Comparison of plasma ferritin concentration with the ratio of plasma transferrin receptor to ferritin in estimating body iron stores: results of 4 intervention trials\textsuperscript{1,2}

Zhenvu Yang, Kathryn G Dewey, Bo Lönnerdal, Olle Hernell, Camila Chaparro, Seth Adu-Afarwuah, Erin D McLean, Roberta J Cohen, Magnus Domellöf, Lindsay H Allen, and Kenneth H Brown

**ABSTRACT**

**Background:** Efforts to develop global programs for the control of iron deficiency require simple, low-cost, and accurate indicators of iron status.

**Objective:** We aimed to compare estimates of body iron (BI) stores, as calculated from either plasma ferritin concentration alone (BI-ferritin) or the ratio of plasma transferrin receptor (TfR) to ferritin (BI-TfR/ferritin).

**Design:** Data were analyzed from 4 previously completed, randomized intervention trials that enrolled infants, schoolchildren, or pregnant women (total n = 1189, after excluding subjects with elevated C-reactive protein).

**Results:** The correlation coefficients between BI-ferritin and BI-TfR/ferritin were >0.95 for all studies. The kappa index ranged from 0.5 to 1.0. All of the sensitivities of BI-ferritin for identifying persons with low iron stores (defined as BI-TfR/ferritin < 0 mg/kg body wt) were >0.90. All of the specificities were >0.80 except the study of pregnant women (specificity = 0.83). The effect sizes of iron intervention trials were significantly greater for change in iron reserves estimated by BI-TfR/ferritin than by BI-ferritin in 2 studies with larger effect sizes (1.11 compared with 1.00 and 1.56 compared with 1.44, respectively; \( P < 0.05 \)) and 1 study with medium effect size (0.70 compared with 0.57; \( P < 0.05 \)). However, there were no significant differences between estimates of these effect sizes for 1 study with a medium effect size and 1 study with a smaller effect size (0.78 compared with 0.83 and 0.37 compared with 0.35, respectively; \( P > 0.2 \)).

**Conclusion:** Plasma ferritin concentration alone provides a good approximation of total BI reserves, as estimated by BI-TfR/ferritin, on the basis of high correlation, sensitivity, and specificity among nonpregnant persons with elevated C-reactive protein. *Am J Clin Nutr* 2008;87:1892–8.

**INTRODUCTION**

Iron deficiency is the micronutrient deficiency that is most commonly recognized around the world, and it results in anemia, impaired neurobehavioral performance, and decreased physical work capacity (1). Despite the increasing implementation of iron-supplementation and -fortification programs, anemia remains a common problem globally (2). To plan and manage intervention programs to control iron deficiency, appropriate indicators of iron status are needed (3, 4). Because of the relative simplicity and lower cost of measuring hemoglobin, the hemoglobin concentration, rather than direct indicators of iron status, is commonly used to estimate the prevalence of iron deficiency. However, the hemoglobin concentration is affected by factors besides iron status, such as malaria, other systemic infections, hemoglobinopathies, and other nutrient deficiencies. Moreover, mild iron deficiency may not result in anemia (1). Thus, more-sensitive and more-specific indicators of iron status are preferable.

Plasma ferritin concentration generally reflects total body iron (BI) stores in most persons (5). However, the acute phase response induced by infection or systemic inflammation can elevate plasma ferritin concentration independent of the iron stores (6). Furthermore, once iron stores are depleted, the plasma ferritin concentration does not quantitatively reflect further reductions of the tissue iron pool (7). In addition, there is concern about the use of ferritin as an indicator of iron status during pregnancy, because of its low specificity (8). Plasma transferrin receptor (TfR) concentrations are a quantitative indicator of total-body TfR mass (9, 10). The major advantage of TfR as an indicator is the possibility of estimating the magnitude of the functional iron deficit once iron stores are depleted (7). The ratio of TfR to ferritin (TfR/ferritin) was designed to evaluate changes in both stored iron and functional iron and was thought to be more useful than either TfR or ferritin alone. TfR/ferritin has been used to estimate BI stores in both children and adults (11). However, the high cost and the lack of standardization of the TfR assay so far have limited the applicability of the method.

Previous studies showed that plasma ferritin alone is a good indicator of BI stores when the ferritin concentration is above the generally accepted cutoff—ie, 12 μg/L (12, 13). However, it is not certain whether plasma ferritin concentration alone provides

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TABLE 1
Characteristics of subjects at each study site

<table>
<thead>
<tr>
<th>Study and age group</th>
<th>Elevated CRP (&gt;10 mg/L)</th>
<th>Plasma ferritin concentration&lt;sup&gt;2&lt;/sup&gt; µg/L</th>
<th>Plasma TfR concentration&lt;sup&gt;2&lt;/sup&gt; mg/L</th>
<th>TfR/ferritin&lt;sup&gt;1&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>Honduras</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>4 mo (n = 140)</td>
<td>7.8</td>
<td>71 (38, 121)&lt;sup&gt;4&lt;/sup&gt;</td>
<td>5.4 (4.6, 6.3)</td>
<td>1.9 (1.6, 2.2)</td>
</tr>
<tr>
<td>6 mo (n = 128)</td>
<td>10.9</td>
<td>43 (17, 68)</td>
<td>5.5 (4.6, 6.7)</td>
<td>2.1 (1.9, 2.6)</td>
</tr>
<tr>
<td>9 mo (n = 116)</td>
<td>6.0</td>
<td>30 (13, 56)</td>
<td>5.7 (4.8, 7.5)</td>
<td>2.3 (2.0, 2.7)</td>
</tr>
<tr>
<td>Sweden&lt;sup&gt;5&lt;/sup&gt;</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>4 mo (n = 98)</td>
<td>1.0</td>
<td>125 (63, 199)</td>
<td>6.7 (5.6, 7.7)</td>
<td>1.8 (1.5, 2.0)</td>
</tr>
<tr>
<td>6 mo (n = 98)</td>
<td>5.1</td>
<td>76 (30, 118)</td>
<td>6.8 (5.6, 8.0)</td>
<td>2.0 (1.7, 2.4)</td>
</tr>
<tr>
<td>9 mo (n = 92)</td>
<td>3.2</td>
<td>48 (20, 73)</td>
<td>7.0 (6.0, 8.8)</td>
<td>2.2 (1.9, 2.6)</td>
</tr>
<tr>
<td>Mexico</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>6 mo (n = 328)</td>
<td>4.0</td>
<td>39 (25, 72)</td>
<td>4.6 (3.6, 5.5)</td>
<td>2.0 (1.7, 2.3)</td>
</tr>
<tr>
<td>Pregnant women (n = 437)</td>
<td>23.6</td>
<td>11 (7, 21)</td>
<td>4.5 (3.5, 5.6)</td>
<td>2.6 (2.2, 2.9)</td>
</tr>
<tr>
<td>Ghana</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>6 mo (n = 260)</td>
<td>7.3</td>
<td>24 (10, 60)</td>
<td>8.0 (6.2, 10.8)</td>
<td>2.5 (2.1, 2.9)</td>
</tr>
<tr>
<td>12 mo (n = 339)</td>
<td>13.6</td>
<td>26 (6, 52)</td>
<td>7.8 (6.5, 10.6)</td>
<td>2.5 (2.2, 3.0)</td>
</tr>
<tr>
<td>Senegal</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Schoolchildren, 9–15 y old (n = 76)</td>
<td>7.9</td>
<td>37 (25, 65)</td>
<td>8.0 (6.2, 9.6)</td>
<td>2.4 (2.1, 2.6)</td>
</tr>
</tbody>
</table>

<sup>1</sup> CRP, C-reactive protein; TfR, transferrin receptor. The Sweden-Honduras study was an iron supplementation trial; the Mexico study was an umbilical cord clamping trial; the Ghana and Senegal studies were micronutrient supplementation trials.

<sup>2</sup> Results exclude subjects with elevated CRP (>10 mg/L).

<sup>3</sup> Ratio of TfR to ferritin = log<sub>10</sub> (TfR × 1000/ferritin).

<sup>4</sup> Median: 25th percentile, 75th percentile in parentheses (all such values).

<sup>5</sup> Both ferritin and TfR concentrations were higher in the Sweden arm of the study than in the Honduras arm of the study, and the ratios were similar.
included in TfR and CRP kits. The average CV for CRP measurements in our laboratory was 1.6% (n = 123), and the between-day CV was 5.0% (n = 28) for the serum control samples provided by the manufacturer. Ferritin controls were obtained from Diagnostic Products Corp. The average CV for ferritin measurements in our laboratory was 7.4% (n = 20), and the between-day CV was 5.6% (n = 10) for the serum control samples (ferritin concentration = 33 μg/L) provided by the manufacturer. The average CV for TfR measurements in our laboratory was 5.8% (n = 62), and the between-day CV was 9.7% (n = 31) for the serum control samples (TfR concentration = 15.6 mg/L) provided by the manufacturer.

**Statistical analysis**

BI stores based on ferritin alone [BI-ferritin (mg/kg)] were calculated by using the following formulas (13):

For infants (≤12 mo of age),

\[
\text{BI-ferritin} = 4.5 \times \left( \ln(\text{ferritin concentration}) - \ln(12) \right)
\]

and for pregnant women and older children,

\[
\text{BI-ferritin} = 4.98 \times \left( \ln(\text{ferritin concentration}) - \ln(12) \right)
\]

BI stores based on TfR/ferritin [BI-TfR/ferritin (mg/kg)] were calculated by using the following formula (4):

\[
\text{BI-TfR/ferritin} = \frac{- \left[ \log (\text{TfR concentration} \times 1000/\text{ferritin concentration}) \right]}{2.8229/0.1207}
\]

Univariate distributions and measures of central tendency were examined for all variables. Both BI-ferritin and BI-TfR/ferritin were slightly skewed (most values for skewness and kurtosis were within -1 and 1). Paired Wilcoxon's tests were used to compare BI-ferritin and BI-TfR/ferritin within each study. Cross-tabulations and correlations were tested for each pair of BI-ferritin and BI-TfR/ferritin values across all studies to assess their agreement. BI stores < 0 mg/kg body wt were defined as low BI stores. McNemar's tests were used to measure agreement in the prevalence of low BI stores between BI-ferritin and BI-TfR/ferritin. To diagnose low BI stores, BI-TfR/ferritin was used as the reference technique, and both the sensitivity and specificity of BI-ferritin were calculated. Effect sizes of interventions on BI stores were calculated for the 3 studies that found a significantly different effect between intervention and control groups. First, the differences of BI between posttreatment and pretreatment measurements were calculated in the Sweden-Honduras study. Second, a general linear model of the difference in BI between the Sweden-Honduras, Mexico, and Ghana studies was built with treatment group as the independent variable. In the Ghana study, the 3 treatment groups were combined into 1 group, because there were no significant differences in BI among the 3 treatments (P > 0.9). Third, BI-ferritin and BI-TfR/ferritin were standardized by using the following formula:

\[
z \text{score} = \frac{\text{observed BI} - \text{mean BI}}{\text{MSE}}
\]

where MSE = mean square error. Then the differences between the BI-ferritin z score and the BI-TfR/ferritin z score in the treatment and control groups were compared by using t tests. SAS software (version 9.0; SAS Institute Inc, Cary, NC) was used in all the analyses, and scatter plots were drawn by using SIGMAPLOT software (version 9; Systat Software Inc, Richmond, CA).

**RESULTS**

The rates of elevated CRP ranged from 1.0% to 10.9% in all age groups across the 4 studies, except among the pregnant women in Mexico (23.6%) and 12 mo old infants in the Ghana study (13.6%) (Table 1). The subjects with elevated CRP were excluded from subsequent analyses. As shown in Table 1, iron status varied widely across study sites and age groups. The median plasma ferritin concentration was highest in younger infants (125 μg/L in 4-mo-old Swedish infants), intermediate in the older children (medians ranged from 24 to 76 μg/L) and lowest for pregnant women and older children (medians ranged from 24 to 76 μg/L) and lowest for pregnant women and older children (medians ranged from 24 to 76 μg/L).

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**TABLE 2**

Comparison of body iron (BI) stores as estimated by ferritin alone or the ratio of transferrin receptor to ferritin (TfR/ferritin) by age group in intervention trials

<table>
<thead>
<tr>
<th>Age group</th>
<th>BI-ferritin mg/kg</th>
<th>BI-TfR/ferritin mg/kg</th>
<th>P2</th>
<th>Proportion with low iron stores (BI-ferritin &lt; 0)</th>
<th>Proportion with low iron stores (BI-TfR/ferritin &lt; 0)</th>
<th>P4</th>
</tr>
</thead>
<tbody>
<tr>
<td>4 mo (n = 226)</td>
<td>9.1 (6.3, 11.4)</td>
<td>8.1 (6.0, 10.5)</td>
<td>&lt;0.001</td>
<td>2.2 (0.3, 4.1)</td>
<td>1.3 (0.2, 2.8)</td>
<td>0.32</td>
</tr>
<tr>
<td>6 mo (n = 768)</td>
<td>5.2 (2.1, 8.3)</td>
<td>5.5 (2.5, 8.1)</td>
<td>&lt;0.001</td>
<td>15.8 (13.2, 18.4)</td>
<td>14.4 (11.9, 16.9)</td>
<td>0.06</td>
</tr>
<tr>
<td>9 mo (n = 203)</td>
<td>5.2 (1.2, 7.5)</td>
<td>4.6 (1.7, 7.2)</td>
<td>0.049</td>
<td>18.2 (12.9, 23.5)</td>
<td>14.8 (9.9, 19.7)</td>
<td>0.05</td>
</tr>
<tr>
<td>12 mo (n = 293)</td>
<td>3.6 (1.9, 6.7)</td>
<td>2.8 (1.7, 5.5)</td>
<td>&lt;0.001</td>
<td>30.7 (25.4, 36.0)</td>
<td>32.8 (27.4, 38.2)</td>
<td>0.06</td>
</tr>
<tr>
<td>Schoolchildren, 9-15 y old (n = 70)</td>
<td>5.5 (3.6, 8.4)</td>
<td>3.9 (2.2, 6.1)</td>
<td>&lt;0.001</td>
<td>12.8 (5.0, 20.6)</td>
<td>12.8 (5.0, 20.6)</td>
<td>NA</td>
</tr>
<tr>
<td>Pregnant women</td>
<td>-0.4 (2.7, 2.7)</td>
<td>1.6 (0.7, 4.8)</td>
<td>&lt;0.001</td>
<td>54.6 (49.3, 59.9)</td>
<td>31.2 (26.2, 36.2)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

1 BI-ferritin, BI stores calculated on the basis of ferritin alone; BI-TfR/ferritin, BI stores calculated on the basis of TfR/ferritin.
2 Paired Wilcoxon test of medians.
3 McNemar test of prevalence of low BI stores.
4 Values in this column are median; 25th and 75th percentiles in parentheses.
5 Values in this column are prevalence; 95% CI in parentheses.
COMPARISON OF FERRITIN AND TfR/FERRITIN RATIO

FIGURE 1. A: Correlation between body iron (BI)-ferritin and the ratio of BI-transferrin receptor (TfR) to ferritin (BI-TfR/ferritin) in Swedish and Honduran infants at 4 mo of age. n = 226; r = 0.96, P < 0.001. B: Correlation between BI-ferritin and BI-TfR/ferritin in Swedish, Honduran, Mexican, and Ghanaian infants at 6 mo of age. n = 768; r = 0.96, P < 0.001. C: Correlation between BI-ferritin and BI-TfR/ferritin in Swedish and Honduran infants at 9 mo of age. n = 203; r = 0.96, P < 0.001. D: Correlation between BI-ferritin and BI-TfR/ferritin in Ghanaian infants at 12 mo of age. n = 293; r = 0.97, P < 0.001. E: Correlation between BI-ferritin and BI-TfR/ferritin among Senegalese schoolchildren (9–15 y old). n = 70; r = 0.96, P < 0.001. F: Correlation between BI-ferritin and BI-TfR/ferritin among pregnant Mexican women at term. n = 333; r = 0.96, P < 0.001.
TABLE 3
Sensitivity and specificity of body iron (BI)-ferritin for identifying low BI stores

<table>
<thead>
<tr>
<th>Age group</th>
<th>Prevalence of low iron stores</th>
<th>Sensitivity</th>
<th>Specificity</th>
</tr>
</thead>
<tbody>
<tr>
<td>6 mo (n = 768)</td>
<td>14</td>
<td>0.92</td>
<td>0.97</td>
</tr>
<tr>
<td>9 mo (n = 203)</td>
<td>15</td>
<td>0.90</td>
<td>0.94</td>
</tr>
<tr>
<td>12 mo (n = 293)</td>
<td>33</td>
<td>0.92</td>
<td>0.99</td>
</tr>
<tr>
<td>Schoolchildren, 9–15 y old (n = 70)</td>
<td>13</td>
<td>1.00</td>
<td>1.00</td>
</tr>
<tr>
<td>Pregnant women (n = 333)</td>
<td>31</td>
<td>1.00</td>
<td>0.66</td>
</tr>
</tbody>
</table>

1. TfR, transferrin receptor.
2. Low iron stores defined as the ratio of BI-TfR to ferritin <0 mg/kg body wt.

The median plasma TfR concentrations ranged from 4.5 mg/L among pregnant women to 8.0 mg/L among older children, and the median TfR/ferritin ranged from 1.8 in the younger infants to 2.6 in the pregnant women. The median amounts of total BI reserves and the prevalence of low BI stores as estimated from BI-ferritin and BI-TfR/ferritin are shown by study and age group in Table 2. There were small, but statistically significant, differences between BI-ferritin and BI-TfR/ferritin in each age group, although the directions of the differences were not consistent among groups. There were no differences in the prevalence of low BI stores (<0 mg/kg body wt), as estimated by ferritin concentration alone or by TfR/ferritin, in any of the studies or age groups (P > 0.05) except pregnant women, in whom BI-ferritin identified a significantly higher percentage with low BI stores (P < 0.001, Table 2). As shown in Figure 1, BI-ferritin and BI-TfR/ferritin were highly correlated (r > 0.95, P < 0.001) in all age groups.

The sensitivity and specificity of BI-ferritin for predicting low BI stores, as determined by BI-TfR/ferritin, were >0.90 except in the group of pregnant women, in whom specificity was lower (specificity = 0.66) (Table 3). As shown in Table 4, there were either high or moderate levels of agreement between BI-ferritin and BI-TfR/ferritin in the different studies, as indicated by the kappa coefficients, which ranged from 0.5 to 1.0 (P < 0.01).

To determine the ability of BI-ferritin to measure the effect of iron interventions, the effect sizes (ie, the differences between the respective treatment groups divided by their pooled SD) of 3 of the intervention trials in infants were compared by using data derived from both BI-ferritin and BI-TfR/ferritin. When there was a lower effect size [Mexico (0–6 mo)], there was no significant difference in the effect sizes measured by BI-ferritin and BI-TfR/ferritin (0.37 compared with 0.35, respectively; P > 0.2). When there was a medium effect size [Ghana (6–12 mo); Sweden and Honduras (4–6 mo)], the estimates of effect sizes derived from BI-TfR/ferritin were slightly but significantly greater than those derived from BI-ferritin in the Ghana study (0.70 compared with 0.57, respectively; P < 0.05), but there was no significant difference in the effect sizes measured by BI-ferritin and BI-TfR/ferritin in Sweden and Honduras (0.78 compared with 0.83, respectively; P > 0.2). When there was a larger effect size [Sweden and Honduras (6–9 mo and 4–9 mo)], the estimates of effect sizes derived from BI-TfR/ferritin were slightly but significantly greater than those derived from BI-ferritin only in the subgroup whose BI-TfR/ferritin was initially >0 mg/kg body wt, even though the sample size was much larger in this latter group (1.00 compared with 0.95, respectively; P = 0.42) (Table 6).

**DISCUSSION**

These analyses indicate that, for most programmatically relevant purposes, total BI reserves (ie, iron status) can be measured as effectively by using plasma ferritin concentration alone as by using the more cumbersome and expensive method that relies on TfR/ferritin. Our results showed that the sensitivity of BI-ferritin was >0.9 for detecting low BI stores, which is the situation when ferritin alone may be expected to be a less sensitive indicator of iron status. In addition, there was no significant difference in effect sizes between BI-ferritin and BI-TfR/ferritin when the effect size of change in iron reserves following intervention was <0.5. In contrast, there were significant differences (except among 4–6 mo-old infants in Sweden and Honduras) in the estimated effect sizes when these were >0.5, mainly because these larger effect sizes occurred when initial iron stores were very low, and BI-TfR/ferritin probably provides a more accurate assessment of iron status under these conditions. Nevertheless, this discrepancy in the estimates of the magnitude of response to intervention is probably of less practical importance, because a large response (>0.5) was detectable with both indicators.

The generally high sensitivity and specificity of BI-ferritin indicate its ability to distinguish iron-deficient persons from those who are iron-replete in population assessment. The low specificity of BI-ferritin among pregnant women could be due to physiologic expansion of blood volume during pregnancy. According to previous studies, the plasma ferritin concentration falls dramatically during pregnancy even when women are supplemented with high doses of iron, but the concentration of TFR does not change (21, 22). Thus, TfR/ferritin would be greater, and apparent iron reserves from BI-TfR/ferritin as well as those from BI-ferritin would be less in pregnant women than in non-pregnant women. In other words, BI-TfR/ferritin and BI-ferritin both tend to underestimate the BI reserves during pregnancy, and were slightly but significantly greater than those derived from BI-ferritin (1.11 compared with 1.00 and 1.56 compared with 1.44, respectively; P < 0.05) (Table 5). When analysis was stratified by initial iron status, BI-TfR/ferritin yielded a significantly greater effect size than did BI-ferritin only in the subgroup that had low BI stores at the beginning of the study (BI-TfR/ ferritin <0 mg/kg body wt) (2.04 compared with 1.47, respectively; P < 0.001). There were no significant differences within the subgroup whose BI-TfR/ferritin was initially >0 mg/kg body wt, even though the sample size was much larger in this latter group (1.00 compared with 0.95, respectively; P = 0.42) (Table 6).
any differential degree of underestimation may partially explain the low specificity of BI-ferritin.

Earlier studies consistently showed that ferritin has sensitivity and specificity similar to those of TfR/ferritin for distinguishing anemia with and without iron deficiency (23). Although some studies showed that TfR made a significant contribution to the detection of iron deficiency (24, 25), other studies showed that TfR did not improve the diagnosis of iron deficiency above ferritin alone (26, 27). The cost of BI-ferritin is much lower than the cost of BI-TfR/ferritin, which is an important consideration for population assessment.

The second purpose of determining BI stores is to evaluate the effect of iron-intervention programs or the effects of other mineral supplements on iron status. One previous review concluded, as the present study does, that ferritin is similar to BI-TfR/ferritin for determining the effect size of iron intervention trials (3). Several reports are also available on the effects of zinc supplements on iron status, and the results of these trials showed that ferritin performed as well as or better than TfR in detecting the effects (28-30).

A notable strength of the current analysis is the wide range of iron status among the studies that were included, which makes broader generalization possible. To further enhance the feasibility of applying BI-ferritin for population assessment, it may be possible to use a dried serum spot method to measure plasma ferritin concentrations in capillary blood (31).

There are a few limitations of using BI-ferritin to estimate BI stores. The most important one is that the ferritin concentration is affected by the acute phase reaction (e.g., systemic inflammation and infection), thereby falsely elevating the estimate of BI stores. Nevertheless, BI-TfR/ferritin is also affected by these situations. In either case, it would be important to measure an acute phase protein to identify persons with systemic inflammation. In the present studies, CRP was elevated in only 10.8% of persons, and the results of these trials showed that ferritin performed as well as or better than TfR in detecting the effects (28-30).

A notable strength of the current analysis is the wide range of iron status among the studies that were included, which makes broader generalization possible. To further enhance the feasibility of applying BI-ferritin for population assessment, it may be possible to use a dried serum spot method to measure plasma ferritin concentrations in capillary blood (31).
programs. At least one acute phase protein (such as CRP or an alternative biomarker) also should be measured to identify those persons whose plasma ferritin concentration may be falsely elevated by concurrent infection or inflammation.

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The authors' contributions were as follows—ZY, KGD, and KHB: the design of the study, analysis and interpretation of data, and preparation of the manuscript; KGD, BL, OH, CC, SA-A, EDM, RJC, MD, LHA, and KHB: the design, implementation, and analysis of the original clinical trials; and all authors: review and critique of the manuscript. None of the authors had a personal or financial conflict of interest.

REFERENCES


