Serum Transferrin Receptor: A Quantitative Measure of Tissue Iron Deficiency

By Barry S. Skikne, Carol H. Flowers, and James D. Cook

This study was undertaken to evaluate the role of serum transferrin receptor measurements in the assessment of iron status. Repeated phlebotomies were performed in 14 normal volunteer subjects to obtain varying degrees of iron deficiency. Serial measurements of serum iron, total iron-binding capacity, mean cell volume (MCV), free erythrocyte protoporphyrin (FEP), red cell mean index, serum ferritin, and serum transferrin receptor were performed throughout the phlebotomy program. There was no change in receptor levels during the phase of storage iron depletion. When the serum ferritin level reached subnormal values there was an increase in serum receptor levels, which continued throughout the phlebotomy program. Functional iron deficiency was defined as a reduction in body iron beyond the point of depleted iron stores. The serum receptor level was a more sensitive and reliable guide to the degree of functional iron deficiency than either the FEP or MCV. Our studies indicate that the serum receptor measurement is of particular value in identifying mild iron deficiency of recent onset. The iron status of a population can be fully assessed by using serum ferritin as a measure of iron stores, serum receptor as a measure of mild tissue iron deficiency, and hemoglobin concentration as a measure of advanced iron deficiency.

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RELIABLE LABORATORY measurements of iron status are important clinically for detecting iron deficiency and assessing its magnitude. These measurements are also important in epidemiologic surveys to determine the prevalence of iron deficiency and evaluate the efficacy of intervention programs to alleviate it. For both purposes, the most important laboratory parameters are the serum ferritin, which reflects residual iron stores, and the hemoglobin concentration, which measures larger deficits in the functional iron compartment. The greatest difficulty is in assessing mild iron deficiency in individuals with absent iron stores but who have not yet developed overt anemia. This stage of iron deficiency is referred to as iron-deficient erythropoiesis or iron deficiency without anemia. A large array of laboratory measurements have been used to identify this stage, including serum iron, total iron-binding capacity (TIBC), transferrin saturation, free erythrocyte protoporphyrin (FEP), mean red cell volume (MCV), and red cell mean index (RCMI). While each of these measurements have merit, no single determination gives a reliable index of mild iron deficiency in the absence of anemia.

Measurements of circulating transferrin receptor have recently been reported to provide a reliable index of iron deficiency anemia. We have developed an enzyme-linked immunosassay (ELISA) for the measurement of serum transferrin receptor using monoclonal antibodies (MoAbs) developed specifically for this purpose. The usefulness of this laboratory parameter in the assessment of iron status, serial phlebotomies were performed in normal volunteer subjects. The induced changes in serum receptor levels were compared with established measurements of iron status during the gradual evolution of iron deficiency.

MATERIALS AND METHODS

Volunteer subjects. Serial phlebotomies were performed in 6 male and 8 female normal volunteers ranging in age from 24 to 46 years. The subjects were selected to represent a wide range in body iron status. Several male volunteers had low ferritin levels because of frequent prior blood donations. The diet of the subjects was not altered during the study, but ingestion of iron supplements or vitamins containing iron was not allowed. All subjects gave written informed consent after the nature of the study was fully explained to them. The investigation was approved by the Human Subjects Committee of the University of Kansas Medical Center under the condition that phlebotomies would be discontinued when the initial hemoglobin level had fallen by 2 g from baseline.

Phlebotomy procedure. Twelve-milliliter blood samples were drawn weekly for 3 weeks to obtain reliable baseline values for laboratory measurements before phlebotomy. Because of the uncertain effect of the rate of phlebotomy on induced changes in laboratory values, the subjects were divided into two groups. In the first group, 250 mL of blood was removed once a week, while in the remaining subjects 75 mL of blood was withdrawn twice weekly. Because the changes in laboratory values were similar with the two phlebotomy rates, the subjects were considered as a single group for analysis. Phlebotomies were performed in both groups until the hemoglobin level in each subject had fallen by 2 g from their baseline mean and remained so for at least 3 weeks. Additional phlebotomies were performed if the hemoglobin concentration rose during this 3-week period.

The following hematologic and biochemical measurements were performed on blood removed at each phlebotomy. A complete blood count was performed by an automated cell counter (Ortho Diagnost Systems, ELT/WS, Westwood, MA), which provided measurements of the hemoglobin, hematocrit, MCV, and RCMl, which is equivalent to the red cell distribution width. Reticulocyte counts were performed by a standard chamber method, the serum iron and TIBC were determined by methods recommended by the International Committee for Standardization in Hematology, and zinc protoporphyrin was measured with a hematofluorometer (Aviv Associates, Bedford, MA), and serum ferritin and serum transferrin receptor were measured with ELISAs using monoclonal reagents.

Estimates of iron removed. The amount of iron removed with each phlebotomy was calculated from the volume of blood taken and the circulating hemoglobin concentration. Blood removed for laboratory determinations was included in the calculation. Because phlebotomies were performed over several months in some individu-
als, correction was made for the amount of iron absorbed from the diet. We assumed an absorption of 3 mg iron daily in men and 2 mg iron daily in women once phlebotomies were instituted.\textsuperscript{13,14} With this convention, iron stores are expressed as a positive value when there is residual storage iron. Negative values denote functional iron deficiency and represent the additional amount of iron removed after stores are depleted, or the amount of iron that must be returned to the body for stores to reaccumulate. Iron status was expressed as milligram per kilogram body weight unless stated otherwise.

Two methods were used to calculate the amount of iron contained in the storage compartment at the outset of the phlebotomy program. The first, termed the hemoglobin method, has been used in many previous studies.\textsuperscript{15} The calculation is based on the amount of iron removed during phlebotomy corrected for the decrease in circulating hemoglobin iron and for absorbed dietary iron during the phlebotomy period. In estimating the decrease in circulating iron, total blood volume was estimated as 61.5 mg/kg in men and 58.9 mg/kg in women.\textsuperscript{16} One gram hemoglobin was assumed to contain 3.38 mg of iron. The decrement in hemoglobin was calculated as the difference between the mean hemoglobin concentration measured before phlebotomy and that measured by the ferritin method, when the former was estimated using a logarithmic transformation.\textsuperscript{20}

The second calculation, termed the ferritin method, assumes that a decrease in serum ferritin level below 12 \mu g/L represents the point of total depletion of iron stores.\textsuperscript{17,18} Iron stores are calculated as the amount of iron removed by phlebotomy at the time when the serum ferritin first falls below 12 \mu g/L minus the estimated amount of absorbed dietary iron. Although the serum ferritin declined in all subjects, the level did not fall below 12 \mu g/L in three subjects at the time when a sustained reduction in hemoglobin level greater than 2 g/dL had occurred. Storage iron depletion was defined in these subjects as a persistent decrease in hemoglobin concentration rather than on the basis of a subnormal serum ferritin.

\textbf{Statistical evaluation.} The phlebotomy protocol generated multiple samples in each subject at each 1 mg/kg decrement in body iron, the average ranging from 1.8 to 3.2. Because all samples were obtained at intervals of at least 3 days, they were treated independently when portraying the results graphically. Analysis of variance was used to compare the changes between baseline, complete storage iron depletion, and development of anemia. Only one value in each subject at each of these points was used for this purpose. Scheffe's test was used to determine the significance of the differences.\textsuperscript{19}

\textbf{RESULTS}

The baseline hemoglobin concentration was within the normal range in all subjects (Table 1). The average decrease in hemoglobin concentration at the time that phlebotomies were terminated was 2.3 g/dL. There was a wide range in the initial serum ferritin concentration among the 14 volunteer subjects, and by design, the serum ferritin level was in the low normal range in more than half of the subjects. The geometric mean serum ferritin was 33 \mu g/L in the 6 male subjects as compared with 48 \mu g/L in the 8 female volunteers. In the three subjects with the highest baseline serum ferritin (150, 150, and 238 \mu g/L), the level did not fall below 12 \mu g/L at the time that anemia had developed. The duration of the phlebotomy program averaged 13 weeks with a range from 6 to 22 weeks, longer periods being required in the subjects with the higher initial serum ferritin levels.

The amount of iron removed during the phlebotomy program ranged from 218 to 1,562 mg, with an average of 792 mg (Table 1). Basal iron stores were somewhat lower when calculated with the hemoglobin method (mean 333 mg) than with the ferritin method (mean 453 mg), and the hemoglobin method was less reliable. Based on the latter method, initial iron stores were less than 100 mg in four subjects, although their baseline serum ferritin was within the normal range. In subject no. 8, the calculated decrease in hemoglobin iron was greater than the iron removed by phlebotomy. Therefore, the ferritin method was used in subsequent calculations. The size of prephlebotomy iron stores was similar when predicted from the baseline serum ferritin and that measured by the ferritin method, when the former was estimated using a logarithmic transformation.\textsuperscript{20} Iron stores predicted from the initial ferritin averaged 489 mg/L as compared with a phlebotomy value by the ferritin method.

\textbf{Table 1. Measurements of Baseline Hematologic Indices, Iron Stores, and Iron Removal in Volunteer Subjects}

<table>
<thead>
<tr>
<th>Subject No.</th>
<th>Sex</th>
<th>Age (yr)</th>
<th>Body Weight (kg)</th>
<th>Phlebotomy Rate (mL/wk)</th>
<th>Hemoglobin (g/L)</th>
<th>Ferritin (\mu g/L)</th>
<th>Phlebotomy Duration (wk)</th>
<th>Iron Removed (mg)</th>
<th>Baseline Iron Stores (mg)</th>
<th>Functional Deficit (mg)</th>
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<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<td>Final</td>
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*Geometric mean.
method of 453 mg/L. An excellent correspondence was observed between the two values when compared on the basis of body weight \((r = 0.904, P < .0001)\) (Fig 1). Based on the ferritin method, the induced deficit in functional iron averaged 339 mg, with a range from 44 to 747 mg (Table 1). The final deficit in functional iron was independent of iron stores originally present in each subject.

To examine the changes in the various iron parameters during repeated phlebotomy, mean values were plotted against the level of iron stores over the range of 8 mg/kg to −5 mg/kg. It should be noted that because some of the subjects had low normal ferritins at the outset of the investigation, more observations were available for estimating lower iron stores than higher iron stores. The results for the iron transport parameters are shown in Fig 2. There was relatively little change in the serum iron level during storage depletion, but once stores were exhausted, there was a relatively abrupt decline to below 50 \(\mu g/L\). The level was further reduced with an increasing functional iron deficit. On the other hand, the TIBC increased with storage depletion from a baseline mean of 300 \(\mu g/dL\) to approximately 400 \(\mu g/dL\) when stores were absent. This finding is in keeping with the inverse correlation between serum ferritin and TIBC in iron-replete normal subjects reported previously. However, the mean TIBC rose above the normal level only after functional iron deficiency had developed. The changes in transferrin saturation were similar to the serum iron; the mean value fell below the lower cut-off level of 16% only when stores were fully exhausted, and the level continued to fall with increasing functional iron deficiency.

There was surprisingly little effect of phlebotomy on measurements relating to the red cell compartment (Fig 3).

![Fig 1](https://example.com/fig1.png)  
**Fig 1.** Relationship between iron stores measured by phlebotomy and predicted from the initial serum ferritin value. The solid line represents the line of identity.

![Fig 2](https://example.com/fig2.png)  
**Fig 2.** Changes in serum iron, TIBC, and transferrin saturation during phlebotomy. The horizontal dashed lines indicate the limits of the normal range. The shaded areas represent ±2 SE.

A significant elevation in FEP occurred only during the later stage of the phlebotomy program. Similarly, the MCV fell progressively, but remained within the normal range above 80 fl. There was a slight upward trend in RCMI values, but the mean levels remained within the normal range.

Enhanced erythropoiesis and iron deficiency have both been reported to elevate the serum transferrin receptor level. It was not known before this study whether the increase in erythropoiesis resulting from phlebotomy would influence the value of the serum receptor as an index of iron deficiency. However, serial determinations in subjects with varying baseline iron reserves indicated that the main determinant was iron deficiency. An example of this is illustrated in Fig 4. In the two subjects with initial iron stores below 500 mg, the receptor level increased sooner in the subject with the lower initial store. In a third subject with an initial store of...
Serum ferritin and receptor levels during phlebotomy are shown in Fig 5. As anticipated, the serum ferritin changed dramatically during the period of storage depletion. The wide range in serum ferritin levels at higher iron stores reflects the fewer number of observations. There was relatively little change in the serum ferritin after stores were fully depleted. The alteration in serum receptor levels was entirely different in that there was little or no change during storage depletion. As iron stores became fully exhausted, there was a progressive increase in serum transferrin receptor levels with increasing deficiency.

These results indicate that the serum ferritin is the most sensitive index of iron status when there are residual iron stores, whereas the serum receptor is more sensitive when there is functional iron deficiency. Because of the reciprocal relationship between serum receptor and ferritin measurements, the ratio of receptor:ferritin portrays iron status over the entire range examined in this study (Fig 6). When plotted logarithmically, this ratio increased from less than 100 in those with ample iron stores to over 2,000 in those with significant functional iron deficiency. A rise above 500 occurred when stores were fully depleted.

The measurements obtained when iron stores were depleted and when anemia developed were compared with the baseline values (Table 2). When stores were depleted, the hemoglobin, serum iron, transferrin saturation, and serum ferritin were all significantly changed, whereas the TIBC, serum receptor, FEP, RCMI, and MCV were not. When anemia developed, all laboratory measurements differed significantly from baseline with the exception of the FEP. The hemoglobin concentration, serum iron, transferrin saturation, serum ferritin, and serum receptor showed the most significant changes (F > 24.0), while the changes in red cell measurements were much less significant. Between storage depletion and the development of anemia, the only significant change occurred in serum receptor levels, which increased from 6.2 mg/L to 8.77 mg/L (P < .001).

One objective of this study was to determine whether the serum transferrin receptor is of value in quantifying mild deficits in functional iron. The ratio of serum receptor:

![Fig 3. Changes in RCMI, MCV, and FEP during phlebotomy. The cross-hatched areas represent values outside of the normal range. The shaded areas represent ±2 SE.](image)

1,102 mg, there was very little change in serum receptor during the removal of 1,489 mg iron over a 4-month period. Further evidence that the serum transferrin receptor levels were minimally influenced by enhanced erythropoiesis due to phlebotomy was obtained by monitoring the absolute reticulocyte counts (reticulocyte count × red blood cell count). The mean value at baseline of 85,600/mm³ increased to 113,700/mm³ when stores were fully depleted, but subsequently fell to 89,400/mm³ at the end of the study. In contrast, the serum receptor levels did not increase significantly until functional iron deficiency had developed. These findings indicate that at the rate of phlebotomy performed in this study, there is little or no influence of increased erythropoiesis on the serum receptor level.

![Fig 4. Serial determinations of serum transferrin receptor during phlebotomy in three subjects with initial iron stores of 107 mg (△), 335 mg (○), and 1,102 mg (O).](image)
ferritin was compared with a previous algorithm based on combinations of the transferrin saturation, serum ferritin, and FEP. In nine subjects with a functional deficit between 50 and 150 mg of iron, mean values of 126 and 121 mg iron were obtained with the ratio and algorithm method, respectively. In eight subjects with a deficit between 150 and 250 mg, the mean values were 215 and 235 mg, respectively. However, the variability was somewhat higher with the ratio method. For example, with functional deficits of 150 to 250 mg iron, the range for the algorithm method was 160 to 240 mg as compared with 95 to 380 mg for the ratio estimate. The variance of 6,646 for the ratio method was also significantly higher than 802 for the algorithm method (F = 8.29, P < .01).

DISCUSSION

For clinical purposes, the major emphasis in laboratory measurements of iron status is in detecting iron deficiency rather than in estimating its severity. Serum ferritin is particularly valuable in anemic patients because a level below 12 µg/L is diagnostic. The MCV and FEP are also useful, but these measurements are also influenced by inflammation and neither measurement is useful for detecting iron deficiency of recent onset. In general, the identification of iron deficiency in an anemic patient poses relatively few problems, at least in the absence of other diseases that influence iron parameters, such as chronic infection, inflammation, or liver disease.

Estimating the severity of mild iron deficiency assumes greater importance in population studies. Earlier surveys relied on single cut-off levels of laboratory parameters to distinguish normal from iron-deficient segments of a population. In the evaluation of the Health and Nutrition Examination Survey (HANES II) in the United States, combinations of measurements were used to define the prevalence of impaired iron status or iron deficiency anemia. Another recent approach is to use algorithms to estimate body iron quantitatively in each sampled individual. Because of the close correspondence between the serum ferritin and body iron stores, this calculation is reliable in otherwise healthy individuals if residual iron stores are present. At the other extreme in patients with overt anemia, the deficit in body iron can be estimated quantitatively from the decrease in circulating hemoglobin concentration. Between these limits, estimating mild deficits in functional iron is more difficult. In the previous report, combinations of the serum ferritin, transferrin saturation, and erythrocyte protoporphyrin were used to estimate body iron between the occurrence of storage depletion and the development of anemia.

Because of recent reports that serum receptor levels are...
elevated in iron deficiency, we undertook this investigation to examine the potential role of this new assay in quantifying mild degrees of iron deficiency. Cell culture studies indicate that the synthesis of transferrin receptor in erythroid cell lines is closely tied to the iron requirements of the cell.3,4 Assuming that circulating receptor levels reflect the total body mass of receptors, it is not surprising that elevations occur both in disorders where there is a marked expansion of red cell mass, such as autoimmune hemolytic anemia and sickle cell anemia, and in iron deficiency. We recently reported our initial experience with serum receptor measurements using an ELISA with MoAbs developed against soluble receptor.5 The mean level in normal subjects was 5.6 mg/L, with a range of 2.8 to 8.5 mg/L (±2 SD). The mean levels in patients with sickle cell anemia and iron deficiency anemia were 33 and 18 mg/L, respectively. In both groups, the receptor level was invariably above the upper normal limit of 8.5 mg/L. These changes are similar to data recently obtained in the rat.5

Our present findings indicate that the serum receptor is a reliable index of early tissue iron deficiency. Although serum receptor levels increased significantly during storage depletion, the mean values remained well within the normal range. Our findings also indicate that in normal subjects undergoing graded phlebotomy, tissue iron needs are a much more important determinant of the serum receptor level than induced increases in erythropoiesis (Fig 3). The most important finding is after depletion of iron stores, when increasing deficits in functional iron lead to an increase in serum receptor. With other iron parameters, some changes were observed as the deficit increased from 0 to 12 mg/kg, but none were as brisk or consistent as the serum receptor. Within this range, the transferrin saturation fell from 11% to approximately 8%, and the serum ferritin declined from 11 to approximately 6 µg/L. These changes justify the prior use of these measurements for estimating mild iron deficiency.20

The FEP and MCV were presumably less useful in the study because sufficient time had not elapsed to replace normal circulating red blood cells with iron-deficient erythrocytes at the time that phlebotomies were terminated. Of all the measurements examined, the serum receptor was the most reliable quantitative guide to a deficiency in the functional iron compartment.

There is some advantage in using a single parameter to estimate body iron in population studies. Because the serum ferritin changed dramatically during storage iron depletion and the serum receptor changed maximally with increasing functional iron deficiency, the ratio of receptor:ferritin appears promising (Fig 6). However, no major advantage in using this ratio was noted. Residual iron stores can be estimated from the serum ferritin when the level is within the normal range, and when the ferritin falls below 12 µg/L, the deficit in tissue iron can be estimated from the serum receptor. The previous algorithm required measurement of the serum iron, TIBC, FEP, and serum ferritin. These laboratory techniques require venous sampling and are cumbersome and costly to perform. One major advantage of using only the serum receptor and ferritin is that both assays can be performed on a few microliters of sample, and therefore are suitable for fingerstick specimens. The technology required for these measurements is identical except for the immunologic reagents.

It will be important to gain further experience with serum ferritin, receptor, and hemoglobin measurements in population surveys. The serum receptor offers a particular advantage in assessing iron status in segments of the population where the prevalence of iron deficiency is high, as in infants, children, and women during pregnancy. In these populations, the serum ferritin is usually close to the iron-deficient range and does not accurately portray differences in functional iron. The serum receptor is more sensitive in detecting iron deficiency in these situations.

REFERENCES


Table 2. Laboratory Measurements Performed Initially and on Developing Storage Iron Depletion and Iron-Deficiency Anemia

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<th>Laboratory Measurements</th>
<th>Basal A (N = 14)</th>
<th>Depletion B (N = 11)</th>
<th>Anemia C (N = 14)</th>
<th>F Value</th>
<th>P Value (A:B)</th>
<th>P Value (B:C)</th>
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<td>Hemoglobin (g/dL)</td>
<td>14.5 (±2.1)</td>
<td>12.7 (±1.8)</td>
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<td>Serum iron (µg/dL)</td>
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<td>46 (±30)</td>
<td>32 (±22)</td>
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<td>Serum receptor (mg/L)</td>
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Abbreviations: RBC, red blood cells; NS, not significant.

*Geometric mean ± 1 SD.
Serum transferrin receptor: a quantitative measure of tissue iron deficiency

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