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Introduction

Iron deficiency (ID) with or without anemia has important consequences for human health and child development. Thus, accurate, non-invasive biomarkers of iron status are needed to monitor the prevalence and distribution of ID in populations and to identify individuals who may benefit from iron supplementation (1). The use of common indicators of iron status, such as plasma ferritin (F), soluble transferrin receptor (sTfR), and erythrocyte zinc protoporphyrin (ZPP), is limited by the influence of confounding factors, such as inflammation and infections like malaria. Measurement of multiple indicators is generally recommended, but this approach may be too costly in low-income settings. There is currently no consensus on a single "best" indicator of iron status, particularly in areas where infections are common. In these settings, it is recommended to measure indicators of inflammation, such as elevated plasma C-reactive protein (CRP) and/or α_1-acid glycoprotein (AGP) (2). This issue of NNA summarizes one manuscript published in the *Journal of Nutrition* and two in the *American Journal of Clinical Nutrition* reporting the results of three population-based surveys in sub-Saharan Africa that compared the use of different indicators of iron status for assessing the prevalence of ID.

Methods

The first study was a nationally-representative cluster survey in Cameroon (3). Plasma F, sTfR, CRP, and AGP were measured among 872 women 15-49 y and 838 children 12-59 mo. Body iron stores were calculated using the ratio of sTfR and F. The authors estimated the national prevalence of ID according to the different indicators and adjustments for inflammation, and assessed whether the different indicators identified the same geographic, demographic, and socio-economic sub-groups at risk for ID.

The second study was a longitudinal study of 96 children aged 6-23 mo, 150 school-age children and 92 women aged 15-25 yr in Côte d'Ivoire (4). F and sTfR were assessed along with indicators of inflammation (CRP and AGP). ID was defined as F < 12 μg/L for infants and <15 μg/L for school-age children and women and sTfR > 8.5 mg/L. Malaria was assessed by rapid diagnostic test and thick and thin blood smears.

The third study was a cross-sectional survey of 680 children 6-35 mo in western Kenya (5). ZPP and plasma F, sTfR, CRP, and AGP were measured, and malaria was diagnosed using thick and thin blood smears. The sTfR/ferritin index was calculated, and ID was defined using multiple-criteria model in which children were considered deficient if ≥ 2 of 3 indicator values were abnormal (F < 12 μg/L, sTfR > 8.3 mg/L, and/or ZPP > 80 μmol/mol heme).

All 3 studies adjusted the iron status indicators mathematically for the presence of inflammation following the suggestions by Thurnham *et al* (2), in which individuals were divided into categories of elevated CRP (CRP ≥5 mg/L), elevated AGP (AGP ≥1 g/L), elevated CRP and AGP or normal CRP and AGP. The study in Côte d'Ivoire also adjusted for the presence of malaria.

Results and Conclusions

The ID prevalence in all 3 studies varied substantially depending on the iron status indicator used. In all cases, the percentage of children and women identified as iron deficient was the lowest when the definition was based on F and the highest with sTfR. In the national survey in Cameroon, for example, 14% of children were identified as iron deficient based on F and 68% based on sTfR, when these iron status indicators were not adjusted for the presence of inflammation and/or malaria. Only the study in Kenya also assessed ZPP, which resulted in an even higher ID prevalence than sTfR (elevated ZPP 83%; elevated sTfR, 61%).

The prevalence of inflammation, as measured by elevated CRP and AGP, was high in all 3 studies, ranging from 4 to 57% depending on the population group. In Côte d'Ivoire, 79% of the school-age children, 42% of the young children and 37% of the women were infected with *P. falciparum.* All 3 studies confirmed that the iron status indicators were influenced by inflammation and that mathematical adjustments for inflammation can be used to "correct" the prevalence of ID. When F was adjusted for the presence of inflammation, the ID prevalence increased. In Kenya for example, 27% of children were identified as iron deficient based on unadjusted F concentrations, but 41% were identified as deficient based on adjusted F concentrations. The adjustment of sTfR for CRP, AGP and/or malaria resulted in a considerable decrease in the estimated prevalence of ID in Kenya and Côte d'Ivoire. Among young children in Côte d'Ivoire, adjustment of sTfR for inflammation only or for inflammation and *P. falciparum* infection significantly decreased the prevalence of ID from 74% to 60% and 54%, respectively. The ratio of F and sTfR was equally affected by inflammation and thus did not have an advantage over the individual indicators. In Kenya, the investigators assessed agreement between ID defined using the multiple-criteria model and ID defined using only F, sTfR, ZPP, or the sTfr/F index and found that in this setting, sTfr was most successful at identifying ID according to the multiple-criteria model.

In the national survey in Cameroon, the prevalence of iron deficiency anemia and the proportion of anemia associated with ID also varied by iron indicator; both increased with increasing prevalence of ID. However, the indicators generally identified the same groups at risk of ID (young children, pregnant women, and those in rural areas and in the North region). The authors concluded that any indicator would be useful for identifying groups at risk of ID but that the choice of indicator for estimating ID prevalence should be based on consideration of the physiological role of the indicator (e.g., whether the biomarker indicates depleted stores, tissue iron deficiency, etc.).

Program and Policy Implications

All studies demonstrate that the estimated prevalence of ID and the program and policy implications of a survey will depend in part on the indicator chosen to represent iron status. In particular, the use of F, even after adjustment for inflammation, tends to produce lower estimates of ID, and sTfR and ZPP produce higher estimates of ID (3-4-fold higher, in these studies). The Cameroon survey also indicates that the choice of iron indicator will influence estimates of the proportion of anemia that is associated with ID and will therefore affect decisions regarding anemia-control strategies (i.e., whether resources should be allocated toward addressing iron deficiency, infection, or other causes of anemia).

Where resources permit, it is advisable to measure multiple indicators of iron status until more specific guidelines are available. Regardless of the iron indicator used, it is also important to measure indicators of inflammation such as CRP and AGP. A better understanding of the relationships between inflammation, infection and iron status indicators and, ultimately, a consensus on the selection and interpretation of indicators to assess iron status under varying contexts are sorely needed. Recent initiatives such as Biomarkers of Nutrition for Development (BOND) (6) and Biomarkers Reflecting Inflammation and Nutrition Determinants of Anemia (BRINDA) are important steps toward addressing these issues.

NNA Editor's Comments *

A limitation of these studies is the lack of a "gold standard" (such as bone marrow iron) with which to compare the available indicators. Nevertheless, all papers highlight the different prevalence estimates of ID based on different indicators (particularly sTfR vs F), recognize the important effects of inflammation on iron status indicators, and call for more work in this area.

Findings from Côte d'Ivoire confirm that malaria affects sTfR concentrations (7). Presence of hemoglobinopathies, such as thalassemia or sickle cell trait, may also affect the measured prevalence of IDA (8). Research is needed to understand the behavior of iron status indicators in the presence of these conditions, and to develop strategies for interpreting the results.

***** These comments have been added by the editorial team and are not part of the cited publication.

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