Revista Brasileira de Hematologia e Hemoterapia
Brazilian Journal of Hematology and Hemotherapy
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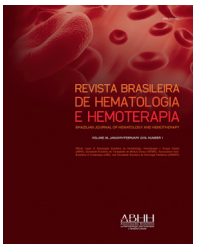

Scientific Comment

Adjusting thresholds of serum ferritin for iron deficiency: a moving target☆

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Iron deficiency anemia (IDA) is widely prevalent in patients of all ages.[1] In children and young adults, the diagnosis of IDA is rather straightforward. In elderly patients, however, the presence of comorbidities usually hampers prompt diagnosis by conventional iron profile tests.[2]

When limited to conventional iron measures during evaluations of suspected IDA in an elderly patient with a normal ferritin level, transferring saturation becomes more reliable for diagnostic purposes. Comorbidity-related inflammation can compromise the accuracy of iron tests, notably serum ferritin, which is an acute phase reactant itself.[2,3] Therefore, in order to ascertain the diagnosis of IDA in elderly patients, it is advisable to take other iron parameters into account, such as transferrin saturation.

Moreover, it is important to question what a 'normal' serum ferritin level really is for this patient, since adoption of commonly used cut-off values (ranging from 15 to 30 ng/mL) to confirm IDA would result in a large number of undiagnosed patients among the elderly.[4] A distinction between absolute and functional iron deficiency in this context is crucial. In absolute iron deficiency, serum ferritin levels tend to mirror low iron reserves unless falsely elevated due to inflammation-related conditions. On the other hand, a chronic inflammatory process is frequently associated with functional iron deficiency, a condition in which, in spite of satisfactory iron reserves with normal or even increased serum ferritin, the availability of iron for the bone marrow is limited substantially due to increased hepcidin transcription.[5]

The study by Babaei et al. [6] in this issue of the Brazilian Journal of Hematology and Hemotherapy aimed at obtaining an appropriate cut-off level for serum ferritin that would better discriminate between elderly patients with and without IDA. The authors had the opportunity – and the privilege – to recruit a very homogeneous cohort of elderly patients in terms of ethnicity, demographics and lifestyle. A threshold of 100 ng/mL for serum ferritin yielded a sensitivity of 60% and specificity of 59% for IDA detection, employing a low transferrin saturation level as the reference test to confirm diagnosis.

In this context, a sensitivity and specificity of around 60% to confirm IDA by a distinct serum ferritin threshold seems reasonable, as shown by Babaei et al. and others.[7] For instance, the cut-off value for hemoglobin A1C to diagnose diabetes mellitus has also been a matter of debate, since the traditionally adopted cut-off point of 6.5% only accounts for a sensitivity of 43%, whereas at a cut-off point of 6.2%, the sensitivity would increase to 60%, in spite of similar specificities for both points.[8]

It is noteworthy, however, that finding a distinctive threshold for serum ferritin in specific populations is a challenging task that relies essentially on the choice of the parameter adopted as the gold standard for IDA diagnosis. Although transferrin saturation levels have been adopted for this in some studies, their use has limitations. For example, when stainable iron in the bone marrow was adopted as the reference standard, transferrin saturation levels below 20% had a sensitivity of 60% and specificity of 48% in detecting IDA

DOI of original article: http://dx.doi.org/10.1016/j.bjhh.2017.02.002.

☆ See paper by Babaei et al. on pages 223–8.

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http://dx.doi.org/10.1016/j.bjhh.2017.03.002

in anemic patients with mean age of 68; hence, there was a considerable overlap between the iron-deficient and iron-sufficient groups.[9] Alternatively, instead of selecting a gold standard method to infer the applicability of a given test to confirm IDA, an interesting and less invasive approach would be the combination of the conventional iron measures with newer reliable parameters such as transferrin receptor, reticulocyte hemoglobin and measurements of the proportion of hypochromic red blood cells which allow early recognition of IDA.[10]

Any effort to improve IDA detection in patients with comorbidities is highly welcome, since misdiagnosing or underdiagnosing this type of anemia by conventional iron tests with fixed reference ranges can lead to insufficient or equivocal treatment. It is important to keep in mind that iron tests are highly volatile in elderly patients with comorbidities, and personalization of reference ranges in this specific population can improve accuracy of IDA confirmation, especially when this condition is clinically suspected.

Conflicts of interest

The author declares no conflicts of interest.

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