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Can Serum Ferritin Be Effectively Interpreted in the Presence of the Acute-Phase Response?

The paper by Coenen et al. (*1*) in this issue addresses the detection of iron deficiency in the presence of chronic disease. This is an important diagnostic challenge because of the frequency of the problem as well as its direct effect on patient management. Iron deficiency and the anemia of chronic disease are the most prevalent (75%) causes of anemia in both hospitalized and ambulatory patients (*2–4*). It is important to differentiate patients who will benefit from therapeutic oral iron from those who not only will not benefit but may even risk iron overload.

The common "gold standard" for the determination of iron stores in clinical practice is the staining of bone marrow aspirate. The goal of the laboratory is to accurately identify iron-deficient patients in such a way as to obviate the need for bone marrow examination in a subset of anemic patients. This is a well-studied clinical problem (*5*), and most authors agree that no single test of peripheral blood can accurately identify all iron-deficient patients in the presence of an acute-phase response. Two frequently discussed multivariate approaches involve ferritin and mean corpuscular volume (*6*) or ferritin plus an indicator of the acute-phase response such as erythrocyte sedimentation rate (ESR) or C-reactive protein (*7–10*).

The anemia associated with acute-phase response or chronic disease has been well characterized in recent reviews (*11, 12*). Erythrocyte survival is modestly reduced and erythropoiesis is iron-deficient, owing to inadequate release of iron from reticuloendothelial stores. This disorder of iron metabolism is one defining characteristic of the anemia of chronic disease. Interleukin-1 (IL-1), the primary mediator of the acute-phase response, mediates the alterations of acute-phase proteins as well as the characteristic disorder of iron metabolism (*13*). Using cluster analysis and logistic discriminant analysis, several colleagues and I found an independent mathematical association between ESR, ferritin, and iron stores (*7*). It is attractive to hypothesize that this relationship reflects concomitant IL-1-mediated changes in acute-phase proteins and iron metabolism. In any event, it is clear that interpretation of serum ferritin values must include consideration of acute-phase response.

Cavill et al. (*14*) showed that the meaningful interpretation of serum ferritin in the presence of chronic disease must also reflect the degree of anemia. When erythrocyte mass is significantly diminished, less iron circulates in these cells and more should appear in storage loci. This increased storage iron should thus be reflected by an increased concentration of serum ferritin.

Since the publication of our postulated relationship between ESR and serum ferritin (*7*), the actions of IL-1 and the interrelationships of iron metabolism and the acute-phase proteins have been studied more extensively (*15,16*). Baynes et al. (*16*) found that the slope of the relationship between iron stores and ferritin is maintained in several chronic diseases, but with an offset toward higher ferritin concentrations. However, this relationship is different for patients with rheumatoid arthritis in their study group.

All investigators agree that serum ferritin concentrations <12 μg/L indicate iron deficiency. Also, all agree a cutoff of 12 μg/L is too low in the presence of an acute-phase response or chronic disease. A review of the literature on rheumatoid arthritic patients in which both ferritin and histologic iron scores are given for each individual reveals 72 patients with ferritin >160 μg/L (*17–22*). Of these 72 patients, only two (2.7%) showed no bone marrow iron by histologic staining; 70 had iron present. Several of these reports appear in the bibliography of Coenen et al. (*1*). However, the results of Coenen et al. are distinctly different, showing six (15%) patients with absent iron and five (12.5%) patients with trace iron among 40 patients with chronic disease and ferritin >160 μg/L.

Most investigators of iron status have suggested there is some ferritin value indicating low likelihood of iron deficiency in the presence of chronic disease. This suggested value generally varies between 45 and 100 μg/L (*23–27*), which is consistent with our findings (*7*), in which the graph of ferritin vs ESR suggested that iron deficiency was unlikely if serum ferritin exceeded 80 μg/L at the highest ESR tested (150 mm/h). In contrast, Coenen et al. report that an increased concentration of ferritin has poor predictive value for excluding iron deficiency. Many of the reports quoted above are consistent with our data; some are not (*28, 29*).

The transferability of "discriminant functions," such as the one we proposed (*7*), from one patient group to others can be fraught with uncertainty (*5, 30*), owing to (*a*) the different patients investigated, (*b*) differences in reference methods or "gold standard," and (*c*) differences in the test methods used. However, the patients in our study (*7*) and in that of Coenen et al. (*1*) seem similar, and it is doubtful that patient selection is sufficient to explain the discrepant findings. The histological iron stains "gold standard" differed in that we used bone marrow aspirations from the posterior superior iliac crest, whereas Coenen et al. used sternal marrow. [Bierman and Kelly (*31*), studying multiple bone marrow aspirations from the posterior superior iliac crest, suggest that the iliac crest provides a more representative and quantitatively larger marrow source than the sternum.] The ESR method used by Coenen et al. appears identical to that used by us, but the ferritin kits used in the two studies differed. Thus, differences in the reac-

tivity of the antibodies in ferritin kits and differences in the isoferritin makeup of patients' samples may partially account for the lack of transferability of our ferritin vs ESR "discriminant function," although many investigators report reasonably similar performance of most kits measuring basic isoferritins (*32–34*) and a similar degree of glycosylation and isoferritin makeup in normal and abnormal specimens (*15, 35*).

Thus, although there are many theoretical reasons for the lack of transferability of the ferritin vs ESR discriminant function from our laboratory to that of Coenen et al., no practical reason is immediately obvious.

Clearly, the discriminant function my colleagues and I presented is useful to find iron deficiency and can obviate the need for bone marrow to detect iron deficiency in some patients. The line drawn in our "discriminant function" was derived by independent mathematical analyses involving cluster analysis and logistic discriminant analysis. The line on our graph of ESR vs ferritin is below that in the paper by Coenen et al., which appears to have been derived from simple linear regression. There do not appear to be any false diagnoses of iron deficiency in our data or in the data of Coenen et al. if our discriminant function is used. Rather, the difference between the two reports is in the likelihood of iron deficiency in patients whose results fall above the discriminant function line, i.e., "false exclusion" of iron deficiency. Such a finding would potentially lead to withholding a beneficial treatment with oral iron.

Publication of the differences between the reports of Coenen et al. and Witte et al. should lead readers and other investigators to evaluate these data in the context of other available data.

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