR) and the ratio of TfR to serum ferritin (TFR:SF) with laboratory indexes of iron status in the 716 infants[1]

	RBC	Hb	MCV	FEP	Fe	TIBC	Sat	Log SF
TfR	−0.19[2]	−0.31[2]	−0.43[2]	0.43[2]	−0.20[2]	0.30[2]	−0.26[2]	−0.30[2]
Log TfR:SF	−0.31[2]	−0.18[2]	−0.42[2]	0.32[2]	−0.19[2]	0.45[2]	−0.30[2]	
Log SF	0.28[2]	0.11[3]	0.33[2]	−0.23[2]	0.16[2]	−0.42[3]	0.26[2]	

[1] RBC, red blood cell count; Hb, hemoglobin; MCV, mean corpuscular volume; FEP, free erythrocyte protoporphyrin; Fe, iron; TIBC, total-iron-binding capacity; Sat, transferrin saturation.
[2] $P < 0.001$.
[3] $P < 0.005$.

Thus, there were 1154 blood samples. We selected 716 samples for which there was sufficient serum, a full set of iron status measures, and a C-reactive protein (CRP) concentration <10 mg/L to avoid the possible effect of inflammation on iron metabolism indicators. Accordingly, some infants had several blood samples included in this analysis. No subject had shown any morbidity in the 2 wk before blood was drawn.

After informed, written consent was obtained from each infant's parents, a venous sample was drawn and the following iron nutrition status indexes were measured: red blood cell count (RBC), hemoglobin, and MCV (model ZBI; Coulter, Hialeah, FL); iron, TIBC, and Sat (6), FEP (Hematofluorometer; Helena, Beaumont, TX); SF (Ferrizyme; Abbott Diagnostics, North Chicago, IL); CRP (Turbox; Orion Diagnostica, Espoo, Finland); and TfR (by using a 2-site enzyme-linked immunoassay with monoclonal antibodies prepared against soluble transferrin-saturated receptor purified from human placenta; 7). TfR was measured after 4 mo of storage at –70°C. The receptor assay was standardized from the protein concentration of transferrin-free receptor isolated from human placenta. Six standards and all serum samples were analyzed in triplicate. The within-assay variability for a single measurement was 3–5%; the interassay variability was <3% (7). The ratio of TfR to SF (TfR:SF) was calculated by dividing TfR (in μg/L) by SF (in μg/L). The study was reviewed by and was in agreement with the standards set by the Institute of Nutrition and Food Technology's Ethics Committee on Human Research.

To evaluate the iron status of the infants, we used as the lower-normal limits for hemoglobin 110 g/L, for MCV 70 fL, for Sat 10%, and for SF 10 μg/L (1); we used an upper-normal limit for FEP of 2.12 μmol/L RBC at age 8 mo and 1.77 μmol/L RBC at age 12–15 mo (8). Iron status was considered to be normal when all of these laboratory indexes were within the reference range; depleted iron stores were defined as SF below normal, iron deficiency without anemia (ID) was defined as normal hemoglobin plus ≥2 abnormal laboratory results, and iron deficiency anemia (IDA) as hemoglobin below normal with ≥2 abnormal laboratory measurements.

Because SF concentration and TfR:SF have a skewed distribution, they were converted to logarithms before means and SDs were determined; the results were retransformed into antilogarithms to recover the original units and were expressed as geometric means and ±1 SD ranges. For the estimate of the medians and 95% CIs of TfR and TfR:SF, we used the calculation of percentiles that does not require the assumption of a normal distribution. Sensitivity, specificity, and receiver operator characteristic (ROC) curves were calculated to measure the performance of TfR, TfR:SF, and SF in the diagnosis of ID (9, 10). Sensitivity was defined as TP/(TP + FN) × 100 and specificity as TN/(TN + FP) × 100, where TP is true positive, FN is false negative, TN is true negative, and FP is false positive. The ROC curve is constructed by plotting the sensitivity on the ordinate as a function of the false positive rate (100 − specificity) for all possible cutoff values of the diagnostic test. The ROC curve is therefore applicable in cases in which the diagnostic test is distributed continuously. This method allowed us to perform multiple tests across a wide range of cutoffs and to decide the optimum cutoff according to the purpose of the test. The area under the ROC curve is the easiest measure of accuracy. This value varies between 0.1 and 1. An area of 0.5 represents the diagonal, attained when no discrimination exists. An area of 1 represents the perfect indicator.

Statistical analysis included analysis of variance (ANOVA), the one-sample Kolmogorov-Smirnov test, and Pearson's correlation. When the results of the ANOVA were significant, identification of significant differences between groups was based on Scheffe's post hoc test. Statistical analyses were performed with use of STATISTICA for WINDOWS (release 4.5; StatSoft Inc, Tulsa, OK).

RESULTS

Of 716 blood samples studied, 20.1% indicated normal iron status, whereas 13.4%, 31.3%, and 12.8% indicated depleted stores, ID, and IDA, respectively. A single abnormal iron laboratory index other than SF was found in 22.4% of the infants. Mean (±SD) values for iron status indicators were RBC, 4.8 ± 0.3 × 10^{12}/L; hemoglobin, 120 ± 9.8 g/L; MCV, 74.4 ± 4.4 fL; Sat, 12.6 ± 6.8%; and FEP, 2.12 ± 1.17 μmol/L RBC. Geometric means for SF and TfR:SF were 10 μg/L (range: 5–22) and 951 (range: 384–2356), respectively. The percentages of abnormal values were hemoglobin, 13.8%; MCV, 11.9%; Sat, 40.1%; FEP, 48.5%; and SF, 46.9%.

TfR, TfR:SF, and SF showed a significant correlation with the laboratory indicators of iron status (**Table 1**). The low *r* values observed were due mainly to a relatively flat regression curve throughout with relatively tight data.

The median and 95% CI for TfR and TfR:SF in infants for whom all laboratory indicators of iron status were within the reference range are shown in **Table 2**. There were no age-related significant differences in either variable. Thus, the upper reference values for TfR and TfR:SF were set at 13.5 mg/L and 975, respectively.

The cumulative probability plot of the natural logarithm of TfR:SF is shown in **Figure 1**. The log-transformed TfR:SF showed a normal distribution (Gaussian, one-sample Kolmogorov-Smirnov test; $d = 0.03$, NS) in the whole group of infants, including infants with iron sufficiency and with different

TABLE 2
Median (95% CI) of serum transferrin receptor (TfR) and ratio of TfR to serum ferritin (TfR:SF) in 144 iron-sufficient infants

Age	TfR	TfR:SF
	mg/L	
8 mo (n = 51)	9.5 (6.3, 13.2)	489 (133, 975)
12 mo (n = 54)	8.3 (5.9, 13.8)	479 (140, 864)
15 mo (n = 39)	8.3 (4.1, 16.0)	569 (106, 1147)
8–15 mo (n = 144)	8.5 (5.9, 13.5)	497 (134, 975)

stages of iron deficiency. There were no significant differences related to age in the distribution of log TfR:SF.

The effect of iron nutritional status on TfR concentration and TfR:SF is reported in **Table 3**. As the severity of the iron deficiency progressed, there was a gradual increase in mean TfR concentration ($P < 0.00001$, ANOVA). Infants with normal values had a significantly lower TfR:SF than did subjects with different stages of ID ($P < 0.00001$, ANOVA). TfR:SF was not significantly different among iron deficiency groups.

Anemic infants (hemoglobin < 110 g/L) had significantly higher TfR and TfR:SF values than did infants without anemia. The increase in these values was more pronounced in infants with a hemoglobin concentration <100 g/L than in those with a concentration ≥100 g/L (**Table 4**).

There was an inverse relation between SF and TfR. TfR concentrations in subjects with SF concentrations of <5, 5–9, and >10 μg/L were 12.2 ± 4.3, 10.4 ± 3.0, and 9.6 ± 3.0 mg/L, respectively ($P < 0.0001$, ANOVA).

For the comparisons of the sensitivity, specificity, and ROC curves among TfR, TfR:SF, and SF, ID was defined as ≥2 abnormal iron status indicators (hemoglobin, MCV, Sat, and FEP), excluding SF. The sensitivity of TfR > 13.5 mg/L and TfR:SF > 975 in the diagnosis of ID was 23.6% and 68.4%, respectively. The specificity was 98.3% and 63.3% for TfR and TfR:SF, respectively. The sensitivity and specificity of SF < 10 μg/L were 63.7% and 60.8%, respectively. However, when SF was included as one of the indexes considered in the diagnosis of ID, the sensitivity and specificity of TfR > 13.5 mg/L were 17.7% and 75.3%, respectively.

To evaluate the usefulness of FEP alone, ID was defined as ≥2 abnormal iron status indicators (hemoglobin, MCV, and Sat), excluding FEP and SF. The sensitivity and specificity of FEP were 81.6% and 57.1%, respectively. With this change in the ID model, the sensitivity and specificity for TfR were 31.1% and 94.9% and for SF were 70.9% and 57.3%, respectively.

ROC curves for TfR, TfR:SF, and SF in detecting ID are shown in **Figure 2**. The areas under the ROC curves were 0.75 ± 0.02, 0.72 ± 0.02, and 0.67 ± 0.03 for TfR, TfR:SF, and SF, respectively. These curves show a higher accuracy of TfR and TfR:SF than of SF in the diagnosis of ID, with a similar performance of TfR:SF and TfR (TfR compared with SF, $P < 0.01$; TfR:SF compared with SF, $P < 0.002$; TfR compared with TfR:SF, NS).

DISCUSSION

A small amount of TfR circulates normally in plasma. It originates from the extracellular chain of TfR present in the membrane of every cell. The erythroid precursors in the bone marrow are the major determinants of these serum concentrations (11, 12). In conditions with increased erythroid marrow mass there is an elevation in TfR concentration, whereas in cases of erythroid hypoplasia or aplasia, serum TfR concentration falls (7, 11–13). The concentration of serum TfR also depends on the adequacy of iron availability to tissues (7, 11–14). When iron stores are exhausted and iron tissue availability is compromised, an early and progressive rise in serum TfR concentration occurs (4).

Our results corroborate the view that TfR is an indicator of iron status in infants. As the severity of the iron deficiency progresses, there is a gradual increase in mean TfR concentration. Furthermore, we observed that TfR correlates with other laboratory measures of iron status. The best correlation was found with MCV and FEP; a lower correlation was found with SF. These results were not surprising because SF is a measure of iron stores whereas TfR is a measure of tissue iron depletion, as are MCV and FEP. Kling et al (15) described a significant association of TfR with hemoglobin, FEP, iron, Sat, and SF (15). Virtanen et al (16) observed that TfR correlates with SF and MCV in infants. There was no correlation between TfR and other laboratory indicators of iron status. Yeung and Zlotkin (17) detected a lack of correlation of TfR with hemoglobin, FEP, and SF. In these 3 previous studies (15–17), most of the infants had iron-sufficient erythropoiesis, whereas in our study only 20.1% of the infants had a normal iron status. Moreover, the larger number of subjects in our study allowed a higher power in the statistical calculation of correlation.

In the infants studied, excluding those who were likely iron deficient, we found an upper reference value of 13.5 mg/L for TfR and of 975 for TfR:SF. These values are higher than those reported in adults when the same TfR assay measurement was used (4, 7). In adults, the upper reference values for TfR and TfR:SF are set at 8.5 mg/L and 500, respectively (4, 7). Other studies showed that infants had significantly higher values for TfR and TfR:SF than did adults (16–19). However, in one study, TfR values comparable with adult reference values were found in infants who were fed iron-fortified formula for the first 7 mo of life (15). The age-related changes in TfR could be explained by a higher erythropoietic activity per unit of body weight during infancy so that the relative contribution of red cell precursors to circulating TfR could be higher in this stage of the life cycle.

An increase in TfR concentrations was found in adults living at high altitudes, probably related to an increase in the total body erythroid mass (20). However, Virtanen et al (16) calculated that, even if the effect of growth is considered, the needs for new red blood cells/kg body wt is lower in infants than in adults. Because most infants classified as having normal iron status originated

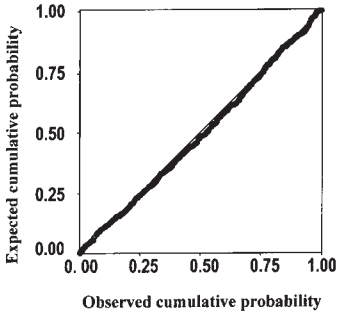

FIGURE 1. Cumulative probability of the natural logarithm of the ratio of serum transferrin receptor to serum ferritin in 716 infants aged 8–15 mo.

TABLE 3
Serum transferrin receptor (TfR), ratio of TfR to serum ferritin (TfR:SF), and SF according to iron status[1]

	TfR	TfR:SF	SF
	mg/L		*ug/L*
Normal iron status (n = 144)	8.9 ± 2.0[a,2]	454 (267–772)[a,3]	19 (12–29)[a,3]
Depleted iron stores (n = 96)	9.2 ± 1.7[a,b]	1545 (998–2392)[b]	6 (4–9)[b]
ID (n = 224)	10.7 ± 2.6[c]	1577 (739–3365)[b]	7 (3–13)[b]
IDA (n = 92)	13.2 ± 5.8[d]	1707 (607–4801)[b]	7 (3–17)[b]
F[4]	40.68	109.1	111.1

[1] Normal, all iron status indexes [hemoglobin (Hb) mean corpuscular volume, transferrin saturation, free erythrocyte protoporphyrin, and SF] within the reference range; depleted, SF < 10 ug/L; iron deficient (ID), Hb > 110 g/L plus ≥2 abnormal iron status indexes; iron deficiency anemia (IDA), Hb < 110 g/L plus ≥2 abnormal iron status indexes. Values within a column with different superscript letters are significantly different, $P < 0.05$ (Scheffe's post hoc test).
[2] $\bar{x}$ ± SD.
[3] Geometric $\bar{x}$ ±1 SD; range in parentheses.
[4] $P < 0.00001$ (ANOVA).

from the groups that had received formula or cereal fortified with iron, and because arbitrary cutoffs of iron status were used in our study to exclude subjects who possibly were iron deficient, it is unlikely that the higher TfR value observed in these infants was due to the presence of subjects with iron deficient erythropoiesis. It is known that that TfR increases just before or at the same time as SF decreases (4). Thus, another possibility is that some subjects with normal iron status may have been at the low end of the normal range, and these infants may have had rapidly declining, but still normal, SF, with compensatory increases in serum TfR. This would have significantly shifted the normal curve for TfR upward. When we attempted to exclude even very slight iron deficiency, we still found in 28 infants who met stricter cutoffs (hemoglobin = 115 g/L, MCV = 74 fL, Sat = 15%, FEP = 1.77 μmol/L RBC, and SF = 15 μg/L) that TfR was higher (upper 95% CI value: 12.8 mg/L) than in adults. Further research is needed to elucidate other physiologic mechanisms that could be involved in age-related changes in TfR.

One important problem in comparing the results of different studies in which the TfR assay was used to evaluate iron status is the wide range of reported values for this measure among laboratories and among different commercial assays (21, 22). Although numeric values obtained with the different TfR assays may differ, they have good correlation and similar abilities to identify iron deficiency if the reference values for that particular assay are used (22–27).

In the group of infants studied, which included iron-sufficient subjects and subjects with different stages of iron deficiency, TfR:SF was normally distributed when converted to a logarithmic scale. Normal distribution of log TfR:SF was also described in pregnant women living in Kingston, Jamaica (N Ahluwalia, unpublished observations, 1993). These results suggest that the current definition of normal and iron deficient is arbitrary and that body iron status is a normally distributed continuum. Our results highlight the difficulty in trying to define iron status.

Usually the performance of a test is measured by calculating the sensitivity and specificity of an optimal cutoff that is based on defining the central 90% or 95% CI of the distribution of test values of a population sample defined as normal. The goal of a diagnostic or screening test is to have both high sensitivity and high specificity. ROC curve analysis is an alternative, useful method for determining the best indicator of a certain health status. In our study, the performance (combination of sensitivity and specificity), measured by ROC curves, of TfR and TfR:SF was better than that of SF in detecting iron deficiency. Furthermore, TfR:SF > 975 and SF < 10 μg/L showed a similarly adequate sensitivity of 68.4% and 63.7%, respectively, and satisfactory specificity of 63.3% and 60.8%, respectively. TfR showed a low sensitivity (23.6%) and good specificity (98.3%). However, its sensitivity improved when a TfR > 10 mg/L was selected as the cutoff (sensitivity: 66.5%; specificity: 71.3%). The sensitivity of TfR in the present study disagrees with the findings in adults of 69% to 94% (24–27). The disagreement in the sensitivity and specificity of TfR observed between our study in infants and studies in adults could be attributed to differences in the criteria used to diagnose ID and to the considerable overlap of TfR values between iron deficient infants and infants with a normal iron status. This overlap may be related to a probably higher variability in the erythroid mass in healthy infants than in healthy adults.

TABLE 4
Serum transferrin receptor (TfR) and ratio of TfR to serum ferritin (TfR:SF) at different hemoglobin concentrations[1]

Hemoglobin concentration	TfR	TfR:SF	SF
	mg/L		*μg/L*
<100 g/L (n = 23)	16.1 ± 7.7[a,2]	2705 (817–8955)[a,2]	5 (2–13)[a,3]
100–109 g/L (n = 76)	12.0 ± 4.6[b]	1320 (504–3458)[b]	9 (4–19)[b]
≥110 g/L (n = 617)	9.8 ± 2.5[c]	879 (374–2065)[c]	11 (5–23)[c]
F[4]	60.87	11.71	24.01

[1] Values within a column with different superscript letters are significantly different, $P < 0.05$ (Scheffe's post hoc test).
[2] $\bar{x}$ ± SD.
[3] Geometric $\bar{x}$ ±1 SD; range in parentheses.
[4] $P < 0.00001$ (ANOVA).

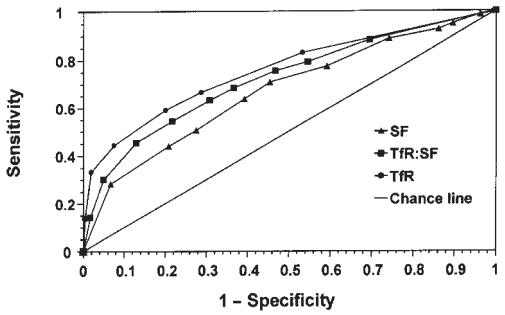

FIGURE 2. Comparison of receiver operator characteristic curves for serum transferrin receptor (TfR), the ratio of TfR to serum ferritin (TfR:SF), and SF in detecting iron deficiency defined as ≥2 abnormal laboratory indexes of iron status (hemoglobin, mean corpuscular volume, transferrin saturation, and free erythrocyte protoporphyrin).

We conclude that TfR and TfR:SF are associated with age-related changes and that TfR and TfR:SF appear to be better indicators of iron deficiency in infants than is SF. Because the performance of TfR and TfR:SF are similar in detecting iron deficiency, TfR seems to be the best isolated measure of iron status in infants. TfR is not an adequate indicator because of its lower sensitivity and high cost; however, its high specificity makes it satisfactory for confirming the presence of iron deficiency. One of the main problems remaining is the assessment of iron status in groups with high prevalences of infection. Both SF and TfR:SF are affected by acute or chronic inflammation. However, because TfR concentration is not affected by acute or chronic inflammatory conditions (2, 3, 25, 28), the measurement of TfR continues to be a useful tool in the assessment of iron status in groups with high prevalences of infection.

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