CORRELATION BETWEEN FERRITIN, IL-6 AND IL-1B: INFLAMMATORY AND THERAPEUTIC IMPLICATIONS IN CARDIOVASCULAR DISEASES

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Abstract: Inflammation plays a central role in the pathogenesis of cardiovascular diseases (CVDs), with the pro-inflammatory cytokines IL-6 and IL-1β exerting direct influence on atherosclerosis progression, endothelial dysfunction, and adverse cardiovascular outcomes. This article reviews the correlations between ferritin, an inflammatory and metabolic biomarker, and the cytokines IL-6 and IL-1β, emphasizing their relevance in chronic inflammatory states and their association with cardiovascular dysfunction. Ferritin, often elevated in response to IL-6 and IL-1β activity, reflects both an attempt by the organism to mitigate oxidative damage and a marker of inflammatory aggravation. Recent studies, including clinical trials with anti-inflammatory agents such as canakinumab, colchicine, and tocilizumab, suggest that targeted inhibition of these inflammatory pathways can significantly improve cardiovascular outcomes. Finally, this review highlights the need for personalized therapeutic strategies, considering patients' inflammatory profiles and biomarkers, to optimize clinical interventions and improve prognosis in CVDs.

Keywords: Ferritin; IL-6; IL-1β; inflammation; cardiovascular diseases; biomarkers; atherosclerosis.

Introduction

Ferritin, an essential protein for iron metabolism, performs the function of intracellular sto-

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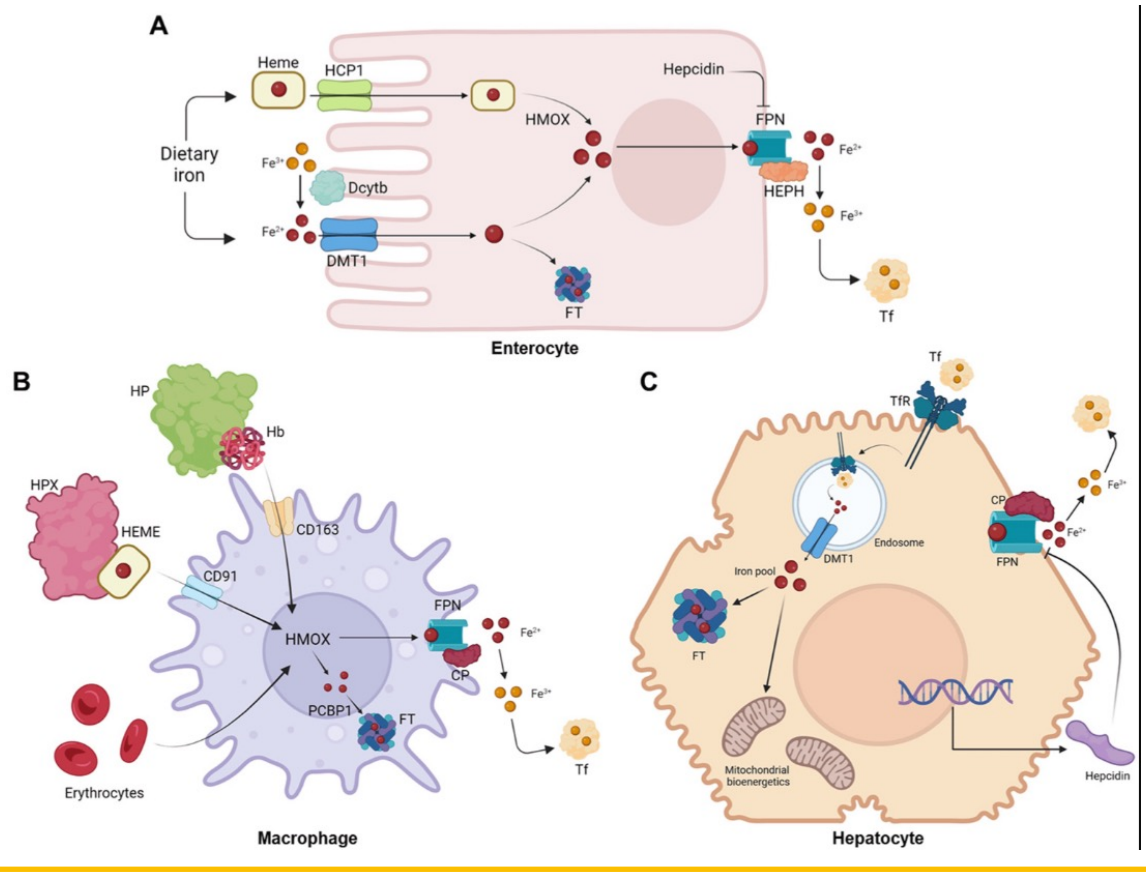
rage of this mineral, being able to protect it in its protein structure. After the reduction of ferric iron (Fe^{3+}) to ferrous iron (Fe^{2+}) by the action of duodenal cytochrome B, iron can be absorbed by enterocytes, enabling their transit and cellular storage (Kowdley et al., 2020).

Figure 1: Cellular metabolism of iron - (A) Iron from the diet is absorbed by enterocytes. (B) Macrophages participate in the process of recycling iron from erythrocytes. (C) Hepatocytes act as the main cellular site for iron storage. Abbreviations: CD163—Cluster of differentiation 163, hemoglobin-haptoglobin receptor; CD91—Cluster of differentiation 91, also known as Protein 1 related to the low-density lipoprotein receptor (LRP1) or α2-macroglobulin receptor; CP—Ceruloplasmin; Dcytb—Duodenal cytochrome B; DMT1—Divalent metal carrier 1; FPN—Ferroportina; FT—Ferritin; Hb—hemoglobin; HCP1—Heme transporter protein 1; HEPH—Hephaestus; HMOX—Heme oxygenase; HP—Haptoglobin; HPX—Hemopexin; PCBP1—Poly(RC)-binding protein 1; Tf—transferrin; TfR—Transferrin receptor



Source: Fonseca, 2023

Ferritin comes in two distinct forms: when it is devoid of iron, it is called apoferritin, with a molecular weight of around 440 kilodaltons; in the presence of iron, its structure changes, forming holoferritin, which can reach up to 900 kilodaltons (Carrillo et al., 2015).

From a structural point of view, ferritin is composed of 24 monomers distributed in light (L) and heavy (H) subunits, whose distribution is dependent on the tissue in question. The L subunit predominates in organs such as the liver, spleen, and bone marrow, while the H subunit manifests itself more intensely in the heart (Mahroun et al., 2022).

Its main biological function is to store iron in a non-toxic way, preventing its participation in Fenton reactions, in which interactions with hydrogen peroxide could generate hydroxyl free radicals. This mechanism is exploited by neutrophils and macrophages as part of the innate immune response, in an attempt to eliminate phagocytosed microorganisms (Slaats et al., 2016). At the same time, ferritin is essential for the balance of physiological iron levels, being a sensitive marker both for the identification of iron deficiency and for the evaluation of overload states, in which iron tends to be deposited in macrophages in the form of hemosiderin (Ruscitti et al., 2022).

Iron metabolism is also largely influenced by inflammatory and infectious processes, in which bacterial particles, such as lipopolysaccharide, and pro-inflammatory cytokines, such as interleukins 1β, 6, 18 and Tumor Necrosis Factor (TNF), promote the downregulation of ferroportin 1, mediated by hepcidin. This hormonal interaction reduces the release of iron into the plasma, favoring its accumulation in hepatocytes and macrophages and increasing the translation of ferritin by the iron-response protein (Kowdley et al., 2020; Carrillo et al., 2015; Slaats et al., 2016).

Other physiological and hormonal conditions, such as variations in the levels of thyroid hormones, cortisol, prostaglandins, changes in intracellular messengers, and states of hypoxia, ischemia, or hyperoxia, also modulate serum ferritin levels, reinforcing the complexity of its regulation in different metabolic and pathological states.

The ferritin H subunit has an immunomodulatory role, being responsible for reducing iron uptake by transferrin, an essential element for cell proliferation and differentiation. This action is reflected in the inhibition of processes such as blastogenesis, myelopoiesis, and T lymphocyte activation (Carrillo et al., 2015; Slaats et al., 2016).

Ferritin, in addition to its classic role in iron metabolism, is also involved in innate and adaptive immunity, acting as an acute-positive phase protein. Its hepatic expression increases in response to stimuli such as tissue injury, trauma, infections, autoimmune diseases, and neoplasms (Mahroun et al., 2022; González et al., 2010; Urquizo et al., 2019).

During the acute inflammatory response, plasma ferritin levels peak within the first 24 to 48 hours, predominantly in the form of H-subunit monomers. This increase aims to restrict the availability of iron for free radical reactions, negatively modulate antibody synthesis by B lymphocytes, and suppress myelopoiesis and T lymphocyte activation (Urquizo et al., 2019; Carrillo et al., 2015).

In the molecular context, ferritin H exerts negative feedback regulation on the chemokine receptor CXCR4, an important cofactor in the activation of mitogenesis-activating protein kinase (MAPK). This effect, in turn, reduces the proliferation, differentiation, and migration of inflammatory cells, while also promoting the synthesis and release of IL-10, a cytokine with anti-inflammatory properties (Li et al., 2006; Gray et al., 2001).

In parallel, ferritin can also activate inflammatory pathways through interaction with TIM-2 (T-cell/Transmembrane Immunoglobulin and Mucin Domain) proteins, triggering the release of inflammatory mediators such as IL-6, inducible nitric oxide synthetase, and other mediators regulated by the NF-κB pathway, often activated by protein kinase (Carrillo et al., 2015).

The increase in IL-6 levels in situations of systemic inflammation is widely recognized as one of the main stimuli for hepatic ferritin production, being accompanied by the regulation of hepcidin, a key hormone in the control of iron bioavailability. This increase, which occurs in response to inflammatory stimuli, reflects a physiological adaptation to limit the extracellular availability of iron, avoiding its participation in oxidative processes (Volp, 2008), where the simultaneous presence

of elevated levels of IL-1β intensifies this phenomenon, given its role in the amplification of local inflammatory responses, particularly in the vascular endothelium, where it contributes to the activation of endothelial cells and the expression of mediators pro-inflammatory drugs (Urquizo et al., 2019).

When considered in the context of cardiovascular diseases, the correlation between ferritin, IL-6 and IL-1β raises important questions about the mechanisms that relate systemic inflammation to endothelial dysfunction and the development of structural changes in the vascular wall. Elevated ferritin levels, often observed in chronic inflammatory states, can be interpreted as a reflection of an immunometabolic response that aims to mitigate the damage caused by oxidative stress, while participating in positive feedback loops that intensify the activation of inflammatory mediators, such as IL-6 itself (Katkenov, et al, 2024).

Furthermore, the interaction between these cytokines and ferritin suggests a pathway through which iron metabolism, often altered under inflammatory conditions, can indirectly influence processes crucial for cardiovascular homeostasis. For example, changes in iron bioavailability may interfere with lipid metabolism and endothelial functionality, while the proinflammatory state associated with IL-6 and IL-1β may predispose to the formation of vascular lesions (Justi, et al., 2019).

Thus, the correlation between ferritin, IL-6 and IL-1β highlights the intersection of inflammatory and metabolic processes in the cardiovascular context, pointing to the need for further investigations that explore the role of these mediators in the progression of cardiovascular conditions, with a view to understanding the underlying mechanisms of this interaction at both a systemic and local level.

Materials and Methods

A systematic literature review was conducted using the PubMed and Embase databases, with the aim of identifying relevant studies published between January 2014 and December 2024. The search strategy was structured based on keywords and terms indexed in the Medical Subject Headings

(MeSH) related to cardiovascular diseases and inflammatory mediators, including “Cardiovascular diseases”, “Interleukin-6”, “Interleukin-1β”, “Inflammation” and “Biomarkers”. The search was limited to articles published in English and submitted to peer review, with the intention of encompassing all studies investigating the roles of IL-6 and IL-1β in the context of cardiovascular diseases.

The inclusion criteria established that studies should specifically address the role of IL-6 and/or IL-1β in cardiovascular diseases, have been published within the delimited period, include relevant human and animal models of cardiovascular pathology, and present results related to clinical outcomes, molecular mechanisms, or therapeutic interventions targeting the cytokines in question. Studies that did not directly focus on cardiovascular diseases were excluded, as well as case reports and editorials that did not contain original data or presented insufficient data for inclusion in the analysis.

The collected data were qualitatively synthesized, with the purpose of presenting a comprehensive analysis of the roles played by IL-6 and IL-1β in the context of cardiovascular diseases. When feasible, a meta-analysis was performed to estimate the effect sizes of cytokines on the clinical outcomes evaluated.

Findings

Djahanpour et al. (2023) conducted a systematic review covering 17 studies and identified a strong association between elevated IL-6 and IL-8 levels and the presence of peripheral arterial disease (PAD). Signorelli et al. (2016) described significant elevations in serum IL-6 levels (11.8 ± 1.2 ng/dL) in patients with PAD, evidencing a systemic inflammatory state in these individuals. In patients with chronic limb ischemia at risk of amputation (CLTI), Gremmels et al. (2019) associated elevated IL-6 concentrations with an increased risk of amputations, reinforcing the role of this cytokine as a mediator in severe ischemia conditions. DePalma et al. (2021) observed that ferritin levels correlated with IL-6 levels in patients with PAD, suggesting a relationship between iron metabolism and vascu-

lar inflammation.

The inflammatory response associated with clinical management was also investigated. Sokolik et al. (2021) reported a significant decrease in IL-6 levels, observed both 24 hours and six months after angioplasty and stenting, indicating a reduction in the inflammatory process resulting from the therapeutic intervention (Sokolik, et al., 2021). Guo et al. (2020) suggested that elevated concentrations of IL-6 have greater predictive power for in-stent restenosis compared to high-sensitivity C-reactive protein (hs-CRP), underscoring its potential utility as a diagnostic marker in post-intervention complications (Guo, et al., 2020). In post-myocardial infarction patients, Tardif et al. (2019) identified that colchicine treatment was effective in reducing IL-6 levels, indicating therapeutic anti-inflammatory effects of the medication (Tardif, et al, 2019).

Martínez et al. (2015) corroborated these findings by demonstrating that colchicine significantly decreased serum concentrations of IL-6, IL-1β, and IL-18 in patients with acute coronary syndrome (ACS), reinforcing the positive impact of this intervention on inflammation control (Gotsman, et al, 2014).

IL-1β, a pro-inflammatory cytokine known to be involved in the progression of atherosclerosis and in the pathogenesis of myocardial infarction, has also been investigated as a therapeutic target. Martínez et al. (2015) demonstrated that colchicine substantially reduces IL-1β levels in patients with ACS, evidencing its role in controlling the inflammatory state associated with cardiovascular disease (Martinez, et al., 2015).

Similarly, Gotsman et al. (2014) described an association between elevated IL-1β levels and worse outcomes in patients with heart failure, highlighting the impact of this cytokine on the evolution of heart disease. Ridker et al. (2017), in turn, provided robust evidence showing that the use of canakinumab, an IL-1β inhibitor, reduced concentrations of this cytokine and was associated with lower rates of cardiovascular events. These results point to the relevance of IL-1β blockade as a strategy for reducing inflammation and improving clinical outcomes in patients with cardiovascular diseases (Ridker et al. 2017).

The studies analyzed emphasize the central role of IL-6 and IL-1β as inflammatory mediators in cardiovascular diseases. In different conditions, such as PAD, ACS, heart failure, and post-intervention complications, these cytokines not only reflect the inflammatory state, but are also indicative of prognosis and potential therapeutic targets. The detailed analysis of the methodologies employed, including the methods of cytokine measurement and the clinical outcomes evaluated, allows us to consolidate the understanding of the molecular mechanisms underlying these conditions, in addition to guiding the development of new therapeutic approaches.

Discussions

The review presented here emphasizes the central role of IL-6 and IL-1β in the pathogenesis and progression of cardiovascular diseases (CVDs), with elevated levels of these cytokines consistently associated with adverse clinical outcomes, such as increased risk of myocardial infarction, heart failure, and increased mortality. These findings not only reinforce the relevance of inflammation as an underlying mechanism for CVDs, but also suggest that therapeutic strategies targeting these cytokines may contribute to the modulation of inflammation and, potentially, to the reduction of cardiovascular complications.

In the context of CVDs, inflammation plays a critical role, integrating immunological and metabolic factors that culminate in endothelial dysfunction and the progression of atherosclerosis. IL-6, a multifunctional cytokine, regulates the immune response, the inflammatory process, and hematopoiesis. This molecule is produced by a wide variety of cells, including macrophages, fibroblasts, and endothelial cells, in response to infections, tissue injury, and chronic inflammatory stimuli.

IL-6 promotes the synthesis of acute-phase proteins, such as C-reactive protein (CRP), a marker widely used to monitor systemic inflammation. However, elevated levels of IL-6 are not mere reflections of the inflammatory state, but also play an active role in the progression of CVDs, contributing to endothelial dysfunction, atherosclerotic plaque instability, and the development of cardio-

vascular events, such as infarction and heart failure.

IL-1β, in turn, plays a key role in amplifying the inflammatory response. This cytokine is produced primarily by activated macrophages and exerts its effects by promoting the activation of endothelial cells and the recruitment of leukocytes to the site of inflammation. These actions directly contribute to the advancement of the atherosclerotic process, from the initial phases of monocyte recruitment and foamy cell formation to the advanced stages, with the development of unstable lesions.

In the vascular environment, IL-1β is also able to increase the expression of adhesion molecules, such as ICAM-1 and VCAM-1, facilitating the infiltration of monocytes that differentiate into macrophages and phagocytize oxidized lipoproteins (oxLDL), characteristic of atherosclerotic plaques. This inflammatory cycle perpetuates the progression of atherosclerosis and, by extension, increases the likelihood of serious cardiovascular events.

In addition, IL-6 and IL-1β exert synergistic effects at various stages of atherosclerosis development. IL-6, when binding to its receptor (IL-6R), activates intracellular signaling pathways, such as JAK/STAT, which promote the expression of genes related to inflammation, cell proliferation, and apoptosis. This chronic signaling maintains a pro-inflammatory vascular environment, contributing to plaque instability and increased risk of cardiovascular events. On the other hand, IL-1β, activated by the NLRP3 inflammasome in response to stimuli such as cholesterol crystals, intensifies vascular inflammation by increasing the production of pro-inflammatory cytokines, which amplify immune cell recruitment and vascular remodeling.

Ferritin is often elevated in response to systemic inflammation mediated by IL-6 and IL-1β. Its increase reflects the body's attempt to sequester intracellular iron, reducing the availability of free iron for oxidative reactions that could intensify oxidative stress and endothelial damage. Studies indicate that elevated ferritin levels are associated not only with exacerbated inflammatory processes, but also with the development of atherosclerosis, underscoring its role as an inflammatory marker in CVDs (Gerônimo, et al., 2023).

Recent clinical trials have demonstrated the potential of anti-inflammatory therapies in the

management of cardiovascular disease, reinforcing the importance of inflammation as a therapeutic target. The CANTOS trial, which evaluated the use of canakinumab, an IL-1β inhibitor, highlighted the significant reduction in recurrent cardiovascular events in patients with a history of myocardial infarction. These results corroborate the role of IL-1β in the pathogenesis of atherosclerosis and in the development of cardiovascular complications, pointing to the efficacy of interventions targeting this cytokine in severe inflammatory contexts.

Another relevant study, the Colchicine Cardiovascular Outcomes Trial (COLCOT), evaluated low-dose colchicine, an anti-inflammatory agent widely used in the treatment of diseases such as gout, demonstrating that the drug significantly reduced the risk of recurrent ischemic events in patients who had recently suffered acute myocardial infarction. These findings suggest that colchicine may be repositioned as a therapeutic option to reduce inflammation and improve prognosis in cardiovascular conditions.

Tocilizumab, an IL-6 receptor antagonist, was evaluated in the ASSAIL-MI study, which investigated its effects in patients with ST-segment elevation myocardial infarction (STEMI). This trial demonstrated that early administration of the drug was able to improve myocardial salvage and reduce markers of systemic inflammation, such as high-sensitivity C-reactive protein (hs-CRP) levels. These results underscore the potential of therapies that modulate IL-6-related pathways in the management of STEMI patients, particularly in early stages.

The aforementioned studies reinforce the relevance of anti-inflammatory therapies in the treatment of cardiovascular diseases and suggest that personalized approaches, adjusted to the individual inflammatory profile of each patient, can increase the effectiveness of these interventions. In the context of acute myocardial infarction (AMI), for example, the control of myocardial inflammation has become both a prognostic and therapeutic priority. The initial inflammation after AMI, although necessary for necrotic tissue removal and tissue repair, can become deleterious if exacerbated, leading to worse ventricular remodeling and a higher risk of heart failure.

In this sense, Matter et al. (2023) highlighted the importance of anti-inflammatory strategies

targeting the IL-1 and IL-6 pathways, emphasizing that early interventions appropriate to the patient's inflammatory profile can mitigate the adverse effects of uncontrolled inflammation. IL-1 and IL-6 inhibitors have shown promise in reducing excessive inflammation, contributing to the control of post-AMI cardiac remodeling. In addition, approaches that take into account the ideal time for intervention and the inflammatory burden of each patient seem to be determinant for the efficacy of the treatment.

Additionally, the correlation between elevated levels of IL-1β and IL-6 and biomarkers of inflammation, such as ferritin, reinforces the importance of integrating the analysis of these inflammatory mediators into clinical management. Ferritin, as an acute-phase protein, is often elevated in response to the activity of cytokines such as IL-6, reflecting the body's attempt to sequester free iron and reduce oxidative stress. High ferritin levels, together with high concentrations of IL-6 and IL-1β, have been observed in inflammatory cardiovascular conditions, suggesting that these mediators act on an interconnected axis, promoting the perpetuation of the inflammatory state.

Final Thoughts

The present review highlighted the intersection between inflammatory processes, immune mediators, and the regulation of iron metabolism in the context of cardiovascular diseases. It was evidenced that IL-6 and IL-1β play central roles in the pathogenesis of these conditions, not only as inflammatory mediators, but also as potential therapeutic targets. These mediators are closely linked to ferritin, whose elevation reflects the body's attempt to mitigate inflammatory and oxidative damage, but also points to its contribution to the progression of pathological states.

The studies analyzed reinforce that ferritin, mediated by the inflammatory activity of cytokines such as IL-6, is not only a marker, but also an active participant in the worsening of endothelial dysfunctions, oxidative stress, and vascular remodeling. Elevated ferritin and cytokine levels consistently correlate with adverse cardiovascular outcomes, including increased risk of ischemic

events, progression of atherosclerosis, and mortality.

Recent clinical trials, such as those investigating canakinumab, colchicine, and tocilizumab, offer robust evidence of the potential of anti-inflammatory interventions in the management of cardiovascular disease. These results reinforce the need to integrate personalized therapeutic strategies that consider the individual inflammatory profile and biomarkers, such as ferritin, to optimize clinical outcomes.

In view of this, further investigations that correlate ferritin, IL-6, and IL-1β are essential to broaden the understanding of the mechanisms underlying cardiovascular inflammation and to validate specific therapeutic interventions. The integration of this knowledge into clinical practice can contribute to a more effective and targeted approach to the treatment of patients with cardiovascular diseases, promoting both prevention and improvement of long-term outcomes

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