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Monitoring of iron status in patients with heart failure

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The 2016 ESC/HFA heart failure (HF) guidelines emphasize the importance of identifying and treating iron deficiency (ID) in patients with HF. Iron deficiency can occur in half or more of HF sufferers, depending on age and the phase of the disease. Iron deficiency can be a cause of anaemia, but it is also common even without anaemia, meaning that ID is a separate entity, which should be screened for within the HF population. Although assessment of iron stores in bone marrow samples is the most accurate method to investigate iron status, it is not practical in most HF patients. Levels of circulating iron biomarkers are an easily available alternative; especially, ferritin and transferrin saturation (Tsat). In patients with HF serum ferritin level $<100\,\mu g/L$ (regardless of Tsat value) or between 100 and $299\,\mu g/L$ with Tsat $<20\%$ are considered as recommended criteria for the diagnosis of ID, criteria which have been used in the clinical trials in HF that have led to a recommendation to treat ID with intravenous iron. We discuss the optimal measures of iron biomarkers in patients with HF in order to screen and monitor iron status and introduce some novel ways to assess iron status.

Introduction

The 2016 ESC/HFA guidelines on management of heart failure (HF) emphasize the clinical significance regarding screening and optimal treating of comorbidities among patients with HF.[1,2] Iron deficiency (ID) is a prime example of a disease, which is extremely common in patients with HF, and is easy and cheap to be screened and diagnosed. Importantly, presence of ID translates into impaired exercise capacity, poor quality of life, higher risk of HF hospitalization, and/or premature death.[3,4]

In a large cohort of stable HF patients, ID was identified in nearly 50%,[5] whereas in those with recent decompensation in almost 80%.[6] Although anaemic patients were more often iron deficient than those without anaemia, the difference was surprisingly small (61% vs. 46%).[5]

Iron deficiency is a comorbidity which has received very little attention until the last decade. Most importantly, ID developing in patients with HF has been identified as an important therapeutic target.[7–10]

In front, we need to acknowledge that ID can exist with or without anaemia (defined as a haemoglobin concentration $<13\,g/dL$ in men and $<12\,g/dL$ in women). Although untreated ID can finally lead to anaemia, in patients with HF ID itself reveals several clinical and prognostic unfavourable effects beyond anaemia (e.g. impaired exercise capacity, skeletal muscle dysfunction and reduced muscle mass[11]—all of which are related with poor quality of life and unfavourable outcomes).[12–17] Therefore, ID should be considered as a separate entity, also in the context of screening and monitoring of iron status in the course of HF,[18–20] as it should be in many chronic disorders.[21]

What to measure in patients with heart failure in order to screen/monitor iron status?

Assessment of iron stores in bone marrow samples is the most accurate method to investigate iron status in

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general,[22-26] however, due to its invasiveness and poor availability this diagnostic approach is unsuitable for the broad population of HF patients. Currently, levels of circulating iron biomarkers are indirect but commonly acceptable and clinically applicable methods to diagnose ID and monitor iron status in patients with HF.[27]

Ferritin is one of the most commonly used laboratory measures of iron status worldwide.[28] Low circulating ferritin reflects depleted body iron stores. In a general population, the cut-off of serum ferritin to diagnose absolute ID is usually 30 μg/L,[21,29] although lower cut-off values (i.e. 12-15 μg/L) have also been used.[30,31]

Ferritin is also an acute-phase protein, being involved in immune response and inflammatory reactions. Therefore, in healthy individuals, ferritin is directly and proportionally related to the amount of body iron stores, however, its values increase in case of concomitant acute or chronic inflammation (even due to low-grade inflammation), which is commonly seen in patients with chronic kidney disease or HF.[32] Also, its values have to be interpreted with caution in patients with malignancy, thyroid disease, liver disease, or heavy alcohol intake.[27] Therefore, in patients with HF serum ferritin level <100 μg/L (regardless of Tsat value—for the detailed interpretation of Tsat values in HF see below) or even serum ferritin level between 100 and 299 μg/L with Tsat <20% are considered as recommended criteria for the diagnosis of ID.[1]

Hepcidin constitutes the major regulator of systemic iron metabolism and a part of an innate immune (and antimicrobial) response.[33-38] It is a very conservative molecule released by the liver. Its synthesis is precisely regulated in order to optimize and synchronize iron metabolism and/or immune response. Depleted iron stores, hypoxia, and ineffective erythropoiesis are most common factors inhibiting hepcidin production in the hepatocytes liver and its subsequent release into the circulation, on the contrary, inflammation accompanied or not by infection stimulates hepcidin production. Hepcidin correlates with iron stores more precisely than ferritin, particularly low circulating hepcidin reflects depleted iron stores, even in the presence of concomitant inflammation. The assessment of circulating hepcidin, being difficult and not standardized, is currently used only for research purposes and is not recommended in clinical practice.

The other biomarker commonly used in clinical practice for screening and monitoring of iron status is transferrin saturation (Tsat).[20,21,39,40] It is defined as a ratio of serum iron and circulating iron bound to transferrin (TIBC, total iron-binding capacity) expressed in %. This index allows to estimate the amount of iron available for cellular metabolism in both haemato- and extra-haematopoietic cells.[12] Tsat <20% is used for the diagnosis of depleted iron available for target cells, and this cut-off is applied in both a general population and subjects with chronic conditions accompanied by low-grade inflammation (e.g. chronic kidney disease, HF).

Soluble transferrin receptor (sTfR) is a relatively new diagnostic tool already used by haematologists for diagnosis of ID-related anaemia. It is worthy of noting that regardless of haemoglobin level high sTfR indicates insufficient intracellular iron availability for metabolic needs of all living cells.[41] TfR is the major transmembrane protein which allows for an iron influx to the cell. In case of intracellular iron depletion, its membrane expression is increased, and excessive molecules are released to the circulation. Importantly, the effect of immune response or inflammatory reaction on circulating levels of sTfR is negligible.[42] Based on the pathophysiological evidence, we have proposed a novel definition of ID based on the combined measurement of low circulating hepcidin (indicating depleted iron stores in the body) and high circulating sTfR (indicating depleted intracellular iron, being inadequately low in relation to current metabolic needs).[36,43] The assessments of either circulating sTfR or circulating hepcidin have not been used in any clinical trial for the identification of iron-deficient patients with HF who could benefit from iron therapy. These parameters cannot be recommended to be used in clinical practice.

Therefore, currently accepted and recommended criteria for detecting ID in patients with HF are serum ferritin <100 μg/L or serum ferritin 100-299 μg/L in combination with Tsat <20%.[7,12,44] The aforementioned definition of ID has already been used in few major clinical trials in patients with symptomatic HF, where ID was supplemented.[7-9]

It should be emphasized that neither serum iron nor serum transferrin (or TIBC) alone are reliable and sufficient for the assessment of iron status in patients with HF. It should also be noted that neither haemoglobin level nor any erythropoietic index (e.g. mean corpuscular volume, mean corpuscular haemoglobin, mean corpuscular haemoglobin concentration) can be used for either screening, diagnosing, or monitoring iron status. As it has been already stated, ID is common in patients with HF with normal haemoglobin level or/and normal erythropoietic indices.[45-47]

When to measure iron biomarkers in patients with heart failure in order to screen/monitor iron status?

Every patient with HF is recommended to be screened for ID using two biomarkers: serum ferritin and Tsat[1] (Class I LOE C). This recommendation applies to all patients with HF, regardless of left ventricular ejection fraction, HF aetiology, haemoglobin level, renal or liver function, the presence of other comorbidities. Importantly, assessments of serum ferritin and Tsat performed during an episode of acute HF are also valid.

At the moment, both aforementioned parameters are obligatory to identify patients with HF who are iron deficient and who could benefit safely from intravenous iron therapy. Assessment of haemoglobin level is not needed for the diagnosis of ID; however, at the moment, we do not have evidence if among iron-deficient patients with HF with haemoglobin >15 g/dL intravenous iron supplementation is safe.

If the diagnosis of ID is not confirmed, we suggest to remeasure serum ferritin and Tsat every year during the follow-up ambulatory visits or at any time when an episode of circulatory decompensation occurs.

If the diagnosis of ID is confirmed and intravenous iron supplementation is administered, there is no need to recheck iron status after few weeks. After intravenous iron supplementation, serum ferritin and Tsat are usually artificially increased for 2–3 weeks (sometimes a bit longer), and the interpretation of these values is inconclusive. We suggest to reassess iron status using serum ferritin and Tsat 3 and 6 months after the intravenous iron administration. If ID persists, another calculated dose of intravenous iron is recommended. If iron stores are repleted (based on normal serum ferritin and Tsat), the regular annual monitoring of iron status is recommended.[41,48,49]

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