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LITERATURE REVIEW

Effect of oral iron supplementation on functional capacity in heart failure patients

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Abstract

Introduction: Cardiovascular disease is the leading cause of mortality worldwide. Heart failure (HF) accounts for 13.4% of deaths and reduces the quality of life of patients. Iron-deficiency is a common condition found in heart failure patients, often occurs due to decrease in iron intake, absorption, and chronic inflammation. Oral iron supplementation is a low-cost and easy alternative for iron-deficiency management in heart failure patients.
Method: Literature search was conducted using advanced searching in three large databases: PubMed, Cochrane Library, and Google Scholar. MeSH terms, advanced search and eligibility criteria were used for title and abstract screening after removing duplicates. Critical assessment tools and levels of evidence of the final articles are based on the Oxford Center for Evidence-Based Medicine.
Results: Two systematic reviews and meta-analyses and two RCTs met the PICO and eligibility criteria that had been set. Two systematic reviews and meta-analyses found that oral iron supplementation did not improve the functional capacity of heart failure patients, while the two RCTs found an improvement in functional capacity in heart failure patients who received oral iron supplementation.
Conclusion: Based on critical reviews that have been carried out, currently we do not recommend oral iron supplementation in heart failure patients. Further research may potentially provide different recommendations as oral iron therapy evolves.

Keywords: iron , supplement, iron deficiency, iron deficiency anemia, heart failure

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Case Scenario

Mr. AF, 38 years old, has been treated with a diagnosis of heart failure reduced ejection fraction (HFrEF) for the past 5 years, routinely consuming ramipril 2x5 mg, clopidogrel 1x75 mg, and acetylsalicylic acid 1x80 mg. Patient was admitted to the hospital due to difficulty of breathing and low intake. The patient's clinical condition has worsened, making it difficult for him to walk for the past month. During hospitalization, patient underwent laboratory examination and was found to have anemia (Hb 10.8 g/dL), hyponatremia (123 mEq/L), hyperkalemia (5,9 mEq/L), hypoalbuminemia (2,6 g/dL), low serum iron (30,2 mcg/dL), low ferritin (21 ng/mL) and low transferrin (15%). The patient was referred by a cardiologist to a clinical nutrition specialist to provide nutrition therapy and education appropriate for the patient's condition and to inquire whether oral iron supplementation can help improve the patient's functional capacity. When examined by clinical nutrition specialist, patient was bedridden and still experiencing shortness of breath.

Introduction

Cardiovascular disease is the leading cause of mortality in the world. According to data from the World Health Organization in 2019, 17.9 million people worldwide died from cardiovascular disease, equivalent to 32% of all global deaths.[1] Over 75% of these deaths occurred in low- and middle-income countries. In Indonesia, based on data from basic health research in 2018, the prevalence of heart disease is 1.5%.[2] Patients with heart failure often experience iron- deficiency with or without anemia caused by a decrease in serum iron in the body or inadequate iron production to meet the needs of target tissues due to sequestration. The prevalence of anemia in patients with heart failure is estimated to reach 50% in hospitalized patients.[3] The etiology of iron deficiency in heart failure can be classified into three, namely: decreased in iron intake, decreased iron absorption or increased iron loss.[4] Elevated chronic proinflammatory factors, intestinal oedema, and anorexia are some of the factors that can underlie the occurrence of anemia in heart failure.

Iron deficiency anemia can independently increase mortality in heart failure patients by up to two-fold. Decrease oxygen delivery can also affects hemodynamic and neurohormonal conditions, and can exacerbate the already existing heart failure.[3] Iron is known as a nutrient source for pathogens, therefore iron supplementation is generally delayed until infection is treated. Common side effects of oral iron supplementation include gastrointestinal symptoms such as constipation, nausea, and abdominal pain.[5] Testing is often performed to determine the level of iron in the body that includes serum iron, ferritin, transferrin, and total iron-binding capacity (TIBC) tests.[6]

Iron supplementation in heart failure patients with iron deficiency is thought to improve functional capacity. Meta-analysis by Sindone, et al.,[7] found align results with the recommendation fromEuropean Society of Cardiology's guideline in 2021 which found that intravenous iron improve functional capacity in patient with heart failure. On the contrary, controversial results were found for oral iron supplements in heart failure patients. Research by Zhou, et al.[8] found that oral iron supplementation did not improve functional capacity, but another study by Suryani, et al.[9] found that oral iron supplementation improved the results of the 6-minute walk test (6MWT) in patients with heart failure.

Clinical question

P : Heart failure patients
I : Oral iron supplement
C : Placebo or intravenous
O : Functional capacity

Clinical question: could oral iron supplementation improve functional capacity in patients with iron deficiency and heart failure?

Method

Literature search was performed using combination of MeSH terms and Title/Abstract onthree large databases: Pubmed, Cochrane Library and advanced search on Google Scholar. Search was carried out on 16th January 2023.

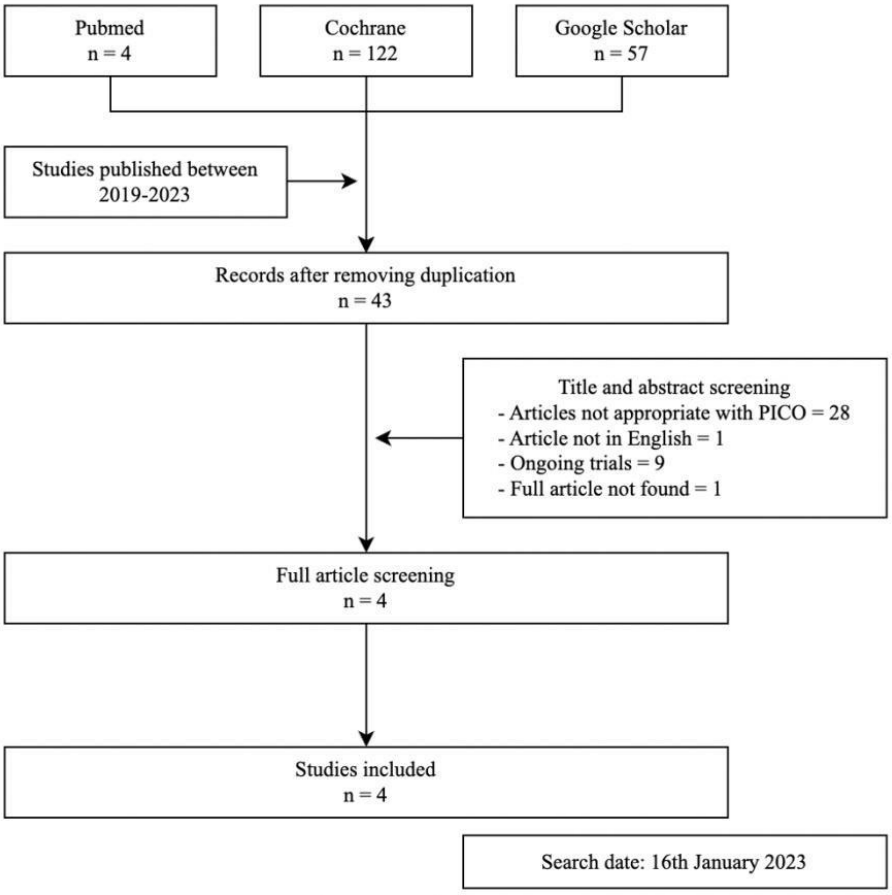

Figure 1 Prisma's flow chart

Table 1 Resources and search strategy

Database	Terminology	Hits	Eligible
PubMed	((oral iron supplement) AND (heart failure)) AND (functional capacity)	2	1
Cochrane	#1 MeSH descriptor: [Iron] explode all trees #2 (iron):ti,ab,kw (Word variations have been searched) #3 MeSH descriptor: [Heart Failure] explode all trees #4 (heart failure):ti,ab,kw (Word variations have been searched) #5 MeSH descriptor: [Administration, Oral] explode all trees #6 (oral):ti,ab,kw (Word variations have been searched) #7 #1 OR #2 #8 #3 OR #4 #9 #6 AND #7 AND #8	122	2
Google Scholar	allintitle: oral iron heart failure	57	1

Results

The authors found four articles in the Pubmed database, 122 articles in the Cochrane Library, and 57 articles in Google Scholar. Duplicate removal was performed using Excel **Table 1**). The articles were assessed for eligibility based on PICO and eligibility criteria (**Figure 1**), resulting in the selection of four articles. The study characteristics of these articles were listed in **Table 2**. The level of evidence for these articles is presented in **Table 3**, and all the articles were found to be relevant for answering the clinical question (**Table 4**).

Discussion

Iron deficiency with or without anemia are co-morbidities that are often found in patients with heart failure and can reduce functional capacity, quality of life, increase hospitalization rates and mortality. Iron in the body, functions as a raw material for hemoglobin and myoglobin which have an important role in oxygen transportation. Other than that, iron is also an important cofactor for many enzymes and proteins that play a role in oxidative metabolic processes, immune system and various other processes.[13] Oral iron supplementation is available in various forms, among which are often used are ferrous sulphate (20% elemental iron), ferrous fumarate (33% elemental iron), and ferrous gluconate (12% elemental iron).[13] To increase the absorption of supplementation, it is best to take it at least 30 minutes before eating or two hours before taking drugs. These three preparations can cause gastrointestinal disturbances such as nausea, vomiting, diarrhea, constipation, and epigastric pain.[13] Other complaints that may be found are metallic taste and yellow teeth. Some foods or drugs to avoid when taking iron supplementation are milk, calcium, antacids, caffeine and high fiber. Those foods and drugs can reduce iron absorption in the gastrointestinal tract.[13]

There are two types of iron deficiency, namely absolute iron deficiency and functional iron deficiency. Absolute iron deficiency (AID) is defined as reduced iron stores in the bone marrow, liver and spleen, whereas functional iron deficiency (FID) is characterized by normal or increased total body iron storage but cannot be formed into erythroid precursors.[14] The European Society of Cardiology defines iron deficiency as serumferritin <100 µg/L (AID) or ferritin 100–300 µg/L with transferrin saturation (TSAT) <20% (FID).[4] The etiology of iron deficiency in heart failure canbe classified into three, namely: decreased ironintake, decreased iron absorption or increased ironloss.[4] Decreased iron absorption that causes AID can be influenced by conditions such as intestinal oedema, anorexia, or gastrointestinal bleeding dueto the use of antiplatelets or anticoagulants. Increased iron loss can be caused by chronic inflammation, increases proinflammatory cytokines and hepcidin. Proinflammatory cytokines in heart failure are produced as a result of intestinal oedema, hypoperfusion and tissue hypoxia. Interleukin-1 (IL-1), interleukin-6 (IL-6) and tumor necrosis factor (TNF) alpha inhibit erythropoietin production in the kidney and suppress the proliferation of erythroid progenitor cells in the bone marrow.[4] IL-6 is also involved in increasing the acute phase protein hepcidin in the liver that plays a role in suppressing ferroportin activity. Reduce ferroportin activity cause a decrease in iron absorption in the duodenum and also reduces the release of stored iron from the reticuloendothelial system.[4]

A systematic review and meta-analysis study conducted by Song, et al.,[10] stated that oral iron supplementation did not improve functional capacity in heart failure patients assessed by 6MWT examination (MD=59.6, CI 95%, -17.89 to 137.08, p=0.13). A systematic review and meta-analysis study by Tan, et al.,[11] also yielded similar results (MD=13.92 m, 95% CI: -47.33 to 19.5, p=0.41). The high heterogeneity (I2=92%, p heterogeneity<0.000001 and I2=75%, p heterogeneity<0.02) in both studies indicate that the results of the RCTs included in both systematic review and meta-analyses have very mixed results. Tan, et al.,[11] explained the source of heterogeneity in their study may be due to one study by Jiang, et al,[15] which after eliminated the heterogeneity became low.

Table 2 Study ch aracteristic

No	Author	Study design	Population characteristic	Total participants	Outcome	Key results
1	Song, et al (2022)[10]	*Systematic review* dan Meta-analysis RCT	Patients age 18–75 years old with HF (EF <50, NYHA II-IV), with iron deficiency or anemia (ferritin <100 ng/mL) who wer given oral iron supplementation for 8-26 weeks.	590 (5 study)	Iron status (ferritin dan TSAT), cardiac function and functional capacity (6MWT)	Oral iron supplement did not reduce mortality (RR=0,77, CI 95%, 0,6-1,16, p=0,28), did not improve functional capacity (6MWT, MD 59,6, CI 95%, -17,89 to 137,08, p=0,13), and did not improve iron status significantly (ferritin: MD = 2,70, 95% CI, –2.41 to 7.81, P=0.30; TSAT: MD= 27.42, 95% CI, –4.93 to 59.78, P=0.10)
2	Tan, et al (2022)[11]	*Systematic review* dan Meta-analysis RCT	Patients with HFrEF (EF<50%) and serum ferritin <100 ng/mL or serum ferritin <100-200 ng/mL with TSAT <20%	582 (4 study)	Primary outcome: LVEF, *6-minute walking test* (6MWT), ferritin Secondary outcome: NT-proBNP, haemoglobin, quality of life, safety and adverse events	Oral iron supplementation improve LVEF (MD = 1,52%, CI 95%: 0,69 to 2,36, p=0,0003, I^2 = 0%) and ferritin (MD = 1,64, CI 95%:0,26 to 3,02, p=0,02, I^2=98%), but did not significantly improve 6MWT (MD= 13,92 m, CI 95%: -47,33 sampai 19,5, p=0,41, I^2=90%)
3	Suryani, et al (2022)[9]	RCT, double blind	Patients with HFrEF (EF <45%, NYHA functional class II-III), Hb <13 (men), <12 (women), ferritin <100 ng/mL or ferritin 100-300 ng/ml with transferrin <20% and eGFR >30 ml/menit/1,73 m^2 was given oral supplementation of *ferrous sulphate* (FS) 200 mg three times a day for 12 weeks	54	Functional capacity measured by 6MWT	Oral ferrous sulphate improve functional capacity (6MWT, p<0,001, CI -86,8 sampai -33,2) in HFrEF patients.
4	Zdravkovic, et al (2019)[12]	RCT, open label	Patients with CDHF, ferritin <100 µg/L and TSAT <20% were divided into 2 groups. Group I was given oral supplementation of ferrous fumarate 350 mg (115 mg elemental iron) two times a day and ascorbic acid 500 mg once a day. Group II was given oral supplementation of *ferric hydroxide polymaltose complex* 357 mg (100 mg elemental iron) without ascorbic acid. Supplementation was continued for 6 months.	201	Haemoglobin, hematocryte, RBC, ferritin, TSAT, 6MWT, dan LVEF	Oral supplementation with *ferrous fumarate* and *ferric hydroxide* increase haemoglobin (group I:p<0,001, group II: p<0,001), hematocryte (group I:p<0,001, group II: p<0,001), RBC (group I:p<0,001, group II: p<0,001), 6MWT (group I: p<0,0001 dan group II: p<0,001), ferritin (group I: p<001, group II: p<0,001) and TSAT (group I: p<0,001, group II: p<0,001), but did not improve LVEF (group I: p=0,8, group II: p=0,4) after 6 months of supplementation

NYHA, New York Heart Association; CI, confidence interval; MD, median; LVEF, *left ventricular ejection fraction*; RCT, *randomized controlled trial*; 6MWT, *6 minute walking test*; HFrEF, heart failure reserved ejection fraction; CDHF, chronic decompensated heart failure; RBC, red blood cell; TSAT, transferrin saturation; Hb, hemoglobin.

Table 3 Validity criteria

	Study design	Number of patients	Randomization	Similarity treatment and control	Blinding comparable treatment	Domain	Determinant	Measurement of outcomes	Quality of evidence*	Level of evidence**
Song Z, et al (2022)[10]	+	+	+	+	+	+	+	+	Moderate	1A-
Tan N, *et al,*(2022)[11]	+	+	+	+	+	+	+	+	Moderate to high	1A-
Suryani LD, *et al* (2022)[9]	+	+	+	+	+	+	+	+	Moderate	1B
Zdravkovic SC, et al (2019)[12]	+	+	+	+	-	+	+	+	Low to moderate	1B

* Quality of evidence according to GRADE guidelines, https://www.ncbi.nlm.nih.gov/pubmed/21208779
**Level of evidence according to Oxford Center of Evidence-based Medicine (CEBM), http://www.cebm.net.
+ clearly mentioned in the article; - not done; ? Not stated clearly
- Systematic review and meta-analysis with troublesome heterogeneity

Table 4 Relevance criteria

Article	Similarity Population	Similarity determinant/intervention/indicators	Similarity outcome
Song Z, et al (2022)[10]	+	+	+
Tan N, *et al,*(2022)[11]	+	+	+
Suryani LD, *et al* (2022)[9]	+	+	+
Zdravkovic SC, et al (2019)[12]	+	+	+

The RCT by Suryani, et al.,[9] conducted a study on 54 HFrEF patients (EF <45%, NYHA II-III) by dividing them into two groups. First group comprise of 27 people received ferrous sulphate 200 mg three times daily for 12 weeks, and the remaining 27 people received placebo. The study concluded that there was an improvement in functional capacity as indicated by an improvementin 6MWT (46.23 ± 35 m vs –13.7 ± 46 m, p<0.001,
CI -86.6 to -33.2). In addition, there are also an increase in ferritin levels (207.3 ± 104 ng/ml vs 111.7 ± 81.4 ng/ml, p = 0.001, CI –160 to –41.87) and TSAT (29.5 ± 10.4% vs 20 ± 10.6%, p = 0.008, CI –16.3 to –2.6). The author tried to explain the difference in results with other studies that might be caused by the difference of oral iron supplements used. This RCT was conducted at the Harapan Kita National Heart Center Hospital Jakarta, Indonesia so it has the same population characteristic as the patient in this EBCR.

The study by Zdravcovic, et al,[12] compared supplementation of 350 mg of ferrous fumarate twice daily plus 500 mg of ascorbic acid (group I), with supplementation of 357 mg ferric hydroxide polymaltose complex once a day without ascorbic acid (group II) for six months in 201 patients with CDHF with ferritin <100 g/L and TSAT <20%. The results of the study found that both ferrous fumarate and ferric hydroxide polymaltose complex supplementation improved 6MWT examination in CDHF patients after six months of supplementation. The study also found improvements in ferritin levels (group I: p<001, group II: p<0.001) and TSAT (group I: p<0.001, group II: p<0.001). This study also concluded thatferric supplements were better tolerated than ferrous supplements. Major limitation in this study was the lack of control group (not provided with iron supplement).

Based on the critical review from this literature, both systematic review and meta-analysis yielded consistent findings, while the results of the two RCTs were different. The characteristics of patients included in the four articles were similar to those of the case patient, thus the research findings can be applied to patient in this case as well. If possible, iron status examination should be conduct as a screening in heart failure patients due to high prevalence of iron deficiency and their proven association with functional capacity in heart failure patients.

Conclusion

Oral iron supplement is an alternative therapy for iron deficiency in heart failure patients. Based on critical reviews that have been carried out in two systematic reviews and meta-analyses as well as two RCTs in this evidence-based case report, oral iron supplementation does not improve functional capacity in iron deficiency patients with heart failure. Currently, we do not recommend oral iron supplementation for patient in this case and heart failure patients with decrease iron status in general. However, it has been shown that decrease iron stores can affect functional capacity in heart failurepatients, therefore routine iron status assessment is advisable. Further research may potentially provide different recommendations as oral iron therapy evolves and improved research data quality is available.

Conflict of interest

The authors declare that there is no conflict of interest related to this article.

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