



CKJ REVIEW

Iron therapy in heart failure patients without anaemia: possible implications for chronic kidney disease patients

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Abstract

Iron deficiency anaemia is a global health problem that manifests as fatigue and poor physical endurance. Anaemia can be caused by dietary iron deficiency, blood loss or a combination of poor iron absorption and ineffective iron mobilization in patients with chronic disease. Nephrologists caring for patients with impaired renal function understand that iron treatment is necessary to provide adequate iron for erythropoiesis during the treatment of overt anaemia. However, a less well-understood health problem is iron deficiency, which creates symptoms that overlap with those of anaemia and often occurs in concert with chronic disease. Recently, several randomized controlled clinical trials have been conducted to investigate the effects of treatment with intravenous iron in heart failure patients with iron deficiency who may or may not also have anaemia. Given that heart and kidney disease are often comorbid, these clinical trials may have implications for the way nephrologists view their patients with iron deficiency. In this article, we review several clinical studies of intravenous iron therapy for patients with iron deficiency and heart failure and discuss possible implications for the treatment of patients with kidney disease.

Key words: anaemia, CKD, heart failure, iron, iron deficiency

Introduction

According to the World Health Organization (WHO), iron deficiency anaemia is the single most common micronutrient deficiency, affecting approximately one-quarter of the world's population [1]. Iron deficiency and subsequent iron deficiency anaemia are multifactorial disorders, but both generally involve inadequate dietary iron uptake due to either poor diet or intestinal malabsorption.

Iron deficiency and the resultant anaemia can be exacerbated by both acute and chronic medical conditions. Conditions that involve blood (i.e. iron) loss, such as colitis [2], pregnancy

and childbirth [3] and surgical procedures [4] may result in temporary iron deficiency. Over the long term, conditions such as heart and kidney disease can lead to anaemia of chronic disease, in which gastrointestinal iron absorption is often impaired [5]. The anaemia in these cases is generally normochromic and normocytic, arising from diminished production and/or survival of red blood cells. A large majority of patients with end-stage renal disease and many patients with earlier stages of chronic kidney disease (CKD) are anaemic and require iron therapy [6]. Among patients with chronic disease, iron deficiency can be further compounded by impaired release of iron stores from the reticuloendothelial system [7]. These perturbations in iron

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uptake and release, mediated at least in part by the cytokine hepcidin, cause a functional iron deficiency. Whether the cause of iron deficiency is acute or chronic, oral or parenteral iron supplementation may be used in an attempt to restore normal iron levels.

Among patients with both heart failure (HF) and CKD, the interplay between these two conditions may synergistically worsen iron deficiency and anaemia status. Pathological changes in patients with HF may cause iron deficiency [8, 9]. These can be compounded by poor nutrition in patients with concomitant CKD, who are advised to follow a low-protein (and thus low-iron) diet [10]. The presence of mucosal oedema and reduced gastrointestinal blood flow can further impede the absorption of dietary iron in these patients [11]. Gastritis or ulceration caused by concomitant pharmacotherapy, as well as proteinuria caused by CKD, may increase iron loss [12, 13]. Finally, administration of anti-platelet drugs or anti-coagulation agents increases susceptibility to bleeding [14].

Several decades ago, anaemia and iron deficiency were differentiated experimentally [15, 16] and a widely accepted notion is that anaemia negatively affects oxygen delivery and gas exchange, while iron deficiency impairs skeletal muscle and endurance tasks [17]. Individuals with either absolute or functional iron deficiency experience diverse and widespread clinical signs and symptoms. The subclinical and clinical manifestations of iron deficiency include impaired ability to perform physical work, impaired cognition, developmental delay and poor pregnancy outcomes [17]. When iron deficiency becomes severe enough to exacerbate anaemia, it can be difficult to parse symptoms caused by systemic iron deficiency from those due to tissue hypoxia caused by low haemoglobin.

It is clear that iron has many functions in the body above and beyond the persistent demands of haemoglobin production. While the use of iron to relieve anaemia is well studied, the potential effect of correcting iron deficiency in the absence of anaemia has only recently become a matter of critical debate [18]. Indeed, the need for randomized controlled trials to address the potential for intravenous (IV) iron to provide clinically relevant beneficial effects in CKD patients, beyond stimulation of erythropoiesis, has recently been highlighted [19].

Physiological roles of iron beyond erythropoiesis: mitochondria and energy

Iron has many critical roles in human physiology beyond its prominent role in erythropoiesis, where it is a key component of haemoglobin [20]. Under physiological conditions, iron can have multiple oxidation states: ferryl (+4), ferric (+3) and ferrous (+2) [17]. This oxidative variability makes iron highly reactive with oxygen, nitrogen and sulphur atoms. Therefore, iron serves as a key cofactor for enzyme complexes that catalyse coordinated oxidation and reduction (redox) reactions in a wide variety of contexts. Protein classes that require iron for their biological activity include haem proteins such as myoglobin and cytochromes and iron-sulphur proteins such as flavoproteins and haem flavoproteins [17]. Iron plays a critical role in energy production by the mitochondrial electron transport chain [20]. Of the 40 enzymes involved in creating adenosine triphosphate via electron transport, 6 are haem-containing cytochrome C proteins and 6 are iron-sulphur proteins [17]. Mitochondrial iron has been directly implicated in the pathophysiology of heteroplasmic mitochondrial DNA disorders of skeletal muscle, which are characterized by deficient iron-sulphur proteins, abnormal mitochondrial iron accumulation and exercise intolerance [21, 22].

In patients with iron deficiency, any of the biological processes described above may be adversely impacted, resulting in physiological deficits. Indeed, the fact that iron is involved in so many fundamental physiological processes beyond its role in haemoglobin has led to the hypothesis that correction of iron deficiency in the absence of anaemia may have clinical benefit. Here, we review a number of studies of IV iron in iron-deficient, non-anaemic, otherwise healthy subjects, as well as some recent clinical trials that demonstrate the benefits of treating iron deficiency in the absence of anaemia in patients with HF; the possible implications for CKD patients are also discussed.

IV iron in iron-deficient, non-anaemic, otherwise healthy subjects

Several clinical studies have investigated the impact of IV iron therapy in otherwise healthy subjects with only marginal iron deficiency. One small trial found that iron supplementation in marginally iron-depleted women resulted in improved adaptation to aerobic training [23]. A follow-up study of the same cohort revealed that endurance capacity was likewise improved by iron supplementation [24]. More recently, the randomized placebo-controlled PREFER study examined the impact of iron supplementation in iron-deficient women with symptomatic, unexplained fatigue. This study found that a single dose of ferric carboxymaltose (FCM) rapidly reduced fatigue and improved cognitive function scores [25]. Together, the results of these trials suggest that fatigue and limited exercise capacity are key symptoms of iron deficiency in the absence of anaemia and that iron supplementation in this context may have significant benefits.

Iron therapy in patients with HF

Much recent research has focused on the impact of iron deficiency in patients with chronic diseases such as HF, because these patients are much more likely to experience iron deficiency than the general population. HF is a global problem, affecting ~26 million people worldwide [26]. Among patients with HF, the prevalence of iron deficiency is estimated to be between 30% and 80%, depending on the duration and severity of HF [27, 28]. Anaemia is also a significant problem in this population, as ~40% of the patients in the European Society for Cardiology registry are anaemic [29]. There is now considerable evidence that in patients with HF, iron deficiency is independently associated with impaired exercise capacity, reduced quality of life and increased morbidity and mortality [30–34]. For example, one study found that non-anaemic HF patients with iron deficiency had a 2-fold higher risk of death than anaemic, iron-replete patients [31]. Thus, significant attention has been focused upon the use of iron supplementation as a means to improve outcomes in patients with HF, even in the absence of overt anaemia.

Two major options exist for the delivery of iron therapy: oral and IV. A more detailed discussion of the factors that may lead a clinician to favour one approach over the other in patients with CKD is presented in the accompanying article by Simon Roger [35]. Among patients with HF, evidence for the efficacy of oral iron is mixed. One study found that oral iron had little effect on haemoglobin levels, iron parameters or cardiac parameters [36]. However, another trial that compared 30 HF patients who received oral iron with 30 who did not found that scores for haemoglobin and red blood cell parameters improved in the

oral iron group [37]. Scores for quality of life, dyspnoea and fatigue improved in both groups, although the improvement was more pronounced in the oral iron group. Another controlled study found that oral and IV iron treatments resulted in similar increases in haemoglobin, but that peak oxygen utilization (VO_2) increased only in the IV iron group [38]. This study, which enrolled only 18 patients, may have been underpowered. A retrospective study of 105 patients with HF and systolic dysfunction found that oral iron supplementation improved iron stores and anaemia to a similar degree as had been previously reported with IV iron therapy, suggesting that oral iron therapy may have some utility in this population [39]. Ultimately the results of adequately powered prospective trials such as the ongoing IRONOUT HF [40] trial are required to provide more complete information as to the efficacy of oral iron in patients with HF. Compared with oral iron, the use of IV iron therapy in patients with HF has been more thoroughly investigated. To better understand the impact of iron supplementation in anaemic and non-anaemic patients with HF, Okonko *et al.* [41] conducted the Ferric Iron Sucrose in Heart Failure (FERRIC-HF) trial. This relatively small, short-term trial used a randomized, placebo-controlled design to examine the impact of IV iron sucrose therapy in patients with HF and iron deficiency with or without anaemia. The study showed statistically and clinically significant improvements from baseline in peak oxygen consumption (pVO_2 ; its primary endpoint), as well as treadmill exercise duration, New York Heart Association (NYHA) functional class and Patient Global Assessment (PGA).

Following on these promising results, a larger and longer clinical trial, the Ferinject Assessment IRon deficiency and chronic Heart Failure (FAIR-HF), was conducted to determine whether IV FCM for iron deficiency could improve symptoms of chronic HF, quality of life and exercise capacity in non-anaemic patients [42, 43]. A total of 459 patients with NYHA functional class II or III who were iron deficient with and without anaemia were enrolled and randomized to receive intravenously administered FCM or placebo. The primary endpoints were the self-reported PGA and NYHA functional class at the end of the study. Among those randomized to receive FCM, significantly more patients reported improvement according to the PGA, or improved one NYHA functional class, as compared with placebo. Patients receiving FCM also demonstrated a significant improvement in the 6-minute walk test (6MWT), indicating that iron treatment was associated with a statistically and clinically significant improvement in exercise tolerance. This effect could be observed as little as 4 weeks after treatment initiation, with no significant change in haemoglobin. Together, these results demonstrated that FCM treatment of patients with HF and iron deficiency resulted in significant improvement in disease symptoms and quality of life.

Subanalyses of the FAIR-HF data set have enabled a more nuanced understanding of the trial's results, particularly with regard to the role of anaemia correction. A subanalysis of the FAIR-HF data set revealed that the primary outcomes of the FAIR-HF trial were similar among patients who were anaemic at baseline compared with those who were not [44]. This finding was subsequently extended to health-related quality of life (HRQOL), as measured using the European Quality of Life 5-Dimensions questionnaire and the Kansas City Cardiomyopathy Questionnaire (KCCQ) [45]. Importantly, iron treatment improved HRQOL independent of the presence of anaemia. Because FCM was equally efficacious and had a similar safety profile in patients with and without anaemia, it has been suggested that iron status should be assessed in all

symptomatic HF patients and that iron supplementation should be considered in all patients with iron deficiency irrespective of anaemia status [44].

The improvements in HF patients' symptoms and HRQOL resulting from correction of iron deficiency may have an additional benefit: reduced treatment costs in these patients [46]. Based on the results of the FAIR-HF study, publically available sources and published literature on HF patients, Gutzwiller *et al.* [47] conducted a model-based cost-effectiveness analysis to compare FCM treatment versus no iron treatment. Per-patient costs and clinical effectiveness of FCM were estimated compared with placebo and cost assessment was based on study drug and administration costs, cost of HF treatment and hospital length of stay. The incremental cost-effectiveness ratio of FCM use was expressed as cost per quality-adjusted life year (QALY) gained in HF. Mean QALYs were higher in patients treated with FCM {difference 0.037 QALYs [bootstrap-based 95% confidence interval (CI) 0.017–0.060]}. The incremental cost-effectiveness ratio of the FCM group compared with the placebo group was €4414 per QALY gained from the iron dosing used in the FAIR-HF study. Sensitivity analyses confirmed the base case result.

The recently completed CONFIRM-HF trial (ClinicalTrials.org, NCT01453608), which was designed to evaluate the benefits and safety of long-term IV iron therapy in iron-deficient patients with HF [47], has largely replicated the findings of the FAIR-HF study. This study enrolled 304 ambulatory symptomatic HF patients with left ventricular ejection fraction $\leq 45\%$, elevated natriuretic peptides and iron deficiency (ferritin < 100 ng/mL or 100 – 300 ng/mL if transferrin saturation $< 20\%$). Patients were randomized in a 1:1 ratio to placebo or FCM. In terms of 6MWT at 24 weeks (the primary outcome), randomization to FCM resulted in a difference of 33 ± 11 m (least squares mean \pm standard error) as compared with placebo. Differences in 6MWT were also detected at weeks 36 and 52 of the trial. FCM treatment also showed significant benefits in terms of the study's secondary endpoints. PGA score and fatigue score were improved from week 12 onwards, while improvement in NYHA class was detected from week 24 onwards. Beneficial effects on quality of life (QoL), as assessed using the overall KCCQ score, were observed at weeks 12, 36 and 52. In addition, treatment with FCM resulted in a considerable reduction in HF hospitalization [hazard ratio 0.39 (95% CI 0.19–0.82)]. The number of deaths and the incidence of adverse events did not differ between the groups over a 1-year period. As with the FAIR-HF study, subgroup analysis revealed that these favourable results were detected in patients with and without anaemia, indicating that management of iron deficiency itself is of clinical importance in patients with HF [48].

Taken together, the results of the studies summarized here suggest that iron deficiency itself is a valid therapeutic target, independent of haemoglobin concentration. Indeed, a very recent meta-analysis of these studies found that treatment with FCM reduced the rate of cardiovascular (CV) hospitalizations and cardiovascular mortality among ambulatory patients with systolic HF and iron deficiency (European Society of Cardiology late-breaking abstract), although a randomized controlled trial will be required to confirm these findings. Moreover, the latest European Society of Cardiology guidelines for the diagnosis and treatment of HF recommend that IV FCM should be considered in HF patients with iron deficiency [serum ferritin < 100 ng/mL and transferrin saturation (TSAT) $< 20\%$] in order to alleviate HF symptoms and improve quality of life [49]. Further study of iron metabolism in patients with chronic

illness may yield insights into the mechanism(s) by which iron supplementation creates therapeutic benefits beyond increasing haemoglobin levels.

Impact of iron treatment in patients with CKD

Impaired renal function is a common comorbidity of HF and there is a growing recognition that iron deficiency is a shared characteristic of these diseases [18]. Indeed, in acute HF, elevated serum creatinine levels and reduced kidney function independently predict mortality, and patients with an estimated glomerular filtration rate (eGFR) < 30 mL/min/1.73 m² have the poorest survival rates [50]. However, there is no established evidence-based therapy for HF patients with cardio-renal syndrome [51].

A number of patients participating in the FAIR-HF study (130 in the FCM group and 73 in the control group) suffered from impaired renal function (eGFR < 60 mL/min/1.73 m²). A *post hoc* analysis was performed to determine the effect of iron treatment on kidney function in this population of patients with HF. Compared with the placebo group, patients in the FCM group experienced modest increases in eGFR; this effect was observed in all pre-specified sub-groups [52]. Thus, in these HF patients without anaemia, treatment with IV iron modestly increased kidney function, probably secondary to the improvement in systolic cardiac function. These data are important, as there was concern that treatment with IV iron might have the opposite effect, by promoting oxidative stress and a pro-inflammatory response, leading to renal injury [53]. Data from the FAIR-HF trial is reassuring in the sense that FCM therapy was effective in HF patients with decreased renal function and no renal toxicity was observed. Furthermore, a subgroup analysis of the CONFIRM-HF trial showed that the beneficial effect on functional capacity observed in patients treated with IV iron was slightly more pronounced in patients with CKD (P-interaction = 0.038), which further encourages use of IV iron in these patients [48].

Iron therapy has the potential to benefit iron-deficient patients in numerous ways. However, these benefits should be considered in the context of the potential risks associated with IV iron, including allergic reactions and infection (discussed in greater detail in the accompanying chapters by Berns, Roger and Macdougall). Although high-molecular weight iron dextran products may cause allergic reactions, these have largely been supplanted by alternate formulations that appear to be much less allergenic [36, 54–62]. Iron is an essential cofactor for bacterial growth and thus a connection between IV iron utilization and infection risk has long been hypothesized. Associations between IV iron utilization and infections among CKD patients have been examined in two recent clinical trials, which produced conflicting results: one trial reported a higher incidence of adverse events in patient receiving IV iron versus the control group [63], whereas the other found no such association [35, 64]. The reader is referred to the accompanying chapter by Macdougall for a more detailed analysis of these two trials and their interpretation. At present, no studies have examined infection risk among HF patients treated with IV iron, therefore the generalizability of any findings in CKD patients to other patient populations remains unclear.

Beyond these two types of risks, there has been some suggestion that IV iron administration in CKD patients results in oxidative damage to peripheral blood lymphocyte DNA [65] protein oxidation [66] and lipid peroxidation [67], although the clinical and biological significance of these changes remains unclear [68]. Indeed, one study found that patients who received IV iron displayed transient increases in peroxide concentration during haemodialysis of similar magnitude to those who did not receive iron.

Further studies are needed to clarify whether impaired anti-oxidative defence mechanisms in the uraemic milieu may result in a greater magnitude or longer duration of oxidative stress following iron injection among vulnerable CKD patients as compared with other patient groups. Further, studies directly comparing oral versus IV iron with respect to impacts on oxidative stress, inflammation and endothelial dysfunction in patients with CKD are lacking. While this review has concentrated on comparisons in iron deficiency between anaemic and non-anaemic patients, there are also many non-haematological effects of iron therapy. Given the diversity of biological pathways in which iron participates—it is necessary for the synthesis of molecules including nucleic acids and amino acids [69, 70] and influences circadian pathways [71—it is not surprising that iron therapy has potential benefits beyond the treatment of anaemia. For example, iron plays an important role in the functioning of the central nervous system. It has been shown that in young women, body iron status in the absence of anaemia is positively associated with executive function [72]. Iron therapy has also demonstrated effectiveness in the treatment of restless leg syndrome (RLS) in non-anaemic patients [73, 74], presumably by replenishing the depleted brain iron stores often found in those with RLS [75]. This finding is of particular relevance to the CKD population, given that up to 25% of dialysis patients are affected by this condition [76]. Although the mechanism by which iron deficiency contributes to RLS remains to be worked out, a link to overproduction of dopamine has been suggested [77].

It may now be time to investigate treating patients' iron deficiency in the absence of anaemia, although further specific randomized clinical trials will be required before this is adopted as the standard of care. As was recently highlighted by a Kidney Disease: Improving Global Outcomes working group [19], such a change in the standard of care will also require a greater understanding of both the underlying mechanisms causing iron deficiency in patients with anaemia of chronic disease and the benefits of iron therapy beyond red blood cell management.

Conclusions

Recent studies in patients with HF have shown that iron deficiency is a condition for which IV iron is beneficial, independent of a patient's haemoglobin concentration. In this patient population, iron deficiency is a pathophysiological feature of disease that deserves therapeutic targeting. Perhaps the next critical clinical question will be to understand the effects of iron treatment in iron-deficient, non-anaemic patients with CKD.

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