

Iron Dysregulation in Cardiovascular Tissue: The Role of Chronic Inflammation in Myocardial Iron Metabolism – A Comprehensive Narrative Review

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ABSTRACT

Background: Iron homeostasis plays a significant role in mitochondrial respiration, cellular energy metabolism, and redox state and is a central aspect of myocardial structure and cellular functions. The iron metabolism disturbances are also becoming a component of the pathogenesis of cardiovascular diseases (CVDs) particularly in inflammation, oxidative stress, and cardiomyocyte injury processes. The histological results could be of help, giving morphological data that can be used to connect the dysregulation of iron and structural reorganization of the myocardial tissue.

Purpose: This narrative review aims to understand the mechanisms behind iron dysregulation in cardiovascular tissue with a particular emphasis on the histology and pathophysiology of how chronic inflammatory responses alter cardiac iron metabolism and lead to injury of cardiomyocytes.

Methods: A comprehensive narrative review was used to synthesize the evidence on the findings of published studies on myocardial iron metabolism, inflammatory signaling pathways, and CVD outcomes. Database search and thematic synthesis of clinical, molecular and histological studies were used to identify relevant literature.

Findings: The data indicate that the impairments in iron homeostasis are factors that cause mitochondrial dysfunctions, oxidative stress, and dysfunctional myocardial energetics. The histological examination presents the iron deposition of intracellular compartments, ferritin storage, and iron transport proteins expression of the cardiomyocytes.

Conclusion: One of the primary mechanisms through which inflammation is related to cardiomyocyte damage and CVDs is iron dysregulation. Additional understanding of myocardial iron metabolism will be useful in the development of specific therapeutic interventions that will restore the iron balance and preserve the cardiac muscle.

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1. Introduction

Iron is a vital trace mineral required in various biological processes, including transportation of oxygen, mitochondrial respiration, deoxyribonucleic acid (DNA) production and redox balancing in cells. The iron is particularly crucial in the cardiac tissue as the mitochondrial oxidative phosphorylation of cardiomyocytes allows continuous contraction. Therefore, the cardiac metabolism and structure depend on the appropriate regulation of myocardial iron homeostasis. The impairment of mitochondria may occur as a result of iron deficiency or excessive load, initiating oxidative stress, and eventually leading to the development of cardiovascular diseases (CVDs), including cardiomyopathy, heart failure, and ischemic heart disease [1,2,3,4]. The association between myocardial iron deficiency and impaired cardiac metabolism has been defined in several pioneering studies, and more recent studies have shed light on the underlying molecular pathways that link iron dysregulation with cardiovascular pathology.

There is a complex of proteins which regulates these processes of iron uptake, storage, and export to maintain the systemic and cellular iron balance. This regulatory framework is concentrated on the hepcidin ferroportin (FPN) axis that regulates the distribution of iron in the body [5,6]. Hepcidin is a peptide hormone synthesized in the liver, and it controls the amounts of iron to be released by binding to FPN, the only cellular iron exporter, thus causing its destruction and limiting the amounts of iron released by macrophages and other cells. The dysfunction of this regulatory pathway modulates iron transport in tissues, such as the myocardium, and can cause pathological iron levels or functional iron deficiency in cardiomyocytes [7]. These are transforming into critical aspects of the dysfunction of the myocardium.

In cardiovascular pathology, chronic inflammation has contributed largely to the deregulation of iron in the heart. Pro-inflammatory cytokines, particularly interleukin-6 (IL-6), stimulate the hepatic synthesis of hepcidin and suppress FPN activity, promoting intracellular iron uptake. This inflammation leads to functional iron deficiency despite having sufficient iron in the systemic stores and to the formation of defective mitochondrial metabolism in the cardiomyocytes. Moreover, inflammatory signaling increases oxidative stress and impairs intracellular iron trafficking, which increases myocardial injury. This inflammatory-iron interaction has been demonstrated to be an important part of the pathophysiology of heart failure and other inflammatory cardiovascular disorders in clinical and experimental studies [8,9].

Along with biochemical and molecular alterations, the histological impact of iron dysregulation in the cardiovascular tissue is increasingly considered. Histopathological examination has revealed that the accumulation of iron in the cardiomyocytes may be seen through certain staining systems, such as Perls Prussian blue staining, whereby the stain details iron-filled granules in the fibers of the myocardium. The iron deposits are normally related to the structural abnormalities, which comprise mitochondrial damage, myofibrillar degeneration, and inflammatory cell infiltration. The histological results can therefore provide direct morphological support that there is a relationship between iron

dysregulation and myocardial damage and cardiac remodeling [10]. Microscopic studies have also highlighted the significance of mitochondrial iron accumulation in cardiomyocytes as a pathological feature of CVDs. Electron microscopy has shown that there is deposition of ferritin in the mitochondrial compartments of the myocardial cells, which shows that there are impaired intracellular iron stores and impaired mitochondrial metabolism. Due to the high dependence of cardiomyocytes on mitochondrial Adenosine Triphosphate (ATP) generation, overloading of mitochondrial iron can impair oxidative phosphorylation and increase the production of reactive oxygen species (ROS), leading to cellular damage and myocardial dysfunction [11].

Ferroptosis, a controlled cell death caused by iron-dependent lipid peroxidation is another key pathway linking iron metabolism and myocardial pathology. Ferroptosis has become an important and interesting mediator of heart injury in CVD, including myocardial infarction, reperfusion ischemia, and cardiomyopathy [12,13]. The decrease in mitochondrial size, membrane rupture and augmentation of intracellular iron deposition in ferroptotic cardiomyocytes indicate that these structural adaptations reflect the effect of the oxidative harm of iron on the cardiac tissue. The results suggest that ferroptosis is a significant intersection of iron metabolism, inflammation, and cell death of myocardial cells [14,15].

The interaction between inflammation, iron homeostasis and tissue cell injury triggers a pro-pathological vicious circle of self-maintaining pathways in the cardiovascular tissue. The inflammatory macrophages could also release cytokines and ROS that could facilitate ferroptosis and iron accumulation in cardiomyocytes. On the other hand, oxidative damage that is caused by iron might trigger inflammatory signaling pathways that worsen myocardial damage and structural remodeling. Histologic symptoms of the cardiac tissue are iron deposition, the presence of inflammatory cells, and the presence of myocardial fibrosis [16,17].

Although the mechanisms of altering myocardial iron handling by chronic inflammation are gaining greater recognition, the exact histological and molecular pathways by which they occur are not completely understood. In particular, the cellular distribution of iron in myocardial tissue, iron metabolism in mitochondria, and histopathological aspects of iron-induced damage to cardiomyocytes remain to be clarified. These mechanisms play a key role in comprehending the potential therapeutic targets to remedy the iron homeostasis and remove myocardial damage.

Therefore, the aim of this systematic review article is to critically examine current evidence regarding iron dysregulation in cardiovascular tissue, and in particular, the histological and molecular pathways between chronic inflammation and myocardial iron metabolism. The purpose of this review is to provide an international perspective of the contribution of iron imbalance to myocardial injury and to determine the emerging treatment intervention in iron-induced CVDs by integrating the results of recent experimental, clinical and histopathological studies.

1. Methodology

1.1. Review Design

The current research was conducted in the form of a comprehensive narrative review with the aim of synthesizing the available information on iron dysregulation in cardiovascular tissue with a particular emphasis on the histological and cellular alterations in the myocardial tissue associated with chronic inflammation. In contrast to systematic reviews, which are carried out in terms of rigorously followed rules of quantitative synthesis, a narrative review approach is informed by the possibility of including different types of evidence, including molecular, histological, and clinical studies, to form a more detailed conceptual image of complex biological processes [18,19]. The review is particularly directed at the myocardial iron metabolism, cardiocyte injury, inflammatory signaling pathways and their structural expression in the cardiac tissue.

1.2. Literature Search Strategy

A systematic literature search was performed to identify the availability of relevant peer-reviewed articles that assessed iron metabolism and its pathology in cardiovascular tissue. The databases search (PubMed, Scopus, Web of Science, and Google Scholar) was done in a systematic manner to identify the studies that covered myocardial iron dysregulation, inflammatory regulation of iron metabolism, and CVDs findings. The search strategy included the combination of the following keywords such as iron metabolism, myocardial iron deficiency, cardiac iron homeostasis, hepcidin, FPN, cardiomyocyte metabolism, and inflammation in heart failure. The Boolean operators (AND, OR) were used to refine search results to cover the literature of interest fully. The search was mainly limited to articles in English from the years 2019-2025 and with special attention to the more recent studies performed on the molecular, metabolic and structural impact of iron imbalance on the cardiovascular tissue. Relevant studies were identified by manually screening the reference lists of identified key articles to ensure that the evidence available was captured exhaustively.

1.3. Study Selection

The selection of the studies was made based on the relevance to the purpose of the present review, namely, the contribution to the process of iron dysregulation in the myocardial tissue and its connection with inflammatory processes in CVDs. It focused on the study that compared the myocardial iron deficiency, mitochondrial dysfunction, cardiomyocyte metabolism, and biomarkers, which were the manifestations of the iron imbalance at the tissue level. Clinical and experimental studies on iron metabolism in heart failure, myocardial infarction, and CVDs were all taken into consideration. According to the screening process, 16 large-sized studies were chosen to be thoroughly reviewed because they were relevant to the metabolism of iron in the myocardium and cardiovascular pathology. In these articles, the involvement of myocardial tissue, cohort, biomarker, and imaging studies was involved to conclude on the role of iron metabolism in cardiac dysfunction. The selected literature was used to present complementary evidence on the molecular, cellular, and clinical aspects of iron dysregulation in CVDs.

1.4. Inclusion and Exclusion Criteria

The inclusion of studies was based on their relevance to the objectives of this review, which is related to their contribution to the study of iron metabolism in cardiovascular tissue and its connection to myocardial dysfunction. The inclusion criteria were the studies had to investigate the metabolism of iron in CVDs, investigate myocardial iron deficiency or iron dysregulation, investigate inflammatory mechanisms involved in iron regulation, or investigate molecular, cellular or histological alterations of the cardiac tissue with respect to iron imbalance. Clinical and experimental studies that presented evidence of a correlation between iron metabolism and myocardial dysfunction were considered eligible. Articles were excluded when they studied non-cardiovascular tissues, iron metabolism outside of cardiac physiology or were not related to iron regulation in myocardial tissue. Moreover, non-scientific reports, commentaries, editorials, and abstracts of conferences without primary findings were not considered so that only relevant and scientifically rigorous evidence could be incorporated in this review.

1.5. Data Extraction and Narrative Synthesis

The selected studies gave relevant information, and the information was qualitatively synthesized to develop a coherent picture of the interaction between iron metabolism and cardiovascular pathology. Important features of a study like the study objectives, population or sample features, study methods, biomarkers of iron metabolism and significant discoveries related to myocardial structure and functioning were used to extract data. Evidence synthesis was then performed using a narrative thematic approach, which allowed the inclusion of the findings of clinical trials, molecular investigations and myocardial tissue sample analyses. These results were sorted into thematic groups, which were the iron deficiency of the myocardial and mitochondrial dysfunction, inflammatory control of iron metabolism, tissue biomarkers of iron imbalance and the contribution of iron dysregulation to myocardial infarction and heart failure. The various types of evidence could be incorporated in this narrative synthesis. It offered a broader conceptual explanation of the role of chronic inflammation in the pathogenesis of iron imbalance and myocardial damage in CVDs.

1.6. Conceptual Framework of the Review

The framework of this review aims to develop the connection between chronic inflammation, iron metabolism, and myocardial structural alterations. The conceptual model promotes the idea that inflammatory signaling alters the iron regulation process, particularly the hepcidin-FPN axis, to intracellular iron homeostasis, mitochondrial dysfunction, oxidative stress, and cardiomyocyte damage. The resultant effects of these interrelated processes are structural and functional changes in cardiovascular tissue. The conceptual relationship between chronic inflammation, iron dysregulation, and myocardial injury is illustrated in [Figure 1](#).

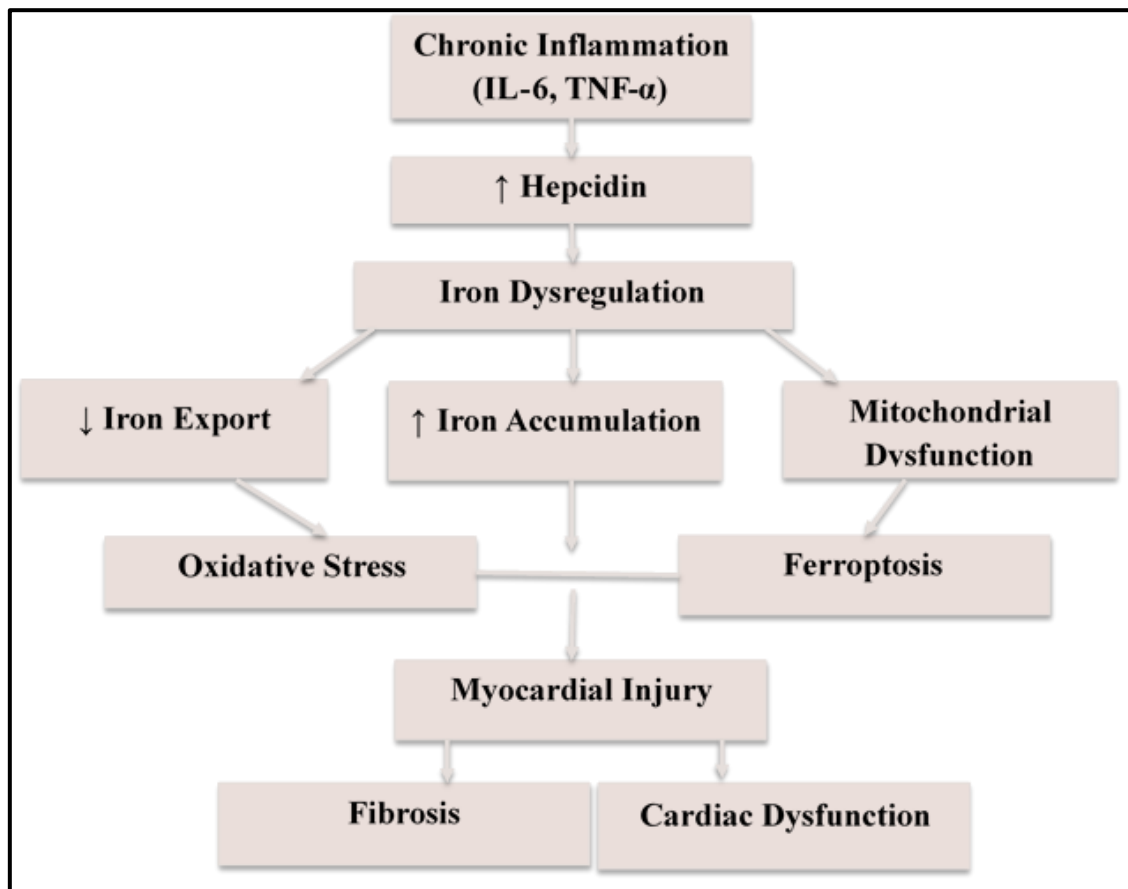


Figure 1. Chronic inflammation–mediated iron dysregulation leading to myocardial injury and cardiac dysfunction

2. Histology of Normal Cardiovascular Tissue and Iron Homeostasis

The myocardium consists of highly specialized cardiomyocytes, which form compact muscular fibers connected by intercalated discs, which allow electrical conduction in synchrony and mechanical contraction coordination. A large number of mitochondria are found in cardiomyocytes due to the perpetual energy requirement necessary to maintain cardiac contractility. On the cellular level, the iron homeostasis of myocardial cells must be strictly controlled since iron plays a crucial role in the mitochondrial oxidative phosphorylation process, the production of heme, as well as the creation of iron-sulfur complexes that are part of the electron transport chain [20,21,22].

The intake of iron in cardiomyocytes occurs mainly through uptake using transferrin receptors and is accumulated intracellularly in ferritin complexes to avoid the development of reactive oxygen species. These mechanisms should be properly controlled to ensure myocardial metabolic activity and structural stability. Myocardial iron balance disruption has been indicated to cause a substantial impact on mitochondrial functioning and cardiac energetics. Historical landmark studies have shown that myocardial iron deficiency in

failing hearts correlates with measurements of impaired mitochondrial enzyme activity and oxidative stress, which have since been confirmed by recent mechanistic studies investigating myocardial iron metabolism [23,24].

The findings of studies of cardiomyocyte gene expression are also additional molecular evidence of the importance of iron metabolism in the myocardial tissue. Iron-deficient patients receiving coronary artery bypass grafting exhibited a much greater expression of transferrin receptor-1 (TfR1) in ventricular tissue. This finding remains highly relevant and has been reinforced by more recent studies investigating myocardial iron regulatory pathways [25].

The changes in cardiac energy production also rely on the changes in myocardial iron metabolism. The researchers showed that in chronic heart failure patients with iron deficiency, reduced phosphocreatine-to-ATP ratios of impaired myocardial energetics, which remains confirmed in recent studies on cardiac mitochondrial metabolism [26].

Additional ultrastructural analyses give histological information on intracellular iron processing of cardiomyocytes. Electron microscopy indicates that ferritin particles are present in the mitochondrial compartments and cytoplasmic structures, indicating intracellular iron storage and control processes. These thick ferritin granules are often concentrated around mitochondrial membranes, indicating that mitochondria can be crucial locations of iron use and storage in heart cells [27]. The localization of ferritin in cardiomyocyte mitochondrial ultrastructure highlights the close relation between the iron metabolism and generation of energy in the myocardial tissue via use of mitochondria (**Figure 2**).

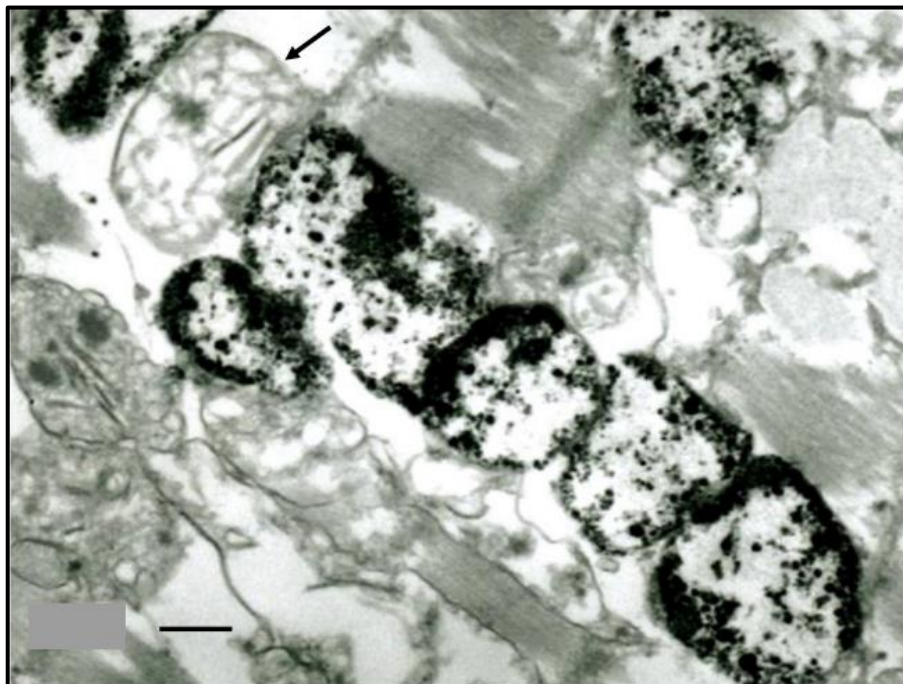


Figure 2. Ultrastructural localization of ferritin within cardiomyocyte mitochondria demonstrates intracellular iron storage mechanisms.

Iron homeostasis in the myocardium is exquisitely controlled under physiological conditions by the interaction of a set of transferrin receptors, ferritin storage proteins, and iron export via FPN. The perturbations of this regulatory network, however, can interfere with mitochondrial respiration and weaken cardiomyocyte's structure. It has been shown in clinical studies that iron deficiency is very common in heart failure patients and closely correlated with systemic inflammation, metabolic dysfunction and unfavourable cardiovascular results [28,29].

3. Cellular Mechanisms of Iron Homeostasis in Cardiac Tissue

The cardiomyocytes have a homeostatic mechanism of iron that is tightly controlled to ensure that iron uptake, cellular iron storage and cellular iron export are controlled. The absorption of iron into the cardiac cells occurs through primarily transferrin receptor-mediated endocytosis into the cells and the surplus intracellular iron is stored as ferritin complexes to prevent oxidative damage. The cellular iron exporter is FPN, which regulates the release of iron by cardiomyocytes and is thus essential in the maintenance of intracellular iron balance [30,31]. The deregulation of these pathways may lead to intracellular iron homeostasis, mitochondrial dysfunction, and a change in the structure of myocardial tissue [32].

Myocardial tissue studies have shown that iron metabolic disturbances have a direct impact on the structure and function of the cardiomyocytes. The study of explanted failing hearts showed that myocardial iron deficiency is linked to reduced levels of mitochondrial enzyme activity, increased oxidative stress, and negative myocardial remodeling [33]. Likewise, molecular investigations of the use of myocardial biopsies of patients undergoing coronary artery bypass grafting, showed that TfR1 was significantly upregulated in the iron-depleted ventricular tissue, indicating that iron uptake pathways were adaptively upregulated in response to intracellular iron depletion [34]. These results indicate that iron regulation is considered a major aspect of ensuring the cardiomyocyte metabolic stability.

Myocardial iron metabolism also interferes with cardiac energy production. Papalia et al. (2022) revealed that patients with chronic heart failure and iron deficiency have highly decreased phosphocreatine-to-ATP ratios by using phosphorus magnetic resonance spectroscopy, which indicates impaired myocardial energetics and mitochondrial dysfunction [35]. These metabolic alterations also confirm the idea that iron supply plays a critical role in the maintenance of mitochondrial oxidative phosphorylation and cardiomyocyte energy metabolism.

At the histological level, impairments in iron export pathways may cause abnormal accumulation of intracellular iron in myocardial fibers. Local iron deposition has been linked to reduced FPN expression in the necrotic cardiomyocytes, indicating that iron

efflux may be impaired during myocardial injury. The histological analysis shows thick intracellular iron deposits, as well as degeneration of myocardial fibers, showing how iron transport defects lead to cardiomyocyte damage (**Figure 3**).

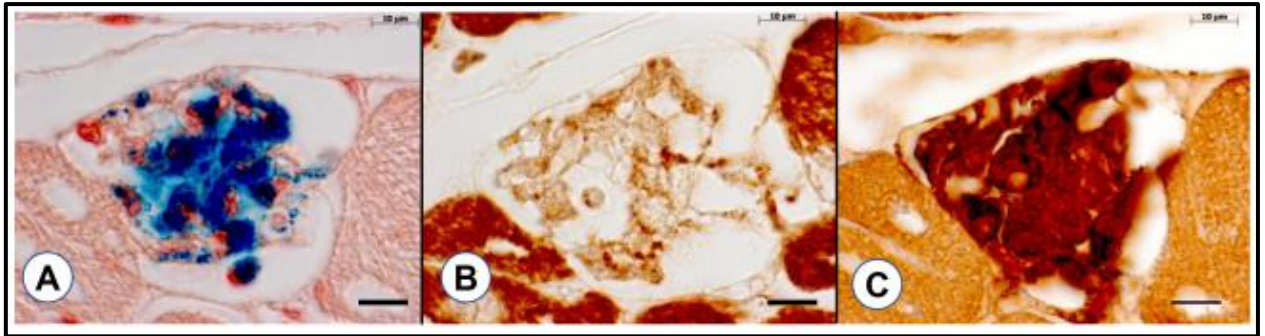


Figure 3. Iron deposition and reduced FPN expression in necrotic myocardial fibers indicating impaired cellular iron export

Thus, Downregulation of FPN is a significant pathway that links iron mis-regulation to myocardial remodeling.

Besides cellular iron transport processes, systemic inflammatory signaling has an effect on myocardial iron metabolism. The clinical cohort studies have reported a good relationship between iron deficiency, inflammatory activation and deterioration of heart failure outcomes. For example, BIOSTAT-CHF cohort studies have indicated that iron deficiency is often accompanied by inflammatory biomarkers and unfavourable clinical outcomes in heart failure patients [36]. Moreover, high concentrations of inflammatory cytokines like IL-6 are associated with worse cardiac performance and heightened risk of mortality in heart failure patients [37]. These findings indicate that inflammatory pathways play an important role in disrupting iron homeostasis in CVDs.

4. Histological Evidence of Iron Dysregulation in Cardiovascular Tissue

The histological research offers the morphological evidence of iron imbalance directly in the myocardial tissue and its role in the injury of cardiomyocytes. The excessive iron deposition in the cardiomyocytes can be seen by employing special histochemical staining procedures, the most commonly employed being Perls Prussian blue staining to identify the ferric iron deposition that has been collected in the tissue section. The presence of iron-positive granules in the cytoplasm of cardiomyocytes is commonly observed in myocardial tissue, which points to the intracellular Iron accumulation and the impairment of the normal iron homeostasis [38].

Histologic analysis demonstrates that morphological abnormalities commonly found in case of iron overload in the cardiomyocytes include myofibrillar degeneration, mitochondrial edema and infiltration of inflammatory cells. These cellular alterations are the signs of oxidative stress caused by excess intracellular iron, which promotes the development of ROS and lipid peroxidation in cardiac cells. These histological alterations

support the idea of the role of iron maladjustment in direct involvement of myocardial tissue damage and pathological remodeling.

Clinical studies also prove that disruptions in myocardial iron homeostasis are strictly connected with dysfunction of the mitochondria and cardiac energetics. Investigations conducted on myocardial tissue in patients with advanced heart failure have found serious depletion of myocardial iron levels and impaired oxidative stress and mitochondrial enzyme activity [39]. Likewise, molecular studies have shown that genes involved in iron metabolism are altered in myocardial tissue, with TfR1 being elevated in iron-deficient cardiomyocytes, and indicating adaptive mechanisms to restore intracellular iron levels [40].

The histological level of iron storage in cardiomyocytes is well visualized by the Perls Prussian blue staining, which points out the iron depositions as blue intracellular granules in the myocardial fibers (**Figure 4**).

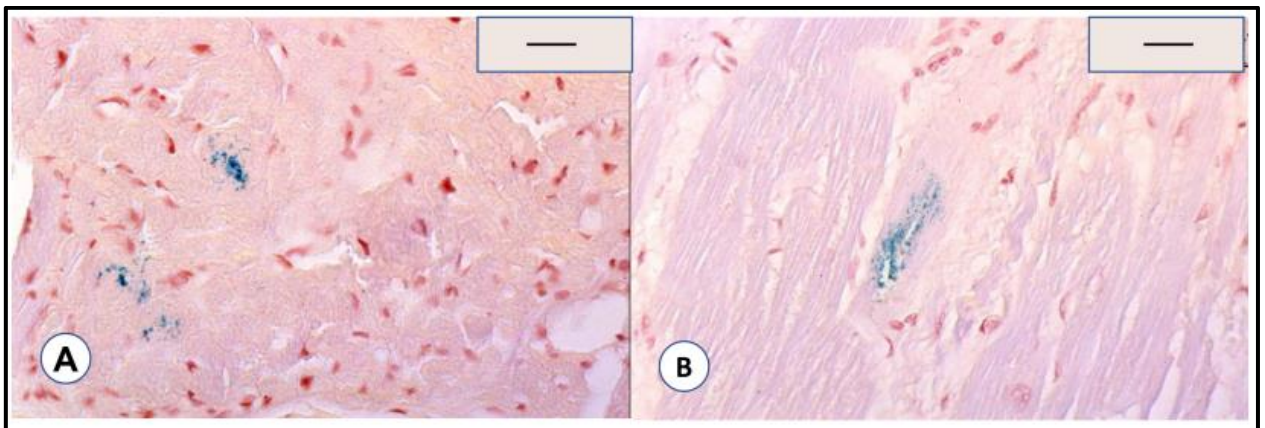


Figure 4. Histological iron deposition in cardiomyocytes demonstrated by Perls' Prussian blue staining (Koeppen, 2024)

These deposits are evidence of abnormal intracellular iron storage, and offer morphologic evidence of impaired iron metabolism in cardiac tissue. Histological staining thus is a significant method in identifying iron overload or redistribution in the myocardial tissue.

The existence and the localization of iron-storage proteins in the cardiomyocytes are further confirmed by the immunohistochemical studies. Ferritin immunostaining shows that ferritin is strongly localized in myocardial fibers, indicating intracellular iron complexation and cellular mechanisms to restrain iron-induced oxidative damage (**Figure 5**).

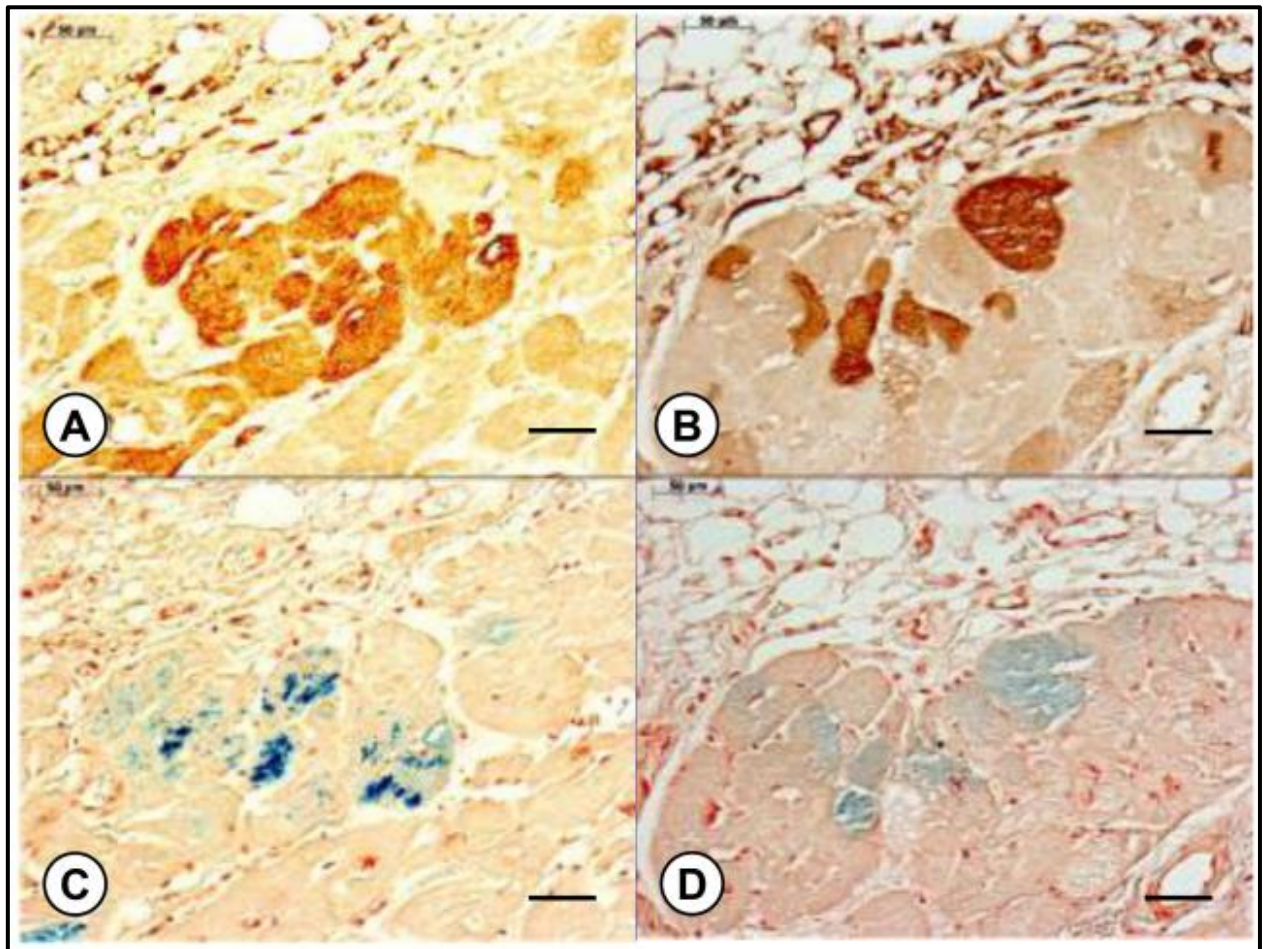


Figure 5. Immunohistochemical localization of ferritin within myocardial fibers indicates intracellular iron storage (Koeppen, 2024).

The presence of ferritin in the cardiomyocytes indicates the activation of protective cellular pathways that strive to buffer surplus intracellular iron and avoid oxidative stress of myocardial structures [41].

All of these histological results confirm that iron misregulation in cardiovascular tissue is characterized by intracellular iron deposition, abnormal expression of iron transport proteins, and structural degeneration of myocardial fibers. These morphological alterations offer important clues to processes by which iron metabolism disruption can cause cardiomyocyte damage and progressive cardiovascular dysfunction.

5. Chronic Inflammation and Myocardial Iron Metabolism

Chronic inflammation is a key factor in iron homeostasis derangement in the cardiovascular tissue. Systemic and cellular iron metabolism is regulated by inflammatory cytokines via the hepcidin-ferroportin regulatory axis, which regulates iron export by cells [42,43]. Hepcidin is a peptide hormone produced mostly by the liver and binds to the iron

exporter FPN, inducing its internalization and degradation, curbing iron release by cells. Higher hepcidin concentrations during inflammation may consequently lead to the decreased iron supply in cardiomyocytes and the development of intracellular iron misbalance [44].

Inflammatory activation and iron metabolism disturbances are strongly related to clinical studies in patients with heart failure. The BIOSAT-CHF cohort analyses have suggested that iron deficiency is very common in exacerbating heart failure and is often accompanied by inflammatory biomarkers, malnutrition, and fluid overload, indicating that inflammation plays an important role in the poor metabolism of iron in CVDs [45].

Additional findings that support the idea that inflammation is linked to iron dysregulation are based on studies that focus on IL-6 involvement in heart failure. High levels of IL-6 have been linked to decreased left ventricular performance, higher risks of atrial fibrillation and increased mortality in heart failure patients. Notably, higher IL-6 levels have also been associated with iron deficiency, and, therefore, it is possible that inflammatory signaling can directly affect iron metabolism in cardiovascular pathology [46].

The mechanisms of intracellular iron storage and transport may also be affected by inflammatory processes. High levels of ferritin found in patients with acute heart failure can be due to inflammation-mediated iron sequestration, as opposed to iron overload. The inflammatory cytokines stimulate the production of ferritin and iron retention in the macrophages and other cells, which results in the lack of circulating iron and the inefficient use of iron by the myocardium.

The interference with iron metabolism in inflammatory conditions may also add to myocardial damage. Clinical trials of patients suffering ST-segment elevation myocardial infarction (STEMI) have shown that iron deficiency correlates with poor myocardial reperfusion and poor cardiovascular outcomes after primary percutaneous coronary intervention. These results indicate that iron metabolism changes could be involved in myocardial recovery and tissue repair after ischemic injury.

All these findings suggest that chronic inflammation upsets the iron regulatory pathways, which results in disturbed iron distribution, disrupted mitochondrial metabolism, and myocardial injury progression. The interaction between inflammatory signaling and iron dysregulation is thus an important mechanism behind CVDs' progression.

6. Ferroptosis and Iron-Mediated Cardiomyocyte Injury

The dysregulation of iron in cardiomyocytes can stimulate a kind of controlled cell death referred to as ferroptosis, which is marked by iron-dependent lipid peroxidation and oxidative damage of cellular membranes [47]. Ferroptosis is a cellular process that occurs when excess intracellular iron is involved in the generation of ROS via the Fenton reaction, which causes lipid peroxidation and eventual damage to cellular membranes. The

degeneration and structural remodeling of cardiomyocytes in CVDs occur in cardiac tissue through this process.

The typical alterations in ultrastructure related to ferroptotic cardiomyocytes at the cellular level include mitochondrial shrinkage, reduction in mitochondrial cristae, and elevation in the density of membranes. These morphological alterations show extreme mitochondrial dysfunction and derailment of normal cell metabolism. Since cardiomyocytes are extremely dependent on mitochondrial oxidative phosphorylation to supply energy, mitochondrial iron metabolism disruptions can severely affect myocardial contractile activity and facilitate cardiomyocyte demise.

Clinical and experimental findings show that iron imbalance is a contributory factor to myocardial injury in heart failure and ischemic heart disease. Myocardial iron deficiency has been linked to disrupted mitochondrial enzyme activity and enhanced oxidative stress in failing hearts, as well as the significance of iron-dependent metabolic pathways in ensuring cardiomyocyte viability [48]. Moreover, changes in myocardial energy metabolism have been observed in individuals with chronic heart failure and iron deficiency, where lower phosphocreatine/ATP ratios demonstrate the inability of mitochondrial energetic capacity [49].

Iron dysregulation has also been reported to cause myocardial injury in cases of acute ischemic events. The clinical trials on patients with STEMI have indicated that iron deficiency correlates with compromised myocardial reperfusion and poor clinical outcomes after primary percutaneous coronary intervention. This finding implies that cardiomyocyte survival and myocardial recovery after ischemic injury can be affected by iron metabolism disturbances.

Furthermore, inflammatory signaling pathways may enhance ferroptotic damage of cardiac tissue. The pro-inflammatory cytokines may alter the iron control pathway and raise the intracellular iron concentration, contributing to the intensification of oxidative stress and ferroptosis of the cardiomyocytes. Inflammation, mitochondrial dysfunction, and iron dysregulation interaction is therefore a significant mechanism that leads to myocardial damage and chronic cardiovascular dysfunction.

7. Histopathological Changes in CVDs

The imbalances in myocardial iron metabolism have emerged as one of the growing structural and functional alterations in various CVDs. Histopathology and molecular studies indicate that the disorders of iron regulation are implicated in the dysfunction of the mitochondria, oxidative stress, and restructuring of myocardial tissue [50,51]. The alterations are particularly evident in such diseases as heart failure, myocardial infarction, and cardiomyopathies, where the disruption of iron homeostasis interferes with the metabolism of the cell and alters the integrity of cardiomyocytes.

The pathological mechanism of myocardial iron deficiency is a serious heart failure, which is associated with the worsening of mitochondrial enzyme activity and reduced energy

production in cardiomyocytes. It has been demonstrated by studies of human heart failure that iron content in the myocardium is reduced due to mitochondrial dysfunction and oxidative stress and this demonstrates the need to have iron-dependent metabolic pathways to maintain myocardial contractility [52]. Clinical evidence also suggests that iron deficiency is very common in heart failure and is linked to increased severity of the disease and poor clinical outcome [53].

Iron dysregulation is also a major cause of myocardial infarction, in which ischemic damage and inflammation of the heart cause changes in the distribution of iron in cardiac tissue [54,55]. The oxidative stress and inflammatory signaling may facilitate intracellular iron redistribution and lead to cardiomyocyte degeneration after ischemia-reperfusion injury [56]. Clinical studies have proven that the iron deficiency correlates with poor myocardial reperfusion and unfavourable prognoses in patients with STEMI.

Similarly, iron metabolism disruptions have also been related to the pathogenesis of cardiomyopathies, with chronic iron regulation abnormalities playing a role in structural alterations in the myocardium and cardiomyopathy. The cardiomyocyte degeneration, mitochondrial abnormalities and progressive myocardial fibrosis are often observed through histological evidence. Excessive oxidative stress under the influence of iron imbalance might trigger fibroblast and extracellular matrix deposition, ultimately leading to the unwanted myocardial remodeling [57,58].

Table 1 summarizes the key histopathological findings of myocardial iron dysregulation in various CVDs. All these findings underscore the critical role of iron metabolism in cardiovascular pathology, and the role of changes in myocardial iron distribution, mitochondrial integrity, and oxidative balance in the structural myocardial injury and progressive cardiac dysfunction.

Table 1. Histological findings associated with myocardial iron dysregulation in CVDs.

Disease	Histological Findings	Iron-related Mechanism
Heart failure	Mitochondrial dysfunction, cardiomyocyte degeneration	Myocardial iron deficiency
Myocardial infarction	Necrosis, inflammatory infiltration	Oxidative stress and iron redistribution
Cardiomyopathy	Fibrosis, cellular degeneration	Chronic iron dysregulation

8. Therapeutic Implications and Future Perspectives

There has been an increasing interest in methods of restoring iron homeostasis in the myocardial tissue as a means of treating CVDs, as a result of increasing recognition of iron dysregulation in the disease. Clinical evidence has shown that iron deficiency is extremely common in heart failure patients and is related to poor cardiac performance, systemic inflammation, and poor clinical outcomes.

The use of intravenous iron supplementation is one of the most studied forms of therapy. It is intended to replace iron levels in the heart muscle and enhance the functioning of the mitochondria. Intravenous iron therapy has shown potential to enhance functional capacity, quality of life (QoL), and exercise tolerance in patients with heart failure and iron deficiency, indicating that iron imbalance correction has the potential to improve cardiomyocyte metabolic performance.

In addition to iron replacement therapy, new studies have aimed to disrupt molecular pathways that govern iron metabolism. The regulation of the hepcidin/ferroportin axis is a promising treatment option in the restoration of iron distribution anomalies in inflammatory conditions. Hepcidin inhibition can potentially restore iron export via FPN and enhance intracellular iron supply in cardiomyocytes, leading to less metabolic dysfunction related to myocardial iron overload.

The possible use of ferroptosis inhibitors has also been mentioned in recent studies in the prevention of iron-mediated cardiomyocyte injury. Ferroptosis-targeted therapies have the potential to prevent iron-induced cellular damage to myocardial tissue by inhibiting lipid peroxidation and oxidative stress. The experimental models indicate that ferroptotic inhibition can decrease myocardial damage and enhance cardiac performance after ischemia.

The therapeutic relevance of iron metabolism is also supported by the clinical studies, which investigate patients with STEMI. It has been shown that iron deficiency is a risk factor for impaired myocardial reperfusion and poor outcomes following primary percutaneous coronary intervention, and, in effect, iron imbalance correction can lead to better myocardial recovery after ischemic injury.

Thus, Future studies must consider enhancing diagnostic methods of identifying myocardial iron imbalance and other novel therapeutic targets engaging in the regulation of iron. Iron-dysregulated CVDs can be improved by the creation of advanced histological imaging technology, molecular biomarkers of iron metabolism, and therapies specific to iron-induced oxidative injury.

9. Conclusion

The iron homeostasis is a crucial component of structural and metabolic integrity of the cardiomyocytes, and the abnormalities of the iron regulation can become a crucial factor of cardiovascular pathology. The dysregulation of iron metabolism has been shown to contribute to the mitochondrial dysfunction, oxidative stress and gradual cardiomyocyte damage as shown by histological, molecular, and clinical data. Inflammatory signaling of chronic inflammation also disrupts iron regulatory pathways, alters the intracellular iron distribution and exacerbates myocardial damage. The myocardial structural degeneration presents direct morphological signs of iron imbalance, such as histological signs of iron deposition in the heart of cardiomyocytes, disproportionate ferritin localization, and fragmented iron export systems. All these processes play part in critical interaction of iron metabolism, inflammation and cell damage in CVDs. An improved insight into the

myocardial iron regulation can thus be valuable in the development of certain treatment interventions that can be used to restore the iron homeostasis, minimize the oxidative damage, and enhance cardiovascular outcomes.

List of Abbreviations: CVDs: cardiovascular diseases; DNA: deoxyribonucleic acid; FPN: ferroportin; IL-6: interleukin-6; ATP: Adenosine Triphosphate; ROS: reactive oxygen species; Tfr1: transferrin receptor-1; STEMI : ST-segment elevation myocardial infarction; QoL: quality of life.

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