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REVIEW

Iron Deficiency in Heart Failure: Looking Beyond Anaemia

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Iron is an essential micronutrient in many cellular processes. Iron deficiency, with or without anaemia, is common in patients with chronic heart failure. Observational studies have shown iron deficiency to be associated with worse clinical outcomes and mortality. The treatment of iron deficiency in chronic heart failure patients using intravenous iron alone has shown promise in several clinical trials, although further studies which include larger populations and longer follow-up times are needed.

Keywords Iron deficiency • Heart failure • Intravenous iron

Introduction

Chronic heart failure (CHF) is an increasingly common condition in Australia, with a prevalence of 1.3% and an incidence of 30,000 cases per year [1]. It is associated with significant mortality, with five-year survival ranging from 50-75% [2]. Chronic heart failure also causes significant morbidity with approximately 22,000 hospital admissions in one year [3]. The Australian Institute of Health and Welfare estimated that CHF led to healthcare costs of $411 million in 1993-1994 [4], while a more recent study concluded that current healthcare expenditure on CHF was closer to $1 billion per annum [3]. Over the last decade, iron deficiency (ID) has been increasingly recognised as both a poor prognostic marker and a potential therapeutic target in CHF patients. This review article aims to provide a summary of the current evidence that exists for the treatment of ID in CHF.

Overview of Iron Turnover

Dietary iron is reduced to Fe^{2+} by duodenal cytochrome B in the lumen of the duodenum and proximal jejunum, where it enters the enterocyte via the divalent metal transporter-1 (DMT-1). Iron is then exported into the circulation by ferroportin, which is located on the basolateral membrane of the enterocyte. Exported iron is subsequently oxidised to Fe^{3+} by hephaestin and bound to plasma transferrin. The transferrin-iron complex is eventually taken up by target cells expressing transferrin receptor 1. Iron is stored in the liver, spleen, and bone marrow as ferritin [5–9].

Hepcidin is a small peptide released by the liver that acts as the primary regulatory hormone for iron homeostasis. It inhibits the absorption of iron by binding and degrading ferroportin, leading to iron accumulation within enterocytes and excretion via shedding of the intestinal cells. As ferroportin is also present in the macrophages of the reticuloendothelial system (RES), hepcidin causes iron sequestration in the RES and reduces the availability of utilisable iron. Hepatic expression of hepcidin decreases in ID and increases in iron overload and inflammatory states [6,7,10].

Definition and Diagnosis of Iron Deficiency in Chronic Heart Failure

Iron deficiency can be classified as absolute or functional [11]. Absolute ID reflects depleted body stores caused by poor

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dietary intake, impaired gastrointestinal (GI) absorption, and chronic blood loss. Functional ID is thought to be caused by increased hepcidin production and subsequent inhibition of the iron exporter ferroportin, leading to impaired absorption and utilisation of iron [7,8]. Chronic heart failure patients are susceptible to both forms of ID [8].

The diagnosis of ID in patients with CHF is complex. The standard cut-off value for diagnosing ID in many other conditions is a serum ferritin level <30 µg/L, which has a sensitivity of 92% and a positive predictive value of 83% [12]. However, ferritin is an acute phase reactant [13] and this cut-off does not appear to apply to patients with chronic diseases such as CHF [14]. This was illustrated in a study by Nanas et al. [15]: out of 37 advanced CHF patients with anaemia, 27 (73%) had ID confirmed on bone marrow aspiration (used as 'gold standard') despite a mean ferritin of 75±59 µg/L.

Currently, a diagnosis of ID in CHF can be made when the serum ferritin level is <100 µg/L (absolute ID), or when the serum ferritin level lies between 100-299 µg/L combined with a transferrin saturation (TSAT) <20% (functional ID) [5,8,16–18]. This is based on the landmark FAIR-HF study [19], which classified CHF patients as having ID based on the above stated criteria, and found improvements in their symptoms, functional capacity, and quality of life (QoL) after treatment with intravenous (IV) ferric carboxymaltose (FCM). This diagnostic criteria for ID has subsequently been incorporated into the 2012 European Society of Cardiology (ESC) Guidelines On Diagnosis And Treatment Of Heart Failure [20].

Aetiology of Iron Deficiency in Chronic Heart Failure

The aetiology of ID in CHF is multifactorial and complex. Aside from reduced dietary intake [21] and chronic GI blood loss, it is believed that CHF causes an inflammatory state which leads to increased hepcidin levels and subsequent ID due to reduced iron absorption and enhanced reticuloendothelial block [8,17,22,23]. However, multiple studies have provided conflicting evidence on the exact cause of ID in CHF. An experimental model found that rats with heart failure and anaemia had decreased hepcidin expression without an upregulation in their intestinal expressions of hypoxia-inducible factor-2a, duodenal cytochrome b, DMT-1, or ferroportin, suggesting that impaired duodenal iron transport (and not elevated hepcidin) was the primary cause of the anaemia [24]. In contrast, two separate rat models with liver congestion showed contradicting results. Suzuki et al. [25] demonstrated decreased transferrin saturation (indicating ID) but no suppression of hepcidin in rats with liver congestion (induced via inferior vena cava ligation), while Ohno et al. [26] showed an increase in hepcidin in their model (liver congestion via pulmonary hypertension induced by monocrotaline injection). Both studies concluded that liver congestion in CHF leads to increased or abnormal expression of hepcidin, which then results in the development of ID and anaemia.

Jankowska et al. [27] provided further insight into the role of hepcidin in CHF. In their study of 321 patients, hepcidin levels changed with the severity of CHF. Patients in New York Heart Association (NYHA) class I had similar haemoglobin (Hb) levels, but increased serum hepcidin and ferritin when compared to healthy subjects. As the severity of CHF worsened based on NYHA class, there was a corresponding decrease in Hb, ferritin, TSAT, and hepcidin. There was also an inverse relationship between hepcidin and inflammatory markers, with the lowest hepcidin levels seen in the group with the highest C-reactive protein (CRP) and interleukin-6. The authors hypothesized that the early phase of CHF is characterised by an increase in hepcidin (by mechanisms other than inflammation), followed by the development of ID due to decreased iron absorption and release, which in turn causes gradual reduction of hepcidin levels as CHF worsens [27].

Prevalence of Iron Deficiency in Chronic Heart Failure

Iron deficiency is common in CHF patients. However, the reported prevalence rates of ID in CHF patients vary widely, ranging from 37% to 61%, due to differences in the definitions of ID and the studies' inclusion criteria (Table 1) [28–32]. It is also recognised that patients do not necessarily have to be anaemic for ID to be present [28]. Nanas et al. [15] showed that in a group of patients with advanced CHF (NYHA IV) and anaemia, ID (diagnosed on bone marrow aspiration) was by far the commonest cause of anaemia, accounting for 73% of cases. Okonko et al. [29] found that ID (defined as TSAT <20%) was present in 43% of 157 consecutive patients with systolic heart failure, and became increasingly more common in those with a higher NYHA class. In a separate large prospective observational study involving 546 stable patients with systolic heart failure, Jankowska et al. [28] showed that ID (as defined by the ESC guidelines) was present in 37% of patients. The same study also demonstrated that ID occurred frequently in the absence of anaemia (32% of non-anaemic patients had ID), and was independently associated with female sex, more advanced NYHA class, higher plasma CRP, and higher brain natriuretic peptide (BNP) levels [28]. Using data from the Third National Health and Nutritional Examination Survey, Parikh et al. [32] found that out of 574 patients with self-reported CHF, ID was present in 61% of patients. The prevalence of ID is less well studied in patients with heart failure and preserved ejection fraction (HFpEF). A small study involving 26 non-anaemic patients with HFpEF showed that ID was present in 15 patients (57%), with nine having functional ID [30]. In the largest international pooled analysis study conducted to date (n=1506 patients) consisting of patients with both systolic heart failure and HFpEF, the reported prevalence of ID was 50% for the entire cohort [31].