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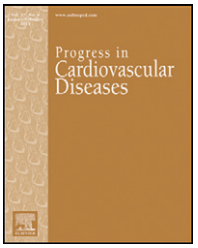

Targeting Iron Deficiency Anemia in Heart Failure

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ABSTRACT

Iron deficiency is common in heart failure (HF) patients, and is associated with increased risk of adverse clinical outcomes. Clinical trials of intravenous iron supplementation in iron-deficient HF patients have demonstrated short-term improvement in functional capacity and quality of life. In some trials, the benefits of iron supplementation were independent of the hemoglobin levels. Additional investigations of iron supplementation are needed to characterize the mechanisms contributing to clinical benefit and long-term safety in HF.

Heart failure (HF) affects an estimated 5.7 million Americans and each year is associated with greater than 1 million hospital admissions and health care costs in excess of $30 billion.[1,2] HF patients with concomitant anemia have increased morbidity and mortality risk when compared with non-anemic HF patients.[3,4] Accordingly, anemia has been identified as a potential therapeutic target to improve clinical outcomes in the HF patient population.[5] Since iron deficiency is common in HF patients, this review will focus on diagnostic testing and treatment strategies for HF patients with iron-deficiency anemia.

Prevalence and etiology of anemia in HF

Reported estimates of the prevalence of anemia in HF patients vary broadly from 10 to 49%.[5,6] A meta-analysis of 153,180 HF patients derived from 34 published studies reported the mean prevalence of anemia to be 37.2% with range from 7% to greater than 50%.[4] This variability in the estimate of prevalence of anemia is attributable in part to inconsistent definitions of anemia across published studies. The World Health Organization (WHO) defines anemia as hemoglobin concentration <13 g/dL in men and <12 g/dL in women; however, the National Kidney Foundation defines anemia as hemoglobin <12 g/dL in men and postmenopausal women and <11 g/dL in premenopausal women, with the 2006 updated guidelines changing the definition to <13.5 g/dL in men and <12 g/dL in women.[7,8] Some studies in HF populations used these published definitions, while others defined anemia based on the population distribution of hemoglobin values, other arbitrary cut-off values, or diagnostic codes from claims data. The definition of iron-deficiency anemia is also inconsistent across published studies. The diagnosis of iron deficiency is based on blood biomarkers of iron homeostasis and reticulocyte and red blood cell measurements.[9,10] Serum ferritin <30 ng/ml in association with low hemoglobin and microcytic hypochromic red blood cells is diagnostic of absolute iron deficiency anemia (severely reduced or absent bone marrow iron stores). In disease states with chronic inflammation, including HF, activation of pro-inflammatory cytokines is associated with increased serum ferritin values independent of iron stores. Inflammation-mediated changes in iron homeostasis are often called functional iron deficiency, and may occur with or without anemia. In the presence of inflammation, iron deficiency anemia is more likely if serum ferritin is <100 ng/ml, transferrin saturation is <16%, soluble transferrin receptors are elevated, reticulocytes are reduced and hypochromic, and erythrocytes are

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Abbreviations and Acronyms

6MWT = 6-minute walk test

CV = cardiovascular

DMT-1 = divalent metal transporter-1

FCM = ferric carboxymaltose

HF = heart failure

IRP = iron regulatory proteins

KCCQ = Kansas City Cardiomyopathy Questionnaire

LV = left ventricular

LVEF = left ventricular ejection fraction

MLWHF = Minnesota Living With Heart Failure

NT-pro BNP = N-terminal-pro brain natriuretic peptide

NYHA = New York Heart Association

QoL = quality of life

VO2 = oxygen consumption or uptake

WHO = World Health Organization

microcytic. The ratio of soluble transferrin receptor to log serum ferritin has been proposed to be an accurate predictor of functional iron deficiency in patients with inflammation and anemia of chronic disease. In an observational study of 37 hospitalized anemic HF patients, bone marrow aspiration demonstrated that 73% of patients had absent iron staining in the bone marrow.[11] Serum ferritin was lower in anemic patients with absent bone marrow iron staining when compared with other anemic patients (75 ± 59 vs. 212 ± 100 ng/ml, $p < 0.001$). Absolute and functional iron deficiency anemia (severely reduced or absent iron stores) is common in HF populations. Based on ICD-9 discharge codes, anemia was present in 17% of a large cohort of hospitalized HF patients (n = 12,065). Within the anemic subset (n = 2082), 21% had iron deficiency and 58% were classified as anemia of chronic disease.[12] In a pooled analysis of 5 European HF cohorts (n = 1506), anemia was defined according to the above WHO criteria, and iron deficiency was defined as a ferritin level <100 ng/ml or serum ferritin 100–299 ng/ml in combination with transferrin saturation <20%.[13] Based on these definitions, anemia was present in 28% of HF subjects, and iron deficiency was present in 50% of HF subjects. Independent clinical predictors of iron deficiency in this cohort included female sex, worse New York Heart Association (NYHA) functional class, lower red blood cell mean corpuscular volume, higher N-terminal-pro-brain natriuretic peptide (NT-pro BNP) levels, and presence of anemia. Iron deficiency is associated with clinical severity of HF and associated with greater mortality risk in patients with concomitant anemia (HR 1.71, 95% CI 1.24–2.36, P = .001) or without concomitant anemia (HR 1.44, 95% CI 1.11–1.87, P = .006).[13–15]

Pathophysiology of functional iron deficiency in inflammation

Iron is an essential dietary micronutrient that functions as a co-factor for numerous proteins and enzymes in the human body. Iron-containing proteins are key regulators of oxygen transport (hemoglobin), muscle iron storage (myoglobin), mitochondrial respiration, cellular redox regulation, vasomotor regulation as an essential co-factor of soluble guanylate cyclase, the downstream target of nitric oxide and other nitrosovasodilators in vascular smooth muscle, and as a transcription factor for signaling pathways involving neurotransmission, innate immunity, cell growth, and inflammation.[16,17]

Total body iron stores are regulated exclusively through control of iron absorption, as there are no known natural metabolic pathways for iron excretion.[18,19] Hepcidin, a hepatocyte-derived peptide hormone, plays a critical role in a negative feedback loop regulation of iron absorption from the intestinal tract.[20] Hepcidin is secreted in response to tissue sensors of increased body iron stores and tissue oxygenation, but is also regulated by other factors including pro-inflammatory cytokines, and gonadal hormones. Hepcidin inhibits transfer of dietary iron to the reticuloendothelial system by inducing degradation of the iron exporter protein ferroportin in enterocytes and macrophages. Dietary iron and recycled iron from senescent red blood cells is bound to transferrin for iron transport, and to ferritin for intracellular iron storage, in a complex regulated system that controls iron availability to the bone marrow for erythropoiesis. Functional iron deficiency occurs when inflammation-induced hepcidin production leads to increased degradation of ferroportin with consequent decreased dietary iron absorption and decreased delivery of macrophage iron to the erythrocyte precursors.[9]

The transferrin receptor is the primary receptor for transfer of iron into the various cell types, but other transporter proteins including divalent metal transporter-1 (DMT-1) and Zip-14, also contribute to intracellular transport of iron, especially in iron overload states.[21] Transferrin-bound iron complexes are processed in endosomes and transferred via DMT-1 for intracellular iron storage (ferritin), or transport to mitochondria or other intracellular environments for incorporation into heme-containing and iron-sulfur cluster containing proteins. A small fraction of body iron stores is bound to citrate and other small molecules within the intracellular and extracellular compartments outside of the reticuloendothelial system.[22] Low molecular weight iron is available for participation in redox reactions via Fenton Chemistry and interactions with nitric oxide and regulates synthesis and activity of iron-containing proteins.[23] Iron regulatory proteins (IRP-1 and IRP-2) play an important role in maintaining iron homeostasis within non-heme tissues. In response to changes in iron availability and redox signals, IRP-1 and IRP-2 bind iron-response elements that regulate transcription of the transferrin receptor, ferritin, and other proteins.[23]

Treatment of iron-deficiency anemia in HF

Oral iron replacement

Oral iron salts are frequently used for iron replacement therapy due to the relative inexpensive cost and ease of administration. However, several important factors may limit success of oral iron therapy. First, gastrointestinal side effects are common and lead to poor compliance with oral iron