Review

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Mechanisms Underlying Iron Deficiency-Induced Cardiac Disorders: Implications for Treatment

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Two billion people worldwide suffer from anemia, which can lead to the onset of cardiac disorders; nevertheless, the precise mechanisms remain unclear. There are at least three distinct mechanisms by which iron deficiency (ID) contributes to the development of cardiac disorders. First, ID increases concentrations of intact fibroblast growth factor-23 (iFGF-23), which promotes left ventricular hypertrophy. Additionally, individuals with ID typically have low circulating levels of vitamin D and an increased body burden of cadmium (Cd). Both factors—high Cd levels and a lack of vitamin D—elevate the risk of various cardiac disorders. Cd is transported in the body via transferrin and as non-transferrin-bound cadmium (NTBCd), with around 50% carried by transferrin. Transferrin-bound Cd is internalized into cells through the transferrin receptor 1 (TfR1), whereas NTBCd uptake occurs via receptors involved in iron transport, such as divalent metal transporter 1 (DMT1), ZIP8, and ZIP14. These receptors, expressed in tissues like the myocardium, contribute to Cd accumulation in the heart. In cases of coronary artery disease, regions of the heart affected by hypoxia, due to reduced blood flow, overexpress TfR1, DMT1, ZIP8, and ZIP14. This increases the uptake of Cd into cardiomyocytes. Cd, once inside the cells, damages mitochondria through oxidative stress, lipid peroxidation, and DNA alterations, leading to cell death. Once destroyed, cardiomyocytes release intracellular potassium which can potentially cause fatal arrhythmia. Cardiac iron bioaccumulation is primarily influenced by two factors: blood iron concentrations and the density of TfR1. Numerous studies have explored the potential benefits of iron supplementation, with varying results. We hypothesize that the extent of beneficial effects from iron supplementation may depend on the presence of specific comorbidities, such as chronic kidney disease or hyperaldosteronism. This hypothesis is based on the observation that certain hormones, including aldosterone and noradrenaline, downregulate the expression of TfR1. Therefore, we propose that co-treatment with iron and aldosterone antagonists could enhance cardiac iron uptake and improve the overall effectiveness of the therapy. Additionally, vitamin D supplementation prior to the onset of disease and chelation therapy after diagnosis could provide some benefits.

Keywords: iFGF-23; iron deficiency; cadmium; vitamin D; transferrin receptor 1; cardiomyocytes

Introduction

Sarnak *et al.* (2002) [1] analyzed the risk of cardiovascular diseases, such as myocardial infarction, coronary artery bypass surgery, and sudden cardiac death, in over 14,000 individuals. Their findings revealed that anemia was associated with these cardiovascular outcomes. Recently, Cirovic *et al.* (2023) [2] speculated that the presence of iron deficiency (ID) could increase the risk of myocarditis in cases of influenza A infection; however, the mechanism by which prolonged ID contributes to the onset and progression of other cardiac diseases, such as heart failure (HF), remains unclear.

The prevalence of ID among individuals with chronic heart failure (CHF) varies between 37.8% and 68%, depending on the study [3–7]. A study involving 1821 individuals with CHF from Poland, Spain, and the Netherlands confirmed the common occurrence of ID in these patients, along with increased long-term mortality compared to those without ID [8].

In a separate cohort study by Klip *et al.* (2013) [9], half of the 1500 individuals with HF were found to have ID. After six months of follow-up, individuals with HF and ID exhibited higher mortality rates compared to non-deficient subjects, a trend that persisted throughout a follow-up period of 2.52 $\pm$ 2.05 years. These studies consistently high-

light the poor long-term outcomes associated with ID in HF patients [8,9]. Additionally, Enjuanes *et al*. (2014) [10] found that individuals with HF and co-existing ID reported a lower quality of life, as measured by the Minnesota Living with Heart Failure questionnaire. Furthermore, results from the DAPA-HF (Dapagliflozin and Prevention of Adverse-Outcomes in Heart Failure) trial demonstrated that individuals with HF and ID face an increased risk of cardiovascular death, worsening HF events, all-cause mortality, and total HF hospitalizations [11].

More recently, Mentz *et al*. (2023) [12] conducted a double-blind, randomized trial involving 3065 patients with HF and reduced ejection fraction. Of these, 1532 received intravenous ferric carboxymaltose, whereas 1533 received a placebo. After 12 months, they found no significant differences in death rates, hospitalizations for HF, or 6-minute walk distances between the ferric carboxymaltose group and the placebo group. In contrast, Avni *et al*. (2012) [13] conducted a systematic review and meta-analysis of the potential benefits of iron supplementation in patients with HF. They noted that although parenteral iron supplementation resulted in fewer hospitalizations and improved quality of life, the mortality rate at the end of the follow-up period was similar between the iron-treated and placebo groups.

Given these findings, the aim of this paper is to analyze the mechanisms by which ID and iron deficiency anemia (IDA) contribute to the development and progression of cardiac disorders, as well as to summarize whether parenteral iron supplementation has yielded desirable results.

Cardiomyocyte Metabolism and Energy Production

Cardiomyocytes are cells that must function continuously throughout life, without interruption. Consequently, a steady production of energy in the form of adenosine triphosphate (ATP) is essential [14]. To meet this demand, cardiomyocytes are rich in mitochondria, and fatty acid β-oxidation serves as the primary energy source. During each cycle of β-oxidation, fatty acids are shortened by one Acetyl-CoA (acetyl coenzyme A) group, which then enters the citric acid cycle. In oxidative phosphorylation, electrons are transported across the inner mitochondrial membrane to generate a proton gradient, ultimately leading to ATP synthesis [14].

Iron-sulfur clusters are critical components of nicotinamide adenine dinucleotide (NADH)-ubiquinone oxidoreductase and succinate dehydrogenase. Iron, along with cytochrome c, cytochrome b, and cytochromes a1-a3, is essential for these clusters to function properly. Therefore, a deficiency in iron reduces electron transport, which hampers ATP production. Moreover, oxygen serves as the final electron acceptor in oxidative phosphorylation, so a lack of either iron or oxygen leads to impaired ATP synthesis [15]. In such cases, anaerobic glycolysis becomes the primary ATP source.

Under normal conditions, iron is transported in the bloodstream bound to transferrin molecules. When transferrin binds to transferrin receptor 1 (TfR1), an endosome forms [14]. The metalloreductase six transmembrane epithelial antigen of prostate 3 (STEAP3) then reduces Fe^{3+} to Fe^{2+}, which is transported into the cytosol by divalent metal transporter 1 (DMT1). Once inside the cytosol, Fe^{2+} is either transported into the mitochondria or stored in ferritin molecules. The density of TfR1 primarily determines the amount of iron that enters cardiomyocytes.

Maintaining proper cellular iron concentrations is crucial, as excess iron is toxic, particularly to cardiomyocytes, and is linked to the development of iron-overload cardiomyopathy, such as dilated cardiomyopathy seen in individuals with hemochromatosis [16]. Conversely, a deficiency in TfR1 leads to early-onset cardiac hypertrophy, a condition caused by ID and associated with mitochondrial dysfunction [17].

The Iron Deficiency–iFGF-23–Myocardial Alterations Axis: A Direct Mechanism of ID-Induced Cardiac Dysfunction

There is some evidence, based on *in vivo* research, linking ID with increased circulating levels of both intact fibroblast growth factor-23 (iFGF-23, the biologically active form) and C-terminal FGF-23 [18–20]. Additionally, two large human studies, one conducted in Poland (involving over 1000 individuals) [21] and another in Sweden (involving 3700 individuals) [22], demonstrated that decreased blood iron levels in elderly populations are associated with elevated circulating concentrations of iFGF-23.

Mirza *et al*. (2009) [23] evaluated the relationship between iFGF-23 and various myocardial morphological parameters using echocardiography in 795 individuals. They found that for every 10% increase in FGF-23, the left ventricular (LV) mass index increased by 0.7%. Moreover, individuals with concentric hypertrophy had significantly higher iFGF-23 levels compared to those without hypertrophy.

In a combined *in vivo* and *in vitro* study, Touchberry *et al*. (2013) [24] demonstrated several FGF-23-induced alterations in cardiomyocytes. They showed that exposure to FGF-23 promoted the expression of proteins such as early growth response 1 (EGR1), β-myosin heavy chain, atrial natriuretic peptide (ANP), skeletal muscle α-actin, and brain natriuretic peptide (BNP), all of which are known markers of cardiac hypertrophy. Additionally, they observed that FGF-23 exposure led to cardiomyocyte enlargement, altered contractility, and increased calcium influx.

Patel *et al*. (2020) [25] investigated whether baseline FGF-23 levels were associated with LV and left atrial morphology as well as function parameters using magnetic resonance imaging at a 10-year follow-up in 2276 individuals. They reported that FGF-23 was linked to higher LV

mass, worse LV global circumferential strain, and worse LV midwall circumferential strain. Functionally, FGF-23 was associated with a lower left atrial total emptying fraction, even after adjusting for covariates. The participants of this study were from the Multi-Ethnic Study of Atherosclerosis (MESA) [25]. In another MESA study, Kestenbaum *et al.* (2014) [26] explored the relationship between FGF-23 and both subclinical as well as clinical cardiovascular disease. They found that elevated FGF-23 levels were associated with an increased prevalence of LV hypertrophy, progressively greater LV mass, and higher prevalence of coronary calcification. Furthermore, they observed that coronary calcification was more extensive in individuals with higher FGF-23 levels, contributing to HF and coronary artery disease (CAD).

Indirect Mechanisms Involved in ID/IDA-Induced Cardiac Disease

There are at least two indirect mechanisms by which ID or IDA can contribute to cardiac disorders. First, individuals with ID are often heavily burdened with cadmium (Cd) [27,28], a cardiotoxic metal [29,30]. The mechanisms involved in increased Cd burden suggest that there is enhanced intestinal absorption of Cd due to the overexpression of intestinal carriers, such as DMT1. This mechanism was described in detail by Cirovic *et al.* (2022) [28]. The Agency for Toxic Substances and Disease Registry reported that, in the case of ID, the intestinal absorption rate of Cd increases by 50% [31]. Second, individuals with IDA commonly have decreased blood levels of vitamin D [32,33].

In a cross-sectional study, de Oliveira *et al.* (2023) [34] included over 240 individuals with and without HF and demonstrated that those with HF had lower vitamin D levels and a higher prevalence of vitamin D deficiency. Scragg *et al.* (2007) [35] showed that lower circulating blood levels of vitamin D were associated with high blood pressure, even after adjusting for body mass index. Ahmad *et al.* (2018) [36] found that individuals with vitamin D deficiency (<20 ng/mL) had the highest prevalence of subclinical myocardial injury, as assessed by 12-lead electrocardiogram (ECG). Additionally, Yılmaz Öztekin *et al.* (2021) [37] reported that vitamin D deficiency was associated with an increased risk of mortality in individuals with HF. Lee *et al.* (2011) [38] found in their multicenter United States study that less than 5% of individuals with myocardial infarction had normal vitamin D serum levels (≥30 ng/mL).

Cadmium-Induced Cardiotoxicity

Cd can disrupt cardiomyocyte differentiation and contribute to congenital heart disease [39]. In some cases, Cd acts as a stronger cardiotoxin than lead (Pb), particularly affecting myosin function [40]. In a study by Chou *et al.* (2023) [41], chronic Cd exposure was simulated in cardiomyocytes over a 12-week period. Mice were divided into three groups: a control group, a low-dose group (100 mg/L Cd chloride [$CdCl_2$]), and a high-dose group (200 mg/L $CdCl_2$). The study found that Cd exposure caused disorganized myofibrils and early necrosis in the left ventricle. Additionally, hematoxylin-eosin staining revealed immune cell infiltration and fibrosis in the interstitial tissue. Cd treatment also increased the expression of matrix metalloproteinase-2 (MMP-2) and MMP-14, markers associated with HF and LV dysfunction [41,42].

Limaye DA and Shaikh ZA (1999) [43] reported that Cd is more toxic to cardiomyocytes compared with hepatocytes. In an *in vitro* study by Chen *et al.* (2015) [44], Sprague-Dawley rat ventricular cardiomyocytes were exposed to $CdCl_2$. The researchers observed elevated levels of endoplasmic reticulum stress markers such as glucose-regulated protein 78 (Grp78), Atf4, and activating transcription factor 6 (Atf6), indicating Cd-induced stress. Moreover, Cd exposure disrupted glycolysis and the tricarboxylic acid (TCA) cycle, reducing ATP production by 30% and promoting apoptosis. Shen *et al.* (2018) [45] used H9 human embryonic stem cells differentiated into cardiomyocytes and noted morphological changes, including cell flattening and the loss of 3D structure after Cd exposure. Cd also reduced heartbeat rates and increased reactive oxygen species (ROS) at a concentration of 30 µmol/L $CdCl_2$. These findings align with previous studies [46–50].

Histological analysis of heart tissue from Cd-treated rats showed hypertrophic cardiomyocytes at lower doses and vacuolation and necrosis at higher doses. Transmission electron microscopy revealed intracellular edema and disorganization of myofibrils at lower doses, whereas higher doses severely altered mitochondrial morphology, leading to a loss of cristae and membrane disruption [47].

In another study, Ghosh *et al.* (2018) [51] treated male albino Wistar rats with $CdCl_2$ via intra-gastric administration (5 mg/kg body weight per day for 30 days). They observed elevated Cd levels in the hearts of treated rats. Histological analysis showed distorted myofibril arrangements and indicated that Cd-induced apoptosis by activating genes like Bcl2-Associated X (Bax) and cleaved caspase-3.

Ali *et al.* [52] treated rabbits (1-month old, weighing 1–1.5 kg) orally with $CdCl_2$ (1.5 µg/g) for 28 days. The experimental group had higher serum levels of troponin T and creatine kinase compared to controls. The toxic effects of Cd on cells are dose-dependent, with higher doses and prolonged exposure leading to necrosis [53,54].

Role of Cadmium Accumulation in Sudden Cardiac Death: the TfR1, DMT1, and Compensatory Mechanism Deficiencies

Saljooghi *et al.* [55] reported that approximately 50% of Cd is transported by transferrin, while the remaining Cd is bound to albumin and citrate. This means that about

50% of Cd is non-transferrin-bound cadmium (NTBCd). Transferrin-bound Cd can be internalized into the cell via TfR1, which is located on the cell surface and binds to the iron-transferrin complex.

For NTBCd, several receptors involved in non-transferrin bound iron (NTBI) uptake may also uptake NTBCd. Among most significant is DMT1, which is expressed in the myocardium and other tissues, and exports iron from endosomes and serves as a major importer of iron into mitochondria [56]. DMT1 exports iron from endosomes and is a major importer of iron into mitochondria [57]. Additionally, ZIP8 and ZIP14, primarily known for zinc transport, also uptake NTBI [58–60]. ZIP8 and ZIP14 are capable of uptaking both Cd and zinc [61–63] and are expressed in cardiomyocytes [64]. In summary, DMT1, ZIP8, and ZIP14 are responsible for the accumulation of NTBCd in the heart.

In cases of severe CAD, an advanced atherosclerotic plaque may be localized along coronary arteries or their main branches. We can roughly divide the myocardium into two regions relative to this stenosis: the region proximal to the stenosis, which has relatively preserved blood flow, and the region distal to the stenosis, which experiences altered blood flow and may cause pain during physical activities. In the hypoxic myocardium distal to the stenosis, cardiomyocytes produce hypoxia-inducible factors (HIFs) [65,66] and promote the overexpression of TfR1 and DMT1, as well as ZIP8 and ZIP14 [67,68]. These receptors facilitate the uptake of transferrin-bound Cd and NTBCd, respectively. Additionally, individuals with ID often have increased blood concentrations of Cd. Consequently, both TfR1-dependent and NTBCd-dependent pathways contribute to the accumulation of Cd in the myocardium distal to the stenosis (Fig. 1).

Once within the cardiomyocytes, DMT1 exports the Cd from the endosome and Cd may then enter the mitochondria by using the same protein (DMT1) [57]. The harmful effects of Cd on mitochondria include inducing oxidative stress, leading to the peroxidation of lipids and other macromolecules, ultimately causing cell death [69,70]. As we discussed, the majority of cardiomyocytes' functions are altered due to Cd presence in a dose-responsive manner. Considering all of these factors, we speculate that DMT1, TfR1, ZIP8, and ZIP14 might be unequally distributed on cardiomyocytes, depending on the level of oxygen.

Compared to nonsmokers, smokers are heavily loaded with Cd [71,72]. Additionally, individuals with chronic obstructive pulmonary disease (COPD) [73], as well as patients with anemia [56] and ID [74,75], and even nonsmokers, may have elevated levels of Cd in their blood. After entering the body, Cd primarily accumulates in tissues such as the kidneys and liver, though smaller amounts also build up in the heart [76]. Cardiomyocytes located in the hypoxic regions of the heart, uptake Cd more efficiently.

It has been suggested that hypoxia draws Cd to the myocardium, where it accumulates, causing mitochondrial damage and exacerbating hypoxia. Cd is already recognized as toxic to mitochondria [70]. As accumulated Cd worsens hypoxia additionally, it induces further expression of DMT1, TfR1, ZIP8, and ZIP14, creating some form of downward spiral or "negative feedback loop" and leading to cardiomyocytes' destruction and death.

We speculate that the poor outcomes in HF patients with coexisting anemia or COPD may be due to a significant Cd burden. Moreover, many cases of sudden cardiac death (SCD) are related to preexisting CAD [77] with a significant number of individuals experiencing SCD or arrhythmic deaths despite having a left ventricular ejection fraction (LVEF) greater than 35% [78].

SCD is a substantial problem in developed countries [77,79], with its incidence in European countries and the USA ranging between 50–100 per 100,000 [79], Goldenberg *et al*. [80] analyzed 3122 individuals with ischemic heart disease (including stable angina) and found that current smoking significantly increases the risk of SCD. A systematic review and meta-analysis suggest that the risk of SCD is threefold higher in current smokers compared to never-smokers, and even former smokers have a slightly elevated risk (relative risk (RR) = 1.38) [81]. Interestingly, COPD also raises the risk of SCD [82,83], likely due to increased Cd load. Thus, all factors that increase Cd load are also risk factors for SCD.

We speculate that Cd accumulation in hypoxic myocardium may damage cardiomyocytes, causing the release of intracellular potassium from damaged cells. High potassium levels could trigger malignant arrhythmias, which have high mortality rates [84]. Therefore, cardiomyocyte damage leading to SCD might not only be caused by hypoxia but also by Cd toxicity. This report highlights potential causes of SCD in individuals with CAD, alongside other factors such as heart defects [85], ventricular arrhythmias [86], non-structural cardiomyopathies [87] or myocarditis [88,89].

Mechanisms Underlying Lack of Improvement in Patients with HF after Iron Supplementation

There are at least two mechanisms that contribute to the improvement of heart function after iron supplementation. Specifically, supplemented iron can enhance heart function both directly and indirectly.

Indirect improvement involves the potentiation of erythropoiesis. In other words, the supplemented iron can be utilized for heme synthesis, leading to an increase in hemoglobin synthesis. Elevated hemoglobin concentrations result in improved oxygenation of all organs, including the myocardium.

On the other hand, cardiomyocytes use iron for myoglobin synthesis, and, more importantly, iron is essential for ATP synthesis. Iron is a crucial component of FeS clusters, which play a vital role in the electron transport within com-

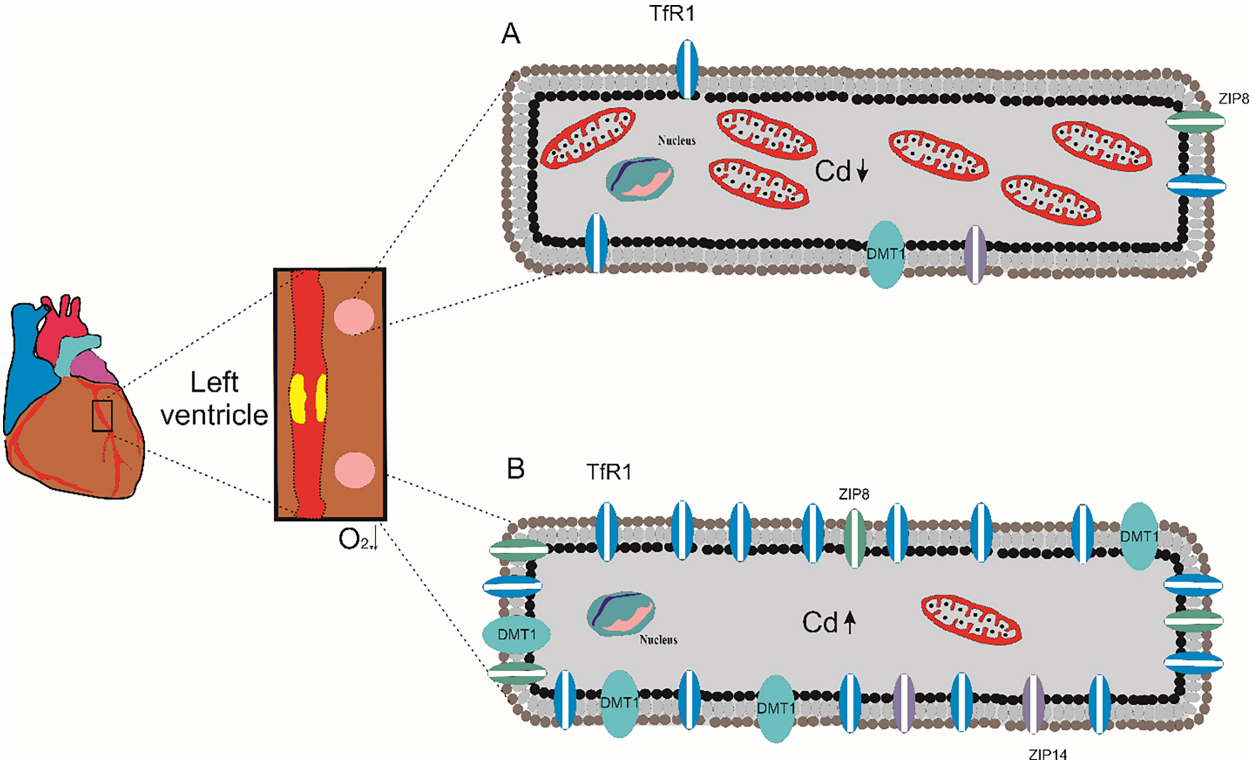

Fig. 1. Schematic representation of mechanisms involved in cadmium (Cd) accumulation in hypoxic myocardium. (A) A normoxic cardiomyocyte is depicted with normal expression levels of transferrin receptor 1 (TfR1), divalent metal transporter 1 (DMT1), ZIP8, and ZIP14. In contrast, (B) when hypoxia occurs, TfR1 (responsible for transferrin-bound Cd uptake), along with DMT1, ZIP8, and ZIP14 (responsible for non-transferrin-bound Cd uptake), become overexpressed, leading to accelerated Cd accumulation in the myocardial region distal to the stenosis. This, in turn, decreases mitochondrial density and promotes cardiomyocyte toxicity. Fig. 1 was created using PowerPoint (PowerPoint for Windows, Microsoft Office Professional Plus 2016, Redmond, WA, USA).

plexes I, III, and IV [90]. To produce ATP, it is necessary to maintain sufficient iron concentrations so that electrons can effectively transport through the inner mitochondrial membrane. Additionally, oxygen serves as the final recipient of electrons, making adequate oxygen levels essential for ATP synthesis. Through iron supplementation, we can enhance ATP synthesis by increasing iron concentrations in cardiomyocytes and by improving oxygen levels.

Two factors determine the extent to which iron can enter cardiomyocytes: the concentration of iron bound to transferrin and the density of TfR1 on the cell's surface. Iron supplementation significantly increases the concentration of iron in the blood, creating an ideal environment for cardiomyocytes to take it up. Using endomyocardial biopsies, Cabrera and colleagues demonstrated that cardiomyocytes upregulate the density of TfR1 in cases of ID [91] (Fig. 2). However, it is also important to minimize the concentrations of factors (hormones) that have the opposite effect, which is to downregulate the density of TfR1 (Fig. 2). It is currently known that hormones like aldosterone and noradrenaline decrease the expression of TfR1 on the surface of cardiomyocytes [92]. A lower estimated glomerular filtration rate is associated with higher blood concentrations of aldosterone [93]. Activation of the renin-angiotensin-aldosterone system is a characteristic of chronic kidney disease (CKD) and is implicated in the development of cardiac fibrosis [94]. Furthermore, chronic sympathoexcitation is a significant contributor to increased cardiovascular risk and mortality in CKD individuals [95]. Therefore, it is reasonable to speculate that elevated blood levels of aldosterone and norepinephrine may interfere with the upregulation of TfR1 induced by ID. This could lead to a decreased uptake of circulating iron by cardiomyocytes, even in individuals with ID. In other words, we can anticipate a better outcome from monotherapy with iron supplementation in individuals with HF without CKD compared to those with both HF and CKD.

Pros and Cons of Iron Supplementation

A meta-analysis revealed that intravenous iron supplementation has several benefits for HF patients with ID, such as reducing overall hospitalization rates and those specifically related to HF [96]. However, intravenous iron supplementation in iron-deficient HF individuals showed no benefits regarding all-cause mortality [96]. Additionally, it is worth noting that although parenteral iron supplementation can induce hypophosphatemic osteomalacia [97], it

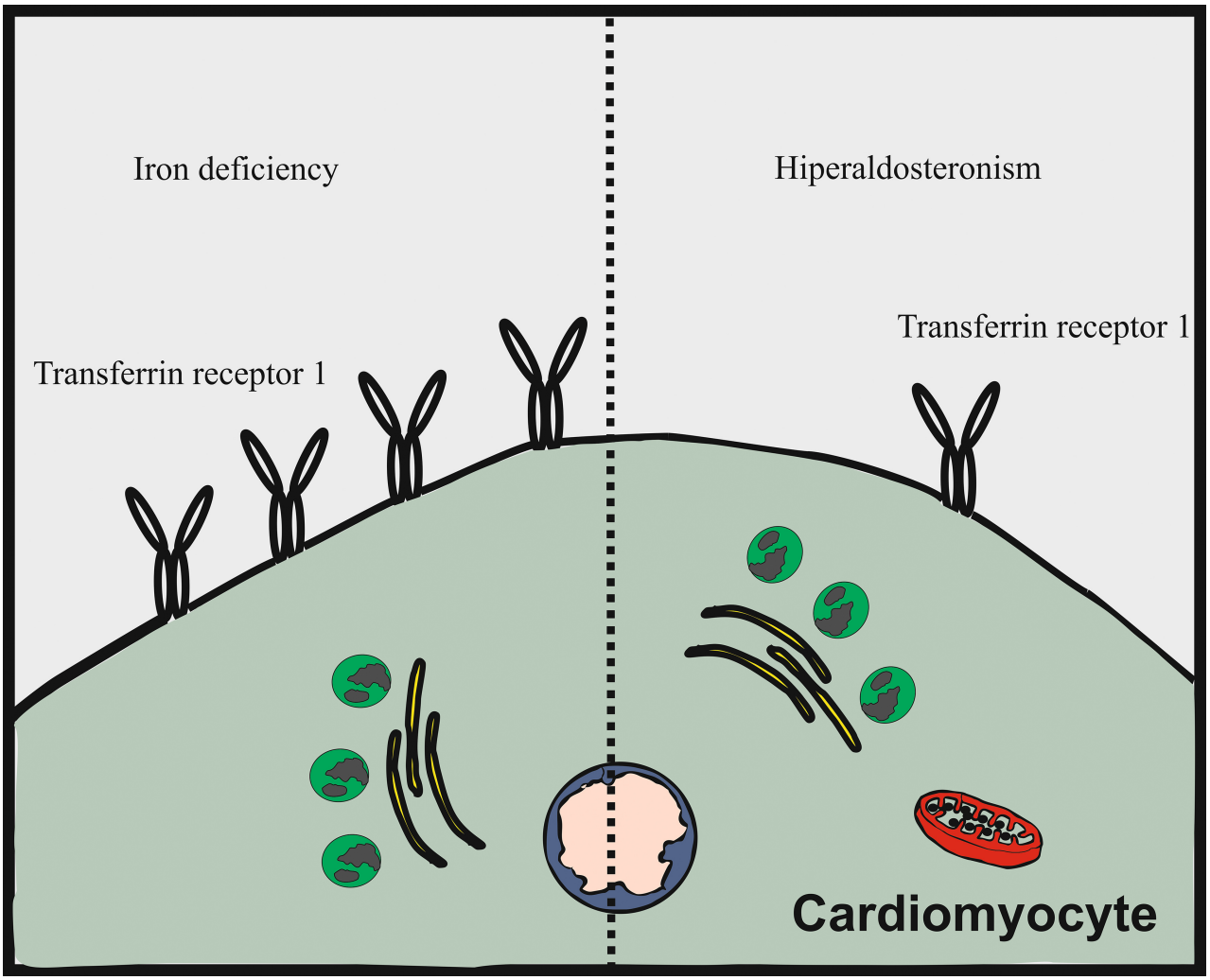

Fig. 2. A schematic approach illustrating how iron deficiency promotes the expression of TfR1 on the left side of the figure, whereas excess aldosterone in the blood downregulates TfR1 expression. Fig. 2 was created using PowerPoint (PowerPoint for Windows, Microsoft Office Professional Plus 2016, Redmond, WA, USA).

has recently been assessed as safe. Nevertheless, parenteral treatment with ferric carboxymaltose may increase levels of FGF-23, and FGF-23 is associated with the development of LV hypertrophy [98,99]. Regarding oral supplementation, the results of the meta-analysis conducted by Tan *et al*. [100] indicate that oral iron supplementation can improve LVEF. Additionally, oral iron therapy has other advantages, such as low cost, which makes it widely used. On the other hand, oral therapy has no significant effects on 6-minute walk distances or quality of life, and sporadic intolerance and mild nausea may occur. Data on the effect of oral iron therapy on HF hospitalization are limited. Both treatment methods increased ferritin and hemoglobin concentrations; however, intravenous therapy had a more pronounced effect on iron availability (assessed by transferrin saturation) [101]. Furthermore, the IRON-HF study revealed an increase in maximal oxygen consumption (peak VO2) in the intravenous therapy group [101].

Thus, a question that naturally arises is whether it is justified to supplement iron in individuals with HF and high blood levels of aldosterone or noradrenalin if parenteral iron may induce adverse effects in the bones and heart, and does not significantly improve cardiovascular outcome.

High levels of aldosterone in the blood may indeed be associated with decreased cellular ATP production in cardiomyocytes due to a disruption in iron uptake. The lack of cellular iron concentrations could potentially trigger the development of interstitial fibrosis, as the deficiency of iron in cells can lead to reduced ATP production, which may serve as a stimulus for myocardial fibrosis. Aldosterone receptor antagonists are known to be highly beneficial for individuals with HF, and we speculate that in individuals with HF and CKD or hyperaldosteronism, co-treatment with aldosterone receptor antagonists and iron may increase iron bioaccumulation in the heart muscle and reduce myocardial fibrosis [102].

There are other factors that can modulate the density of TfR1 on the surface of cardiomyocytes. Sodium-glucose cotransporter 2 (SGLT-2) inhibitors have multiple beneficial effects on iron homeostasis that mitigate ID [103]. SGLT-2 inhibitors can promote erythropoietin (EPO) synthesis and secretion via activation of sirtuin-1 (SIRT-1) [104], which in turn leads to accumulation of hypoxia-inducible factor-2α (HIF-2α) which is responsible for an increased EPO synthesis [105]; SIRT-1 activation has been shown to increase expression of iron carrier DMT1 in the duodenum [106], resulting in increased iron bioavailability. Additionally, a meta-analysis revealed that treatment with SGLT-2 inhibitors is associated with lower interleukin-6 (IL-6), C-reactive protein, tumor necrosis factor-α, and monocyte chemoattractant protein-1 concentrations, indicating that SGLT-2 has anti-inflammatory potential [107]. Serum IL-6 concentrations correlate with serum hepcidin levels, which means that when IL-6 levels are lower the hepcidin concentrations are as well. Since decreased hepcidin concentrations enable iron to enter the bloodstream, this represents an additional mechanism by which SGLT-2 inhibitors increase iron bioavailability [108].

Specifically, SGLT-2 inhibitors promote TfR1 overexpression by generating HIF-2α [109,110]. SGLT-2 inhibitors enhance iron uptake and utilization by peripheral tissues, and this has been primarily demonstrated in the context of hematological examinations, where several authors have shown the beneficial effects of SGLT-2 inhibitors on various hematological parameters. We speculate that SGLT-2 inhibitors could increase the density of TfR1 on the surface of cardiomyocytes [111] and promote iron uptake. Moreover, the beneficial effects of SGLT-2 inhibitors on systemic iron status imply that SGLT-2 inhibitors mitigate systemic mild or moderate inflammation frequently observed in patients with HF [112,113]. Nevertheless, results from the DAPA-HF trial which included 1314 subjects with ID and 1695 persons without ID all having a LVEF $\leq$40% and an elevated N-terminal pro-B-type natriuretic peptide, showed that a group treated with SGLT-2 inhibitor and a placebo group did not differ in any of the primary outcomes such as cardiovascular death, worsening HF event, all-cause mortality, total HF hospitalizations and cardiovascular death [11]. However, individuals included in this study did not receive iron supplementation.

Other Therapy Modalities

As we mentioned earlier, adequate levels of vitamin D could reduce the risk of developing cardiac disorders [114,115]. Therefore, vitamin D supplementation may be beneficial in the prevention of cardiac disorders; however, once the disease has developed, the effects of vitamin D supplementation are limited [116]. It appears essential to introduce vitamin D prior to the onset of the disease. Additionally, chelation therapy can provide benefits for individuals with cardiac disorders, as repeated intravenous ethylenediaminetetraacetic acid (EDTA) has been shown to reduce the risk of cardiovascular events, particularly in individuals with coexisting diabetes, especially when combined with multivitamins and multiminerals [117,118].

Conclusion

There is at least one direct mechanism by which IDA can cause the onset of cardiac disorders, namely the generation of FGF-23. Additionally, increased Cd load and lack of vitamin D contribute to the development of cardiac diseases. The role of intensified Cd accumulation in causing extensive local destruction in hypoxic myocardium should not be overlooked. The highly vulnerable ischemic zones of the myocardium increasingly uptake Cd due to imperfect compensatory mechanisms. Since conditions like hypoxia and ID can induce additional expression of DMT1, TfR1, ZIP8, and ZIP14, ID in all patients with cardiac disorders should be taken seriously and treated vigorously. Chelation therapy could potentially reduce circulating levels of Cd and decrease myocardial uptake.

Excess aldosterone, commonly seen in individuals with HF and CKD, reduces myocardial iron bioaccumulation. Co-treatment with SGLT-2 inhibitors or aldosterone receptor antagonists alongside iron supplementation could yield better outcomes in individuals with HF and CKD. Therefore, we suggest an individualized approach to HF treatment with iron supplementation.

Availability of Data and Materials

Not applicable.

Author Contributions

AlC, AnC, and OEO designed the study. AnC, AS, AI, and DB performed the literature research. AlC, AS, and AI were involved in drafting the manuscript. AlC, OEO, and DB critically revised the paper. All authors contributed significantly to editorial changes of important content. All authors have participated sufficiently in the work and agreed to be accountable for all aspects of the work. All authors gave final approval of the version to be published.

Ethics Approval and Consent to Participate

Not applicable.

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Conflict of Interest

The authors declare no conflict of interest.

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