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INVITED REVIEW

# Iron deficiency and pulmonary arterial hypertension

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**Abstract**

The purpose of this review article is to provide a comprehensive review of iron deficiency in the setting of pulmonary arterial hypertension (PAH) and to evaluate the utility of iron supplementation in PAH. Iron deficiency is present in 33%–46% of patients with PAH and has been associated with reduced exercise capacity, compromised oxygen handling, deterioration of right ventricular function, and even mortality. Iron homeostasis and the pathophysiology of PAH are highly intertwined, which has inspired the use of iron supplementation in patients with iron deficiency and PAH. A literature search was performed to identify all available evidence on iron supplementation for PAH. Limited evidence has suggested poor oral bioavailability of oral iron dosed three times a day, but newer formulations such as ferrous maltol may provide better absorption and clinical benefit, especially when dosed less frequently, such as every other day. Intravenous (IV) iron has been shown in observational studies to improve outcomes, but the single randomized control trial in patients without anemia has failed to show benefits in any measure of exercise tolerance. Larger randomized control studies on oral iron with good bioavailability or IV iron in patients with anemia are warranted to explore the potential utility of iron supplementation in patients with PAH.

**KEYWORDS**
anemia, iron deficiency, pulmonary arterial hypertension

## PULMONARY ARTERIAL HYPERTENSION BACKGROUND

Pulmonary hypertension (PH) is defined as an elevated mean pulmonary artery pressure (mPAP) of ≥20 mm Hg at rest, according to the 6th World Symposium on Pulmonary Hypertension.[1] The elevated mPAP can be caused by abnormalities in the precapillary pulmonary arterioles, postcapillary pulmonary veins due to an increased left atrial pressure, or a combination of both (Table 1). To better categorize conditions on the basis of similar presentation, hemodynamic characteristics, and treatment strategies, PH is classified into five clinical groups by the World Health Organization (WHO) (Tables 2 and 3). Pulmonary arterial hypertension (PAH), classified as WHO Group 1 PH, is a type of precapillary PH characterized by an elevated pulmonary vascular resistance (PVR) of ≥3 Wood units and a normal preload measured by pulmonary artery wedge pressure of ≤15 mm Hg (Table 1).[2] PAH is a serious but rare cardiopulmonary disease affecting 15–50 persons per million within the United States and Europe, with a 7-year survival rate of only 49%.[3,4] Elevated PVR can cause increased resistance for the

TABLE 1 Hemodynamic profiles of PH

| Classification | Mean pulmonary artery pressure, mm Hg | Pulmonary arterial wedge pressure, mm Hg | Pulmonary vascular resistance, WU |
|---|---|---|---|
| Isolated precapillary PH | >20 | ≤15 | ≥3 |
| Combined precapillary and postcapillary PH | | >15 | ≥3 |
| Isolated postcapillary | | >15 | <3 |

Abbreviations: PH, pulmonary hypertension; WU, Wood units.

right ventricle (RV), leading to RV hypertrophy and, ultimately, right heart failure.

Several conditions are associated with PAH, including connective tissues (such as scleroderma, systemic lupus erythematous, and mixed connective tissue disease), drug and toxins (methamphetamines, phentermine), certain congenital heart diseases with uncorrected left to right shunt, HIV, schistosomiasis, and cirrhosis with portopulmonary hypertension. Genetics may play a role in PAH as well. Heterozygous bone marrow protein receptor type 2 (BMPR2) mutation plays a role in approximately 75% of familial PAH and up to 25% of those who do not have a family history of PAH.[5] BMPR2 encodes the type 2 receptor for the bone marrow protein that is crucial for vascular cell proliferation.

The pathophysiology of PAH involves an overproduction of vasoconstrictors and downregulation of vasodilators, leading to increased vascular resistance. In addition, the imbalance of these mediators may cause proliferative dysregulation, leading to obstructive pulmonary vasculature remodeling with aberrant intraluminal angiogenesis and an increased tendency of thrombosis.[6] Currently, three mediators have been explored as medical therapy targets, including nitric oxide (NO), prostacyclin, and endothelin-1 (ET-1). NO is a potent vasodilator of the lung arterioles and an inhibitor of platelet activation and vascular smooth muscle cell proliferation. NO levels have been observed to be lower in patients with idiopathic PAH and have also been correlated with more severe disease.[7,8] Another vasodilator, prostacyclin, is an arachidonic acid metabolite that also has platelet inhibition activity. Both prostacyclin synthase and prostacyclin metabolite have been shown to be lower in patients with PAH, highlighting the role of prostacyclin in the pathophysiology of PAH.[9,10] By contrast, ET-1, a potent vasoconstrictor that promotes vascular smooth muscle cell proliferation, is higher in PAH.[11] ET-1 has also been shown to be inversely correlated with pulmonary blood flow and cardiac output.[12]

Current therapies mainly aim to restore the balance by decreasing ET-1 (eg, endothelin receptor antagonists) and increasing NO-mediated vasodilation (eg, soluble guanylate cyclase stimulators and phosphodiesterase 5 inhibitors) as well as prostacyclin analogues and agonists. Other supportive therapy, including diuretics, oxygen, and oral anticoagulants, has been suggested by the 2015 European Society of Cardiology and European Respiratory Society (ESC/ERS) PAH guideline as well.[5] However, these therapies may improve symptoms and slow the progression of the disease, but they do not cure the disease. With an increased understanding of nutrition insufficiency in PAH, some have turned to nutrition supplementations as new approaches to improve patients' quality of life and exercise tolerance, such as iron supplementation.

## IRON DEFICIENCY IN PAH

Iron deficiency is commonly observed in PAH, with an estimated prevalence of 33%–42% of patients with precapillary PH, 43%–45% of patients with idiopathic PAH, and 46% of patients with systemic sclerosis-associated PAH.[13–16] The consequences of iron deficiency in patients with PAH have been reported regardless of the presence of anemia, including reduced exercise capacity measured by 6-min walk distance (6MWD), as well as compromised oxygen handling, including reduced oxygen transport and consumption at skeletal muscle level.[14,17–19] Some studies also found that iron deficiency is associated with an increased mPAP, reduced cardiac index (CI), deterioration of RV function, worse New York Heart Association (NYHA) functional class, and even mortality.[13,16,20] Considering these negative outcomes of iron deficiency and potential benefit of optimizing iron status, current PAH guidelines recommend intravenous (IV) iron supplementation in patients with PAH and iron deficiency or anemia.[5]

Iron is involved in multiple important physiologic processes, including immune surveillance, cellular proliferation, and the mitochondrial respiratory chain.[21] Most important, iron is essential for oxygen transport, by facilitating the production of hemoglobin in erythrocytes and myoglobin in the heart and skeletal muscle.[14] When

TABLE 2 WHO classification of PH

| |
|---|
| **1. PAH** |
| **1.1.** Idiopathic PAH (iPAH) |
| **1.2.** HeriTable PAH |
| **1.3.** Drug and toxin-induced PAH (see Table 3) |
| **1.4.** Associated with |
| 1.4.1. Connective tissue disease |
| 1.4.2. HIV infection |
| 1.4.3. Portal hypertension |
| 1.4.4. Congenital heart diseases |
| 1.4.5. Schistosomiasis |
| **1.5.** PAH long-term responders to calcium channel blockers |
| **1.6.** Pulmonary veno-occlusive disease (PVOD) and or pulmonary capillary hemangiomatosis (PCH) |
| **1.7.** Persistent pulmonary hypertension of the newborn (PPHN) |
| **2. PH due to left heart disease** |
| **2.1.** PH due to heart failure with preserved LVEF |
| **2.2.** PH due to heart failure with reduced LVEF |
| **2.3.** Valvular disease |
| **2.4.** Congenital/acquired cardiovascular conditions leading to postcapillary |
| **3. PH due to lung disease and/or hypoxia** |
| **3.1.** Obstructive lung disease |
| **3.2.** Restrictive lung disease |
| **3.3.** Other lung disease with mixed restrictive/obstructive pattern |
| **3.4.** Hypoxia without lung disease |
| **3.5.** Developmental lung disorders |
| **4. Chronic thromboembolic pulmonary hypertension (CTEPH)** |
| **4.1.** Chronic thromboembolic pulmonary hypertension |
| **4.2.** Other pulmonary artery obstructions |
| **5. PH with unclear multifactorial mechanism** |
| **5.1.** Hematologic disorders |
| **5.2.** Systemic and metabolic disorders |
| **5.3.** Others |
| **5.4.** Complex congenital heart disease |
| **5.5.** Sarcoidosis |

Abbreviations: HIV, human immunodeficiency virus; LVEF, left ventricular ejection fraction; PAH, pulmonary arterial hypertension; WHO, World Health Organization.

iron deficiency occurs, oxygen supply is reduced and erythropoiesis is impaired, resulting in anemia, which is defined as a hemoglobin level <13 g/dl in adult males and <12 g/dl in adult nonpregnant females (Table 4).[22] Anemia has been associated with decreased cardiac function, reduced quality of life, and neurological impairment.[21] Interestingly, when a small group of patients with iron deficiency and PAH were compared according to their anemia status, there was no significant difference in exercise capacity, suggesting that iron deficiency may be an independent factor from anemia that affects functional status in PAH.[14]

Iron homeostasis, anemia, and the pathophysiology of PH are tightly intertwined (Figure 1). Iron absorption is tightly regulated by hepcidin. High concentration of iron in the gastrointestinal (GI) tract induces hepcidin production, which reduces iron absorption and maintains iron homeostasis.[6,13] In patients with PAH, inflammation of the pulmonary vasculature can induce hepcidin expression, causing undesirably impaired iron absorption. Iron, in turn, also has immunomodulatory effects, such as the regulation of T-cell polarization and dendritic cell function.[21] Additionally, iron deficiency mimics a state of hypoxia, which can induce vasoconstriction and pulmonary vasculature remodeling, both of which are central to the pathophysiology of PAH. Hypoxia can also cause an increased production of erythropoietin by the kidney, which in turn increases iron consumption through erythropoiesis. Furthermore, hypoxia can cause inflammation to occur through the release of cytokines and subsequently reduces iron absorption by raising hepcidin levels.[6] Endothelial dysfunction is related to iron as well, because iron affects NO and ET-1 production and modulates endothelial adhesion molecules. Lastly, vascular remodeling has been related to iron deficiency. For example, patients with PAH and BMPR2 deficiency experience a proinflammatory state that promotes vascular remodeling and stimulates hepcidin expression, eventually leading to iron deficiency.[13,14,21]

The definition of iron deficiency varies among clinical trials, involving biomarkers such as ferritin, transferrin saturation (TSAT), soluble transferrin receptor (sTfR), and sTFRF index (sTfR/log ferritin) (Table 5).[13] Chronic disease with prominent inflammation can raise ferritin and lower serum iron levels and TSAT, but it does not influence sTfR.[23] The sTfR index and C-reactive protein level may be the best prognostic biomarker for clinical impairment associated with iron deficiency. A more simplified method that uses sTfR alone as a single marker (>4.5 mg/L for women and >5.0 mg/L for men) also provides good prediction for the association between iron deficiency and clinical outcome.[13] Unfortunately, sTfR is not routinely available outside of research setting. One example of a commonly used definition in practice is serum ferritin <100 mcg/L or serum ferritin 100–299 mcg/L and TSAT <20%.

## ORAL IRON FOR IRON DEFICIENCY IN PAH

Oral iron is an inexpensive, safe, and effective way to replete iron for most patients with uncomplicated and nonemergent cases of iron-deficiency anemia. Compared

**TABLE 3** Risk level of drugs and toxins known to induce pulmonary arterial hypertension

| Definite | Likely | Possible |
|---|---|---|
| • Aminorex<br>• Fenfluramine<br>• Dexfenfluramine<br>• Toxic rapeseed oil<br>• Benfluorex<br>• Selective serotonin reuptake inhibitors (maternal use linked with persistent PH of the newborn) | • Amphetamines<br>• Dasatinib<br>• L-tryptophan<br>• Methamphetamine | • Cocaine<br>• Phenylpropanolamine<br>• St John's wort<br>• Amphetamine-like drugs<br>• Interferon α and β<br>• Some chemotherapeutic agents such as alkylating agents (mitomycin C, cyclophosphamide) |

Abbreviation: PH, pulmonary hypertension.

Adapted from the 2015 European Society of Cardiology/European Respiratory Society guidelines for the diagnosis and treatment of PH by Galiè et al.[5]

**TABLE 4** World Health Organization definition of anemia

| Population | Nonanemia hemoglobin, g/dl | Anemia hemoglobin, g/dl | | |
|---|---|---|---|---|
| | | Mild | Moderate | Severe |
| Children 6–59 months of age | ≥11.0 | 10.0–10.9 | 7.0–9.9 | <7.0 |
| Children 5–11 years of age | ≥11.5 | 11.0–11.4 | 8.0–10.9 | <8.0 |
| Children 12–14 years of age | ≥12.0 | 11.0–11.9 | 8.0–10.9 | <8.0 |
| Nonpregnant women (≥15 years of age) | ≥12.0 | 11.0–11.9 | 8.0–10.9 | <8.0 |
| Pregnant women | ≥11.0 | 10.0–10.9 | 7.0–9.9 | <7.0 |
| Men (≥15 years of age) | ≥13.0 | 11.0–12.9 | 8.0–10.9 | <8.0 |

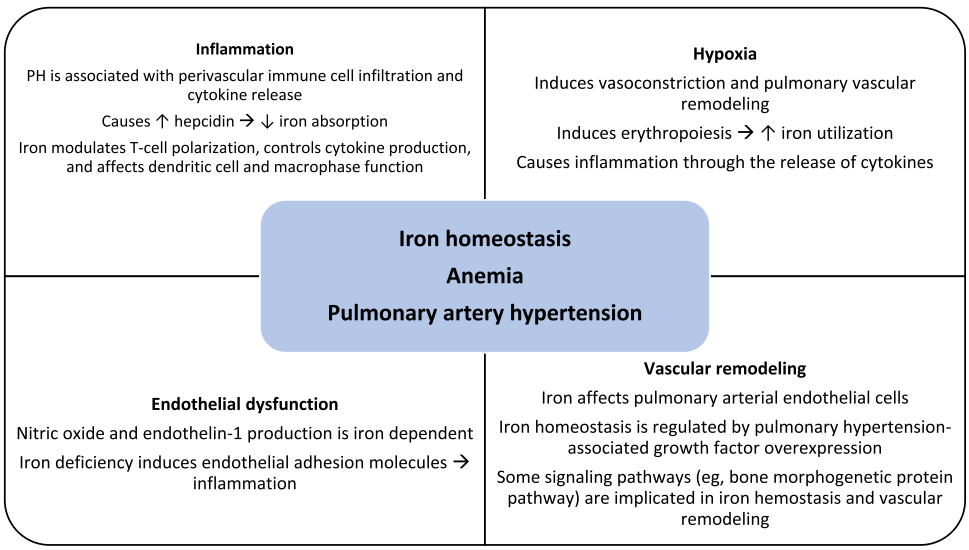


**FIGURE 1** The interplay of iron homeostasis, anemia, and pulmonary arterial hypertension. Adapted from Sonnweber et al.[21]

with IV iron, oral iron is more accessible and convenient, as it eliminates the need for IV access and the potential for infusion reactions or anaphylaxis. There are a few oral iron products available on the US market, with varying percentages of elemental iron (Table 6). GI side effects are the most common adverse events with all types of oral iron, including nausea, black stool, flatulence, constipation, epigastric distress, metallic taste, and vomiting.[24,25] A systemic review with >10,000 patients showed that GI side effects were seen in 32.3% with ferrous sulfate, 47% with ferrous fumarate, and 30.9% with ferrous gluconate. Enteric coating seemed to

**TABLE 5** Examples of various definitions of iron deficiency

| | |
|---|---|
| **ID definition 1** | Serum ferritin <30 mcg/L and TSAT <16% |
| **ID definition 2** | Serum ferritin <100 mcg/L and TSAT <20% |
| **ID definition 3** | Serum ferritin <100 mcg/L or serum ferritin 100–299 mcg/L and TSAT <20% |
| **ID definition 4** | sTfR >4.5 mg/L for women and >5.0 mg/L for men |
| **ID definition 5** | sTFRF index >3.2 if CRP level is <0.5 mg/dl, or sTFRF index >2 if CRP level is >0.5 mg/dl |

Abbreviations: CRP, C-reactive protein; ID, iron deficiency; sTfR, soluble transferrin receptor; sTFRF, soluble transferrin receptor-ferritin; TSAT, transferrin saturation.

improve the GI side effect profile, but it was associated with reduced absorption.[25] Ferrous sulfate was found in another systemic review to have an odds ratio of 3.05 (95% confidence interval, 2.07–4.48) for GI side effects, compared with IV iron. A subgroup analysis in patients with inflammatory bowel disease or pregnancy showed similar findings.[24]

Ruiter and colleagues[14] found oral iron dosed three times daily to be poorly absorbed in patients with PAH (Table 7). In this observational study, oral iron (ferrous fumarate 200 mg three times a day) was given to 21 patients with iron deficiency for 4 weeks. Three patients did not complete the course, owing to constipation and nausea. Of the 18 patients who completed the course, only two patients significantly increased their serum iron levels after 4 weeks. Additionally, 44% of patients did not have notably increased serum ferritin. There were 14 patients who still had TSAT values below normal after treatment. The authors suspected that the small response to oral iron suggested impaired iron uptake, which may be attributed to GI edema, decreased iron release from storage sites or enterocytes due to inflammation, and increased hepcidin levels induced by high levels of interleukin 6. This study, however, was limited by its small sample size, observational nature, and a lack of controls. Iron dosing may also play a role in oral absorption, as recent data suggested less frequent dosing, such as dosing every other day, may induce less interference with hepcidin, improve GI tolerability, and lead to better absorption.[28]

New formulations of iron are also developed to improve absorption. One study investigated the effect of pyrophosphate sucrosomial iron, which is a formulation of ferric pyrophosphate with a phospholipid bilayer and a sucrester matrix with ascorbic acid.[26] This innovative formulation demonstrates higher iron bioavailability and improved GI tolerance. In this study, pyrophosphate sucrosomial iron 30 mg daily was administered in five patients with idiopathic PAH and iron deficiency for 16 weeks. At week 16, the 6MWD was significantly improved (500 [390–500] vs 530 [410–550] m; $P = 0.043$), although the iron status was not significantly changed compared with baseline. The authors concluded that treatment with oral sucrosomial iron was a potential therapeutic option for patients with PAH. This study was extremely limited by its small number of participants who received iron and the lack of statistical analysis that compares the treatment and a matched control group. Moreover, this iron formulation is not available on the Unites States market. Larger prospective randomized control trials are needed to validate the results.

Another iron preparation that is available on the market, called ferric maltol, was evaluated in the Oral Iron Supplementation with Ferric Maltol in Patients with Pulmonary Hypertension (ORION-PH) study.[27] Ferric maltol 30 mg twice a day for 12 weeks was administered in 22 patients with PH and iron deficiency. Included patients had hemoglobin levels of 7–12 g/dl for female patients or 8–13 g/dl for male patients, serum ferritin <100 mcg/L or 100–300 mcg/L, and TSAT <20%. There were 14 patients with PAH, 1 with PH due to left heart disease, and 7 with inoperable chronic thromboembolic PH. All patients were receiving medical treatment for PH. Compared with baseline, patients had significantly improved iron status, including hemoglobin, serum iron, TSAT, and ferritin. There was also significant improvement in 6MWD and N-terminal–pro hormone brain natriuretic peptide (NT-proBNP). Signs of significantly better RV function, manifested as decreased RV dimensions and increased RV fractional area change, were observed. Functional class was improved in five patients and unchanged in the remaining patients. Ferric maltol was found to be well tolerated, with only two patients stopping the trial early because of GI side effects and pneumonia, respectively. Although this was a small, open, and unanonymized trial, the preliminary positive results were encouraging.

**TABLE 6** Oral iron replacement therapy summary

| Iron preparation | Elemental iron (per milligram of mineral salt) | Selected formulation/brand names | Elemental iron per milligram (tablet) or milliliter (liquid) | Dosing | Adverse effects |
|---|---|---|---|---|---|
| Ferrous fumarate | 33% | Ferretts (OTC) 325 mg tablet | 106 mg/325 mg | 29–150 mg of elemental iron (one tablet) once every other day or on MWF | Constipation<br>Darkening of stools<br>Nausea<br>Stomach cramps<br>Vomiting<br>Dental discoloration<br>Diarrhea<br>Heartburn<br>Urine discoloration<br>Flatulence<br>Abdominal distention<br>Abdominal distress |
| | | Ferrimin 150 (OTC) tablet | 150 mg per tablet | | |
| | | Generic: 324 mg tablet | 106 mg/324 mg | | |
| | | Generic: elemental iron 29 mg tablet | 29 mg per tablet | | |
| Ferrous gluconate | 12% | Fergon (OTC) 240 mg tablet | 27 mg/240 mg | 27–38 mg of elemental iron (one tablet) once every other day or on MWF | |
| | | Generic: 240 mg tablet | 27 mg/240 mg | | |
| | | Generic: 256 mg tablet | 28 mg/256 mg | | |
| | | Generic: 324 or 325 mg tablet | 37.5 mg/324 or 325 mg | | |
| Ferric maltol | Contains 30 mg elemental iron complexed with 201.5 mg trimaltol per capsule | ACCRUFeR (prescription) 30 mg capsule | 30 mg | 30 mg of elemental iron twice daily (manufacturer's labeling); some experts prefer 30–60 mg of elemental iron once every other day or on MWF | |
| Ferrous sulfate | 20%–30% | B Protected Pedia Iron (OTC) 75 mg/ml solution | 15 mg/ml | 65 mg of elemental iron (one tablet or equivalent as liquid) once every other day or on MWF | |
| | | Fer-In-Sol (OTC) 75 mg/ml solution | | | |
| | | FeroSul (OTC) 220 mg/5 ml elixir | 8.8 mg/ml | | |
| | | FerrouSul or FeroSul (OTC) 325 mg tablet | 65 mg/325 mg | | |
| | | Slow Fe (OTC) 142 mg ER tablet | 45 mg/142 mg | | |
| | | Slow iron (OTC) 160 mg ER tablet | 50 mg/160 mg | | |
| Polysaccharide–iron complex | Dose strength is indicated as the amount of elemental iron | NovaFerrum (OTC) drops | 15 mg/ml | 50–200 mg of elemental iron (one tablet or equivalent as liquid) once every other day or on MWF | |
| | | Navaferrum 125 (OTC) liquid | 25 mg/ml | | |
| | | Various OTC capsules: EZFE 200, Ferrex 150, Ferric-X 150, iFerex 150, Myferon 150, NovaFerrum 50, Nu-Iron 150, PIC 200, Poly-Iron 150 | The number in the name is the milligrams of elemental iron | | |

Abbreviations: ER, extended release; MWF, Monday, Wednesday, and Friday; OTC, over-the-counter.

**TABLE 7** Summary of studies on oral iron for iron deficiency in PAH

| Study | Definition of iron deficiency | Iron dosing | Patient characteristics | Efficacy | Safety |
|---|---|---|---|---|---|
| Ruiter et al.[14]<br>Open-label observational study | Iron <10 μmol/L AND TSAT <15% (F) or <20% (M) | Ferrous fumarate 200 mg orally three times a day for 4 weeks | $N = 21$<br>All F<br>All with iron deficiency and with or without anemia | 4 weeks before vs after:<br>• Serum iron: ↑ significantly in 2 patients<br>• TSAT: 9% ± 3% vs 12% ± 4%; 14 patients did not reach normal TSAT<br>• Serum ferritin: 12 ± 7 vs 32 ± 20 mcg/L, $P < 0.05$; 8 (44%) patients did not reach normal ferritin level | Three patients did not complete the course because of constipation and nausea. |
| Ghio et al.[26]<br>Open-label observational study | Iron <10 μmol/L AND TSAT <15% (F) or <20% (M) | Pyrophosphate sucrosomial iron 30 mg orally and ascorbic acid 70 mg for 16 weeks | $N = 5$<br>All with iron deficiency and with or without anemia | 16 weeks before vs after:<br>• Serum ferritin: 16 [15–24] vs 22 [20–24] mcg/L ($P = 0.715$)<br>• Hgb: 13.7 [12.8–13.7] vs 13.4 [12.4–13.5] g/dl ($P = 0.686$)<br>• TSAT: 12% [10%–24%] vs 10% [9%–13%] ($P = 0.686$)<br>• 6MWD: 500 [390–500] vs 530 [410–550] m ($P = 0.043$) | N/A |
| Olsson et al.[27]<br>Explorative, open-label, single-center, observational study | Ferritin <100 mcg/L OR Ferritin = 100–300 mcg/L and TSAT <20% | Ferric maltol 30 mg orally twice a day for 12 weeks | $N = 22$<br>All had iron-deficiency anemia (Hgb: 7–12 g/dl [F], 8–13 g/dl [M])<br>Age (median [range]): 57 (49–71) years<br>F: $n = 18$ (82%)<br>PAH: $n = 14$ (64%) | 20 patients completed study<br>12 weeks before vs after:<br>• Serum iron: 5.4 ± 2.0 vs 19.7 ± 11.7 μmol/L$^{-1}$ ($P < 0.001$)<br>• Ferritin: 13.1 ± 6.7 vs 36.6 ± 19.8 mcg/L ($P < 0.001$)<br>• TSAT: 7.5% ± 3.1% vs 31.7% ± 19.6% ($P < 0.001$)<br>• Hgb: 10.7 ± 0.9 vs 13.6 ± 1.3 g/dl ($P < 0.001$)<br>• 6MWD: 331 ± 147 vs 381 ± 131 m ($P = 0.004$)<br>• NT-proBNP: 496 [254–902] vs 298 [160–484] ($P = 0.003$)<br>• Improvement in WHO functional class: $P = 0.091$ | Two patients did not complete 12 weeks of treatment because of side effects.<br>Pneumonia ($n = 1$)<br>Diarrhea ($n = 3$)<br>Cold ($n = 2$) |

*Notes*: Data are presented as mean ± SD, *n* (%), or median [interquartile range], unless otherwise stated.

Abbreviations: F, female; Hgb, hemoglobin; M, male; N/A, not applicable; NT-proBNP, N-terminal–pro hormone brain natriuretic peptide; TSAT, transferrin saturation; WHO, World Health Organization; ↑, increased; 6MWD, 6-min-walk-distance.

## IV IRON FOR IRON DEFICIENCY IN PAH

The utility of IV iron is expanding, as it can circumvent the absorption issue and avoid GI side effects commonly seen with oral iron. At the time of writing this review, there were six formulations of IV iron available (Table 8). IV iron also has some limitations, including the potential to cause allergic or infusion reactions, including urticaria, palpitation, facial flushing, and myalgias, as well as life-threatening anaphylaxis. However, anaphylactic reactions are extremely rare but are more commonly seen with iron dextran.[29] One retrospective study has found that compared with ferric carboxymaltose (FCM), iron dextran carries a 12-fold greater risk of anaphylaxis. Other formulations, such as ferumoxytol, ferric gluconate, and iron sucrose, carry a 5-fold, 2-fold, and 1.5-fold greater risk compared with FCM, respectively.[29]

IV iron is also more expensive than oral iron. Many insurance plans require documentation of treatment failure or intolerance with oral source before authorizing the infusion.[30,31] According to an analysis done by the Health Care Cost Institute in 2017, private health plans paid $4316 per visit for FCM, $3087 for ferumoxytol, $1502 per visit for iron dextran, $825 per visit for iron sucrose, and $412 for sodium ferric gluconate complex.[32]

In the past decade, IV iron supplementation has been shown to improve cardiovascular and functional outcomes in patients with heart failure with or without anemia.[20,33–35] Several heart failure guidelines now recommend iron supplementation in patients with iron deficiency and heart failure to improve functional status, quality of life, and exercise capacity.[33,36] Such promising results have also triggered the investigation of using IV iron in PAH.

Viethen and colleagues explored the therapeutic potential of IV FCM by administering a single infusion of ≤1000 mg in 20 patients with iron deficiency and PAH with or without anemia (Table 9).[37] All patients were assessed at baseline and at 2 months after iron treatment. Compared with baseline, the study found a significant improvement of iron status (serum iron, ferritin, TSAT), anemia status (hemoglobin, mean corpuscular volume), and quality of life as assessed by the SF-36 questionnaire (100-point scale). Moreover, there was also a clinically meaningful and statistically significant improvement in exercise capacity, measured by 6MWD. A subset of eight patients who had cardiopulmonary exercise testing showed an increase in anaerobic threshold ($+100.1 \pm 37.0$ ml/min, $P = 0.03$), which was a marker of oxygen utilization and delivery during exercise. However, peak $VO_2$, an indicator of peak exercise capacity, was increased, albeit insignificantly compared with baseline, indicating the persistent hemodynamic limitation at higher exercise levels inherent to the underlying disease. This study also stratified patients based on their anemia status and RV function. IV iron was beneficial for both patients with anemia (hemoglobin ≥ 12 g/dl, $n = 10$) and patients without anemia (hemoglobin < 12 g/dl, $n = 10$), but patients with anemia seemed to derive more pronounced benefit, with greater improvement in both 6MWD (+35.3 vs +19.7, $P = 0.4$) and quality of life (+9.8 vs +2.7, $P = 0.125$). When stratified by RV function, iron supplementation provided benefit in patients with either preserved or reduced RV function, but there was no significant difference between the two groups. This study was limited by the lack of randomization and long-term follow-up. However, it did demonstrate the promising role of IV iron to safely restore iron status in patients with iron deficiency and PAH, clinically improve exercise capacity, and significantly enhance quality of life. The benefit was seen regardless of anemia or RV function, although a more pronounced effect was seen in patients with anemia.

Another open-label study by Ruiter and colleagues also evaluated the effect of FCM on exercise capacity and explored possible mechanisms underlying the altered exercise capacity.[38] FCM 1000 mg was administered intravenously for a period of 2 h in 15 patients. After a follow-up of 12 weeks, the total body iron store was increased, but the 6MWD did not change significantly. Iron improved submaximal exercise capacity (exercise endurance time, the time to reach anaerobic threshold) but not maximal exercise capacity (maximal workload, peak oxygen uptake). The altered exercise capacity might be due to enhanced oxygen handling in oxidative cells, as both myoglobin concentration and mitochondrial oxidative capacity in biopsied quadricep muscle cells were significantly higher with iron therapy, but RV function was not, as measured by CI and ventricular ejection fraction. The change in RV function, however, might be a long-term outcome that could not be captured by this study because of the short follow-up time. Lastly, the quality of life, as measured by the SF-36 questionnaire, was significantly improved, but it was mainly driven by the improvement in mental instead of physical health. The authors concluded that supplementation of iron intravenously in patients with iron deficiency and idiopathic PAH could improve exercise endurance capacity, which might be explained by increased quadriceps muscle oxygen handling, instead of improved RV function.

The only randomized, double-anonymized, placebo-controlled studies conducted on IV FCM was conducted by Howard and colleagues.[23] They conducted two 12-week crossover studies, in which 39 patients in

**TABLE 8** Intravenous iron replacement therapy summary

| Iron preparation (brand name) | Elemental iron, mg/ml | Maximum single dose in adults | Administration in adults | Adverse effects |
|---|---|---|---|---|
| Ferric carboxymaltose (Injectafer)<br>750 mg/15 ml | 50 | Weight ≥50 kg:<br>• Two-dose regimen: 750 mg once; after ≥7 days, administer another 750 mg (max 1.5 g total)<br>• One-dose regimen: 15 mg/kg as a single dose (max 1 g)<br>• Weight <50 kg:<br>• 15 mg/kg once; after ≥7 days, administer another 15 mg/kg once | Slow intravenous push at 100 mg/min or diluted in normal saline and infused over ≥15 min | Hypophosphatemia<br>Flushing<br>Hypertension<br>Skin rash<br>Vomiting<br>Injection site reaction<br>Nasopharyngitis |
| Ferric derisomaltose (Monoferric)<br>1000 mg/10 ml | 100 | Weight ≥50 kg: 1 g as a single dose or up to three doses of 500 mg administered over 7 days<br>Weight <50 kg: single dose of 20 mg/kg | Intravenous infusion up to 1 g over ≥20 min | Hypophosphatemia<br>Skin rash<br>Nausea |
| Sodium ferric gluconate complex (Ferrlecit)<br>62.5 mg/5 ml | 12.5 | Multiple doses of 125–250 mg | Administer diluted over 1 h or undiluted (slowly) at a rate of up to 12.5 mg/min | Hypertension, hypotension<br>Diarrhea, nausea, vomiting<br>Injection site reaction<br>Dyspnea |
| Iron sucrose (Venofer)<br>20 mg/ml | 20 | Multiple doses of 100–300 mg | Slow intravenous injection of 100–200 mg over 2–5 min or diluted in 100 ml of normal saline over 15 min | Hypertension, hypotension<br>Headache<br>Nasopharyngitis<br>Pruritus<br>Nausea, vomiting, diarrhea, peritonitis<br>Injection site reaction |
| Ferumoxytol (Feraheme)<br>510 mg/17 ml | 30 | Single dose of 1020 mg or two doses of 510 mg, given 3–8 days apart | Diluted in normal saline or 5% dextrose and infused over ≥15 min | Hypertension, hypotension<br>Headache<br>Pruritus<br>Diarrhea, constipation, vomiting<br>Hypersensitivity reaction |
| Iron dextran (InFed)<br>50 mg/ml | 50 | Single dose of 1000 mg (diluted in 250 ml normal saline) given over 1 h or multiple doses of 100 mg | Slow intravenous injection ≤50 mg/min | Cardiac arrhythmia<br>Pruritus, anaphylaxis<br>Abdominal pain, diarrhea<br>Leukocytosis |

**TABLE 9** Summary of studies on intravenous iron for ID in PAH

| Study | ID definition | Iron dosing | Patient characteristics | Efficacy | Safety |
|---|---|---|---|---|---|
| Viethen et al.[37]<br>Open-label, matched-pair pilot study | Iron <10 μmol/L<br>AND<br>Ferritin <150 mcg/L<br>AND<br>TSAT <15%<br>AND<br>CRP <25 mg/L | FCM: 800–1000 mg IV × 1 (NTE 15 mg/kg) | $N = 20$ matched pairs<br>All had ID with or without anemia<br>PAH WHO FC II or III, stable on therapy for ≥12 weeksAge: 61.9 ± 14.0 years<br>F: $n = 12$ (60%)<br>iPAH: $n = 13$ (65%)<br>PAH with CTD: $n = 6$ (30%) | 8 weeks before vs after:<br>• Serum iron: 5.7 ± 0.4 vs 11.1 ± 1.1 μmol/L ($P \leq 0.001$)<br>• Ferritin 29.3 ± 6.3 vs 145.2 ± 25.4 mcg/L ($P \leq 0.001$)<br>• TSAT: 7.5% ± 0.7% vs 19.3% ± 2.3% ($P \leq 0.001$)<br>• Hgb: 12 ± 0.6 g/dl ($P < 0.001$)<br>• MCV: 80 ± 1.8 vs 85.0 ± 1.5 ($P < 0.001$)<br>• 6MWD: 346.5 ± 28.3 vs 374.0 ± 25.5 m ($P = 0.007$); compared with control, net increase is 37.8 m ($P = 0.003$)<br>• QoL[a] : 44.3 ± 3.7 vs 50.6 ± 3.6 ($P = 0.01$) | Well tolerated overall<br>Influenza-like symptoms ($n = 1$)<br>Minor skin discoloration at infusion site ($n = 1$) |
| Ruiter et al.[38] Open-label observational study | Iron <10 μmol/L<br>AND<br>Ferritin <100 mcg/L<br>AND<br>TSAT <15% (F) or <20% (M) | FCM: 1000 mg × 1 | $N = 15$<br>Patients with ID and iPAH with or without anemia<br>Age: 57 ± 13 years<br>F: $n = 14$ (93%)<br>mPAP: 46 ± 15 mm Hg<br>mRAP:7 ± 4 mm Hg<br>CI: 2.9 ± 1.3 L/min/$m^2$ | 12 weeks before vs after:<br>• Serum iron: 9.6 ± 4.8 vs 16.1 ± 6.1 μmol/L ($P < 0.05$)<br>• Ferritin: 44 ± 79 vs 199 ± 225 mcg/L ($P < 0.05$)<br>• TSAT: 13.6% ± 6.7% vs 27.3% ± 13.4% ($P < 0.001$)<br>• Hgb: 13.4 ± 1.7 vs 15.1 ± 1.5 g/dl ($P < 0.001$)<br>• MCV: 82 ± 4 vs 88 ± 3 ($P$ = NS)<br>• 6MWD: 409 ± 110 vs 428 ± 94 m ($P = 0.07$)<br>• Time to reach anaerobic threshold: 75 ± 33 vs 238 ± 43 s ($P < 0.001$)<br>• Exercise endurance time: 269 ± 89 vs 405 ± 210 s ($P < 0.001$)<br>• Maximal $VO_2$, CI at rest, RVEF, LVEF ($P$ = NS)<br>• Myoglobin concentration: 0.3 ± 0.2 vs 0.4 ± 0.1 mM ($P < 0.05$)<br>• Mitochondrial oxidative capacity: 0.06 ± 0.01 vs 0.09 ± 0.02 nmol/$mm^3$/s ($P < 0.05$)<br>• QoL[a] : 47 ± 19 vs 56 ± 19 ($P < 0.05$) | Frontal headache ($n = 2$) |
| Howard et al.[23]<br>Two randomized, double-anonymized, | Iron <10.3 μmol/L<br>OR<br>Ferritin <37 mcg/L | Europe: FCM 1000 mg or 15 mg/ | Europe: $n = 39$<br>Iron-deficient iPAH or heritable PAH | 12 weeks before vs after:<br>• Iron group: | None |

**TABLE 9** (Continued)

| Study | ID definition | Iron dosing | Patient characteristics | Efficacy | Safety |
|---|---|---|---|---|---|
| placebo-controlled crossover studies | OR<br>TSAT <16.4%<br>OR<br>sTfR >28.1 nmol/L | kg if weight < 66.7 kg × 1 | Age: 49 ± 14.5 years<br>F: $n = 29$ (74%)<br>mPAP: 47 (8.5) mm Hg<br>mRAP: 11 (2.8) mm Hg<br>CI: 2.6 (1.2) L/min/m$^2$ | • Serum iron: 12.8 [10.3] vs 16.3 [9.3] μmol/L<br>• Ferritin: 17 [13.0] vs 146 [137.5] mcg/L ($P = 0.0003$)<br>• TSAT: 12.4% [15.3%] vs 24.0% [17.8%]<br>• Hgb: 13.5 [2.8] vs 15.0 [1.5] g/dl<br>• sTfR: 41.7 [22.8] vs 27.4 [17.5] nmol/L ($P < 0.0001$)<br>• Endurance time: 272.0 [187.5] vs 253.0 [211.3] s<br>• 6MWD: 427.0 [65.0] vs 426.5 [71.5] m<br>• PVR: 7.3 [2.4] vs 6.2 [2.7] WU<br>• Placebo group:<br>• Serum iron: 10.9 [8.3] vs 16.2 [5.4] μmol/L<br>• Ferritin: 14 [18.0] vs 134.5 [114.0] mg/L<br>• TSAT: 14.1% [10.4%] vs 24.4% [11.6%]<br>• Hgb: 13.6 [3.6] vs 14.6 [1.6] g/dl<br>• sTfR: 38.2 [16.0] vs 26.3 [8.5] nmol/L ($P < 0.0001$)<br>• Endurance time: 216.0 [163.5] vs 273.0 [125.5] s<br>• 6MWD: 451.0 [107.5] vs 433.0 [119.3] m | |
| | | China cohort: Iron dextran 20 mg/kg | China: $n = 17$<br>Iron-deficient iPAH or heritable PAH<br>Age: 30 ± 11.0 years<br>F: $n = 15$ (88%)<br>mPAP: 49 (16) mm Hg<br>mRAP:7 ± 4 mm Hg<br>CI: 2.7 (0.7) L/min/m$^2$ | 12 weeks before vs after:<br>• Iron group:<br>• Serum iron: 8.5 [6.5] vs 14.0 [7.5] μmol/L<br>• Ferritin: 11 [10] vs 98.0 [86.8] mcg/L ($P = 0.0003$)<br>• TSAT: 11% [8.3%] vs 24.5% [20.8%]<br>• Hgb: 14.4 [2.4] vs 15.4 [2.3] g/dl<br>• 6MWD: 427.5 [102] vs 463.5 [68.8] m<br>• QoL[a] : 6.0 [10] vs 5.0 [7.3]<br>• PVR: 9.1 [3.5] vs 11.1 [4.9]<br>• Placebo group:<br>• Serum iron: 12 [2.8] vs 16.5 [4] μmol/L<br>• Ferritin: 13 [3.3] vs 169.5 [45.5] mg/L<br>• TSAT: 14.5% [4.3%] vs 26.0% [7.8%]<br>• Hgb: 12.9 [1.7] vs 13.4 [1.1] g/dl<br>• 6MWD: 515.5 [75.5] vs 505 [71.5] m | |

(Continues)

**TABLE 9** (Continued)

| Study | ID definition | Iron dosing | Patient characteristics | Efficacy | Safety |
|---|---|---|---|---|---|
| Kramer et al.[39]<br>Retrospective matched-cohort study | Ferritin <100 mcg/L<br>OR<br>Ferritin = 100–300 mcg/L and TSAT <20% | FCM: 500–1000 mg | $N = 117$<br>◦ Patients with ID and who received FCM: $n = 58$ (50%)<br>◦ Patients without ID and who did not receive FCM: $n = 59$ (50%)<br>All patients were receiving stable, targeted PAH therapy for ≥3 months<br>All patients were receiving stable, targeted PAH therapy for ≥3 months | 18 months before vs after:<br>• Iron group:<br>• Serum iron: 7.5 [4.9] vs 10.2 [4] μmol/L ($P < 0.01$)<br>• Ferritin: 21 [17] vs 61 [111] mcg/L ($P < 0.01$)<br>• TSAT: 10% [7%] vs 16% [11.7%] ($P < 0.01$)<br>• Hgb: 12.2 [3.1] vs 13.2 [2.9] g/dl ($P < 0.01$)<br>• 6MWD: 378 ± 16 vs 401 ± 15 m ($P < 0.05$)<br>• WHO FC: 2.6 ± 0.1 vs 2.4 ± 0.1 ($P < 0.05$)<br>• Placebo group:<br>• Serum iron: 14.4 [5.7] vs 14.1 [7.9] μmol/L<br>• Ferritin: 100 [138] vs 80 [156] mg/L<br>• TSAT: 23% [10%] vs 24% [11.5%]<br>• Hgb: 14.1 [2.4] vs 13.6 [2.5] g/dl<br>• 6MWD: 403 ± 13 vs 383 ± 15 m<br>• WHO FC: 2.6 ± 0.1 vs 2.6 ± 0 | Transient influenza-like symptoms occurred in one patient; a temporary, minor skin discoloration at infusion site in one patient |
| | | | Age: 60.9 ± 16.1 years<br>F: $n = 72$ (64.1%)<br>mPAP: 42.4 (13.8) mm Hg<br>mRAP: 8.6 (4.2) mm Hg<br>CI: 2.5 (0.5) L/min/$m^2$ | | |

*Notes*: Data are presented as mean ± standard deviation, *n* (%), or median [interquartile range], unless otherwise stated. Values in parentheses for mPAP, mRAP and CI are standard deviation.

Abbreviations: CI, cardiac index; CRP, C-reactive protein; CTD, connective tissue disease; F, female; FC, functional class; FCM, ferric carboxymaltose; Hgb, hemoglobin; ID, iron deficiency; iPAH, idiopathic PAH; LVEF, left ventricular ejection fraction; M, male; MCV, mean corpuscular volume; mPAP, mean pulmonary arterial pressure; mRAP, mean right atrial pressure; NS, not significant; NTE, not to exceed; PAH, pulmonary arterial hypertension; PVR, pulmonary vascular resistance; QoL, quality of life; RVEF, right ventricular ejection fraction; sTfR, soluble transferrin receptor; TSAT, transferrin saturation; WHO, World Health Organization; 6MWD, 6-min walk distance.

[a]QoL assessed by SF-36 questionnaire (100-point scale).

Europe received FCM 1000 mg (or 15 mg/kg if body weight was <67 kg) or saline, and 17 patients in China received iron dextran (20 mg of iron per kilogram of body weight) or saline. The results showed a well-tolerated side effect profile and an improved iron status. However, there was no effect on any measure of exercise capacity, including cardiopulmonary exercise testing, 6MWD, and cardiopulmonary hemodynamics, as assessed by right heart catheterization, cardiac magnetic resonance, or plasma NT-proBNP at 12 weeks. Notably, however, patients recruited in this trial did not have anemia (hemoglobin median [interquartile range], 13.7 g/dl [2.7 g/dl] in Europe group, 13.0 g/dl [2.9 g/dl] in China group), and most of them were in the less severe function class (classes I and II: 60%); thus, they might be less likely to derive clinical benefit from iron replacement. This study also included patients with heritable PAH, which may not respond as well to iron repletion owing to underlying genetic mutations as the etiology of the disease. In contrast, iron studies in patients with heart failure, which showed benefits of iron supplementation, had a prevalence of anemia in around 50% of participants.[20,40]

Recently, a retrospective matched-cohort study on IV FCM was conducted in 117 patients.[39] The investigators compared 58 patients with iron deficiency receiving FCM to 59 controls who did not receive FCM. In patients with iron deficiency, the use of FCM resulted in a significant and sustained improvement of serum iron, ferritin, and TSAT over 18 months. Fourteen patients in the FCM group had recurrent iron deficiency after a mean of about 10 months, requiring a second dose of FCM. Besides better iron status, FCM administration also significantly improved 6MWD and WHO functional class. There was also a significant reduction of hospitalization for worsening PAH at 12 months compared with baseline in the FCM group. The control group, on the other hand, did not demonstrate any significant improvement in any of the outcomes measured. No serious side effect has been observed with FCM. This study has further strengthened the benefit and safety of iron supplementation with FCM in patients with iron deficiency with or without anemia, although some patients may need additional doses to correct recurrent iron deficiency after the initial dose.

## CONCLUSION

The intertwined underlying pathophysiology of iron and PAH, along with the prevalence of iron deficiency in patients with PAH and the positive results of using IV iron in patients with heart failure, has inspired research into using iron supplementation in patients with PAH. Oral iron supplementation with traditional formulation (eg, ferrous fumarate 200 mg) dosed three times a day showed limited utility due to poor absorption. However, newer oral formulations such as ferrous maltol and pyrophosphate sucrosomial iron, with intrinsically improved bioavailability, have demonstrated possible clinical benefits, including improved exercise capacity measured by 6MWD. Dosing oral iron less frequently, such as every other day, may further improve absorption and reduce GI side effects. The use of IV iron circumvents the absorption issue, but it comes with higher cost and the risk of infusion reactions. IV iron has not consistently demonstrated improved outcomes. Whereas observational trials showed potential improvement in iron status, exercise endurance, and quality of life, the single randomized control trial in patients without anemia did not find any significant improvement in any measure of exercise capacity or cardiopulmonary hemodynamics. Although more trials are needed, preliminary evidence suggests that patients with anemia and PAH may derive clinical benefit from iron supplementation. Currently available studies were limited by small sample size, lack of long-term analysis, and a variable definition of iron deficiency. Larger, more robust, randomized control studies on an easily absorbable oral iron or IV iron in patients with anemia are warranted to explore the potential utility of iron supplementation in patients with PAH.

## CLINICAL PRACTICE IMPLICATIONS

Based on available evidence, the benefit of screening and treating iron deficiency outweighs the risk in patients with anemia and PAH. Iron supplementation can be considered if the patient has anemia (hemoglobin <12 g/dl in women and <13 g/dl in men) and iron deficiency (serum ferritin <100 mcg/L or serum ferritin 100–299 mcg/L and TSAT <20%).[13,22,27] IV iron can be used initially to replete iron store. FCM is the formulation with the most evidence, and it is given conveniently as a one-time dose of 1000 mg infusion. However, it is much more expensive than other formulations such as iron sucrose, which can be dosed as 200 mg daily for 5 days. If an oral agent is chosen, ferric maltol 30 mg twice daily showed efficacy in patients with PAH. An alternative formulation commonly used in the United States is ferrous sulfate, with a dosing regimen of 325 mg every other day demonstrating improved absorption and reduced GI tolerance.[28] The duration of oral iron varies in the literature, but trials with positive results used oral iron for 12–16 weeks as opposed to 4 weeks in trials

showing negative results.[14,26,27] In summary, clinicians may consider using IV iron such as FCM 1000 mg for one dose in patients with anemia and iron deficiency followed by ferrous sulfate 325 mg every other day for 16 weeks in patients with PAH.

## AUTHOR CONTRIBUTIONS

Michelle Lan, Sheryl Wu, and Timothy M. Fernandes equally contributed to the conception and design of the review. All authors drafted the manuscript, critically revised the manuscript, agree to be fully accountable for ensuring the integrity and accuracy of the work, and read and approved the final manuscript.

## CONFLICT OF INTEREST

The authors declare no conflict of interest.

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