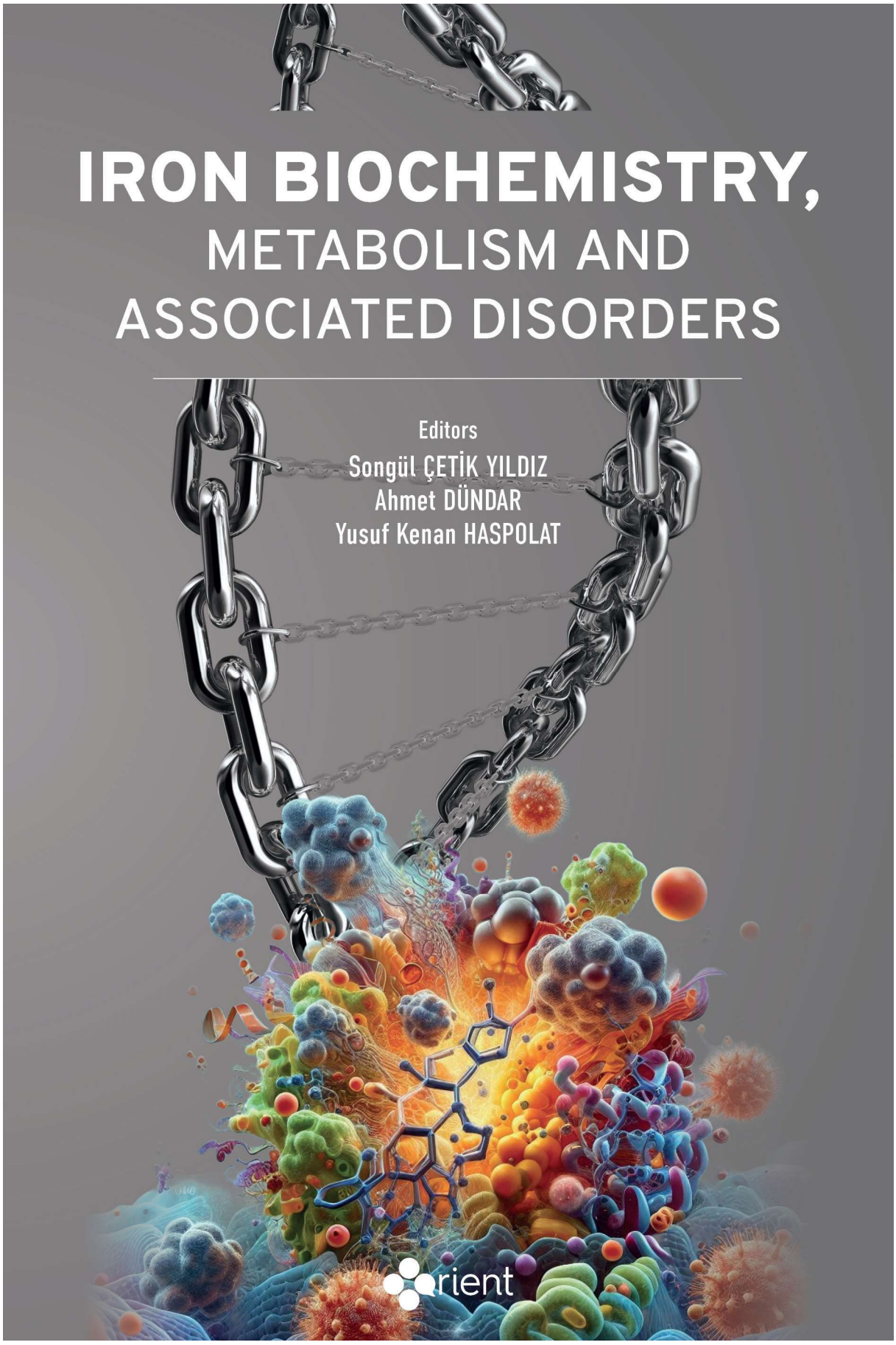
IRON BIOCHEMISTRY, METABOLISM AND ASSOCIATED DISORDERS

Editors
Songül ÇETİK YILDIZ
Ahmet DÜNDAR
Yusuf Kenan HASPOLAT



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Preface

Iron is one of the most essential trace elements for life, playing indispensable roles in a wide spectrum of biological processes ranging from cellular respiration and DNA synthesis to immune regulation and redox homeostasis. Its unique chemical properties allow it to participate in electron transfer reactions, making it a central component of numerous enzymes and metabolic pathways. However, the same redox activity that makes iron biologically valuable also renders it potentially toxic when its homeostasis is disrupted. Therefore, the regulation of iron metabolism represents a finely balanced system that is critical for maintaining physiological integrity.

In recent decades, remarkable progress has been made in our understanding of iron biochemistry and metabolism. Advances in molecular biology, genetics, and clinical medicine have revealed intricate regulatory networks governing iron absorption, transport, storage, and utilization. Key discoveries—such as the hepcidin–ferroportin regulatory axis—have significantly deepened our understanding of systemic iron homeostasis and have opened new avenues for the diagnosis and treatment of iron-related disorders. Despite these advances, dysregulation of iron metabolism remains a major global health concern. Iron deficiency anemia continues to be one of the most prevalent nutritional and hematological disorders worldwide, affecting millions of individuals, particularly women and children. Conversely, conditions characterized by iron overload—such as hemochromatosis, transfusion-related iron accumulation, and certain genetic disorders—can lead to severe tissue damage and multi-organ dysfunction. In addition, growing evidence highlights the role of iron dysregulation in a wide range of pathological conditions, including cardiovascular diseases, liver disorders, neurodegenerative diseases, metabolic syndromes, infections, and cancer.

The aim of this book, *Iron Biochemistry, Metabolism and Associated Disorders*, is to provide a comprehensive and integrative overview of the current knowledge surrounding iron biology. Bringing together contributions from experts in the field, this volume explores iron from multiple perspectives—ranging from its fundamental biochemical properties to its involvement in complex disease processes.

The chapters included in this book examine the biological and metabolic significance of iron, its chemical and redox properties, and the molecular mechanisms regulating systemic and cellular iron homeostasis. Particular emphasis is placed on the hepcidin–ferroportin axis, iron storage systems such as ferritin and hemosiderin, and emerging concepts such as ferroptosis, an iron-dependent form of regulated cell death that has attracted significant attention in recent biomedical research. Beyond the molecular foundations, the book also addresses the clinical and pathological dimensions of iron metabolism. Topics include iron deficiency anemia, genetic disorders of iron metabolism, hemochromatosis, iron overload toxicity, and dysregulation of iron homeostasis in diseases affecting the liver, lungs, cardiovascular system, and nervous system. The role of iron in the tumor microenvironment, infectious diseases, metabolic disorders, and pregnancy is also explored, highlighting the systemic and interdisciplinary importance of iron biology. Furthermore, recognizing the rapid evolution of biomedical technologies, this volume also includes perspectives on the application of artificial intelligence in clinical iron assessment. The integration of biochemical data with predictive modeling represents an emerging frontier that may significantly enhance diagnostic precision and personalized treatment strategies.

We hope that this book will serve as a valuable resource for researchers, clinicians, graduate students, and healthcare professionals interested in iron metabolism and its clinical implications. By integrating biochemical insights with clinical perspectives, we aim to contribute to a deeper understanding of iron biology and to stimulate further research in this dynamic and rapidly evolving field.

Editors

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HEMOCHROMATOSIS: PATHOGENESIS, CLINICAL FEATURES, AND TREATMENT

NURGİZEM KAYNARCA
GOZDE HASBAL CELIKOK

Introduction

Hemochromatosis (HC) is an inherited disorder characterized by progressive iron accumulation due to impaired regulation of systemic iron homeostasis. The condition most commonly results from *HFE* p.Cys282Tyr homozygosity, although non-*HFE*-related forms involving *HJV*, *HAMP*, *TFR2*, and *SLC40A1* variants are also recognized. Recent classifications additionally include digenic inheritance and molecularly undefined cases. Biochemically, increased transferrin saturation (TS) represents the earliest and most consistent indicator of disease, often preceding elevation of serum ferritin (SF). Clinical manifestations may remain absent for years despite substantial iron accumulation and can involve the liver, joints, heart, pancreas, and endocrine organs. Diagnosis relies on serum iron parameters and confirmatory genetic testing, while therapeutic phlebotomy (periodic removal of blood to reduce total body iron stores) remains the standard treatment for reducing iron overload (IO). This review of hemochromatosis covers definition through treatment, with emphasis on pathogenesis and classification.

1. Definition and Overview

Hemochromatosis (HC) is an inherited iron overload (IO) disorder characterized by excessive intestinal iron absorption resulting from hepcidin deficiency [1]. More broadly, primary IO disorders are defined as genetic conditions associated either with abnormally low hepcidin levels [2] or with impaired binding of hepcidin to ferroportin (FPN), the transmembrane protein responsible for exporting iron from the cell [1, 3]. In contrast, secondary IO may arise from different causes such as, disorders of erythropoiesis, increased red blood cell turnover, chronic liver disease, or excessive alcohol consumption [4]. Collectively, these inherited disorders result in progressive systemic iron accumulation due to dysregulated hepcidin activity [3, 5, 6].

2. Iron Metabolism and Regulation

Iron is the second most abundant metal in the Earth's crust, accounting for approximately 5% of its total composition [7]. In biological systems, iron is essential for DNA synthesis, electron transport, oxygen transport through hemoglobin and myoglobin, ATP production, spermatogenesis, and enzymatic reactions involved in the electron transfer chain. In the human body, approximately 65% of total iron is associated with hemoglobin, about 10% is found in non-hemoglobin components such as myoglobin, enzymes, and cytochromes, and the remaining fraction is present in iron stores distributed throughout the body [8, 9].

Under physiological conditions, body iron levels are regulated by a negative feedback mechanism, such that increasing iron stores lead to a reduction in intestinal iron absorption. Dietary iron is absorbed primarily in two forms: Heme (organic) iron and non-heme (inorganic) iron, each of which utilizes distinct absorption mechanisms. Although heme iron is absorbed more efficiently than non-heme iron, the overall proportion of dietary iron absorbed by the intestine remains relatively low [10].

Physiological iron balance is regulated by iron regulatory proteins (IRPs), which control both intracellular iron concentration and iron-dependent cellular functions [11, 12]. Among these, IRP1 and IRP2 play a central role in cellular iron homeostasis by binding to iron-responsive elements (IREs) located in the untranslated regions of mRNAs encoding proteins involved in iron uptake, storage, and export, including transferrin receptor 1 (TFR1), divalent metal transporter 1 (DMT1), ferritin, and FPN. Under conditions of low intracellular iron, IRPs bind to IREs, thereby promoting iron uptake and limiting iron storage, whereas at high iron concentrations they dissociate from IREs, resulting in reduced iron import and increased iron sequestration [13]. While ferritin is primarily localized within cells, it allows iron to be maintained in a non-toxic, bioavailable form. Circulating ferritin levels, which are likely reflected in macrophage secretion, are clinically used as an indicator of body iron stores [5, 14].

3. Pathogenesis of Hemochromatosis

The disorder was first described in 1865 by Armand Trousseau, who reported patients presenting with what later became known as bronze diabetes and cirrhosis. Approximately two decades later, the German pathologist Friedrich Daniel von Recklinghausen introduced the term hemochromatosis, proposing that a circulating blood factor (hemo-) was responsible for tissue injury and abnormal pigmentation (-chromatosis). The recognition of excess iron as the underlying cause of organ toxicity required several additional decades and is largely attributed to Joseph Sheldon in 1935, who also first suggested a genetic basis for the metabolic defect [15-18].

Abnormally increased intestinal iron absorption was identified in the 1950s as the central pathophysiological feature of HC [19], establishing dysregulated iron homeostasis as the core mechanism of disease and leading to the adoption of therapeutic phlebotomy as the mainstay of treatment [20]. Subsequent genetic studies provided definitive evidence for the inherited nature of the disorder. In 1977, Marcel Simon and colleagues demonstrated a tight linkage between the major histocompatibility complex and the putative HC gene on chromosome 6p [21], paving the way for the identification of the *HFE* in 1996 [22]. Early investigations suggested that up to 95% of cases were attributable to homozygosity for the 845 G→A substitution (p.Cys282Tyr, C282Y variant) [23, 24].

Further research revealed that the genetic basis of HC is more heterogeneous than initially assumed. In addition to *HFE*, pathogenic variants have been identified in several other iron-regulating genes, including those encoding transferrin receptor 2 (*TFR2*), FPN (*SLC40A1*), hepcidin (*HAMP*), and hemojuvelin (*HJV*) [25-28]. While simple or compound heterozygosity for p.C282Y and p.H63D, as well as certain digenic constellations (e.g., p.C282Y with p.S65C), may cause mild elevations in TS or ferritin levels, these genotypes are not typically associated with clinically significant IO [29-32]. In contrast, pathogenic variants affecting hepcidin synthesis or FPN function give rise to non-*HFE* forms of HC, most of which follow an autosomal recessive inheritance pattern, except for FPN-related disease, which is autosomal dominant [5, 6].

Apart from the genes encoding the key players of the hepcidin-FPN axis (*HAMP* and *SLC40A1*), *HFE* and *TFR2* encode membrane proteins involved in sensing circulating iron levels and transmitting signals required for appropriate hepcidin regulation. *HJV* encodes a bone morphogenetic protein (BMP) coreceptor that is essential for BMP-dependent hepcidin transcription. Accordingly, most forms of HC are inherited in an autosomal recessive manner, with the exception of ultrarare gain of function mutations in *SLC40A1*, which confer hepcidin resistance and functionally recapitulate hepcidin deficiency [5, 33].

At the molecular level, dysregulation of the hepcidin-FPN axis represents the central mechanism underlying IO. Hepcidin is synthesized primarily by hepatocytes and represents the central hormonal regulator of systemic iron homeostasis [34]. Hepcidin binds to FPN, the only known cellular iron exporter, thereby blocking

iron efflux and inducing FPN internalization and degradation [35, 36]. This process, which involves proteasome-dependent pathways mediated by *RNF217*, *UBA6*, and *NDFIP1*, constitutes a critical checkpoint controlling iron flux from enterocytes into the circulation [37].

Deficiency or loss of hepcidin function, as observed in *HAMP* mutations, results in constitutively increased intestinal iron absorption and unregulated systemic iron transport, leading to progressive iron accumulation. Under physiological conditions, hepcidin-mediated downregulation of FPN increases intracellular iron in enterocytes, promoting degradation of hypoxia-inducible factor-2 (HIF-2) and reducing expression of iron absorption genes such as *DMT1* and *DCYTB* [38].

Hepcidin expression itself is tightly regulated. It is upregulated in response to IO and inflammation and suppressed during hypoxia or increased erythropoietic activity. This regulation is mediated predominantly through BMP-dependent signaling pathways, particularly BMP2 and BMP6 derived from liver sinusoidal endothelial cells, which govern hepcidin transcription and systemic iron balance [39-41].

4. Genetic Basis and Classification

HC has historically been classified according to the causative gene and its chromosomal localization, giving rise to distinct subtypes that include *HFE*-related, *HJV*-related, *TFR2*-related, and FPN-associated forms. In this former classification (Table 1), Type 1 disease is linked to mutations in the *HFE*, whereas early onset forms arise from pathogenic variants in *HJV* or *HAMP*. Additional subtypes include alterations in *TFR2* and *SLC40A1*, reflecting the genetic heterogeneity of the disorder.

Table 1. *Former classification of hemochromatosis*

Type	Gene	Chromosomal Location
Type 1	*HFE*	6
Type 2A	*HJV* (hemojuvelin)	1
Type 2B	*HAMP* (hepcidin)	19
Type 3	*TFR2* (transferrin receptor 2)	7
Type 4A	*SLC40A1* (FPN)	2
Type 4B	*SLC40A1* (FPN)	2

A more recent molecular classification proposed by the International Society for the Study of Iron in Biology and Medicine (BIOIRON Society) groups HC into 4 categories based on genetic mechanisms rather than clinical phenotype (Table 2). This updated framework emphasizes the underlying molecular mechanisms rather than clinical phenotype alone and accommodates the expanding spectrum of genetic variants associated with IO [5].

Table 2. *Novel molecular classification of hemochromatosis*

Category	Molecular Pattern
HFE-related	p.Cys282Tyr homozygosity or compound heterozygosity of p.Cys282Tyr with other rare *HFE* pathogenic variants
Non-*HFE*-related	Rare pathogenic variants in *HJV*, *HAMP*, *TFR2*, or gain of function *SLC40A1* variants
Digenic	Pathogenic variants in two different iron-related genes (double heterozygosity and/or double heterozygous-homozygous combinations)
Molecularly undefined	No pathogenic variants identified after sequencing of known genes (provisional diagnosis)

5. Risk Factors and Disease Penetrance

The penetrance and clinical expression of HC are influenced by demographic and genetic factors. *HFE* p.C282Y homozygosity represents the strongest genetic determinant of overt disease, and a positive family history in first-degree relatives further increases risk. The condition is most prevalent in individuals of Northern European ancestry and is less common among Afro-American, Hispanic, and Asian populations. Sex significantly affects disease expression, as men are affected two to three times more frequently than women and tend to develop severe complications such as diabetes mellitus and liver cirrhosis at an earlier age. In women, clinical manifestations are more likely to occur after menopause or following hysterectomy [42].

6. Types of Hemochromatosis

6.1. HFE-related Hemochromatosis

HFE-related HC, formerly known as Type 1 HC, is the most frequently inherited form of IO and is caused by pathogenic variants in the *HFE*. The most common mutation is a guanine-to-adenine (G→A) transition at nucleotide 845, resulting in a cysteine-to-tyrosine substitution at amino acid position 282 (p.Cys282Tyr, C282Y) [3, 43, 44,]

At the molecular level, homozygosity for p.C282Y disrupts a critical disulfide bond within the HFE protein, altering its conformation and preventing proper membrane localization [45]. Under physiological conditions, HFE participates in iron sensing by interacting with transferrin receptors (TFR1 and TFR2), BMP receptor complexes, and hemojuvelin, thereby contributing to appropriate regulation of hepcidin expression [1, 46, 47].

Impaired *HFE* function reduces the ability to upregulate hepcidin synthesis despite increasing iron stores. Consequently, FPN remains active on enterocytes and macrophages, promoting excessive iron absorption and release into circulation. This establishes the molecular link between *HFE* mutations and systemic iron accumulation [1, 47-49]. In contrast, extremely rare gain of function variants in FPN are associated with hepcidin resistance [1, 5].

Another genetic subtype is the p.H63D variant. This mutation does not cause significant IO by itself but may act as a cofactor for phenotypic expression of IO, primarily when combined with C282Y. The C282Y/H63D genotype is compound heterozygote [50]. Individuals homozygous or heterozygous for H63D are not at increased risk of developing clinical IO compared with those without this mutation, although elevations in TS and SF may be observed [51].

A third genotype is associated with the S65C mutation. S65C may lead to increased serum iron and SF levels but has not been associated with excess tissue iron stores and is therefore considered a polymorphism without clear clinical significance [52, 53].

6.2. Non-HFE-related Hemochromatosis

Formerly known as Type 2 hereditary HC or juvenile HC (JH), is a rare and severe early-onset form of IO associated with mutations in the *HJV* or the *HAMP* [28, 54]. Both forms are characterized by marked hepcidin deficiency and typically present at a younger age compared with *HFE*-related HC. *HJV*-related HC results from pathogenic variants in *HJV*, which encodes hemojuvelin, a protein involved in hepcidin synthesis and related to the BMP co-receptor pathway [28, 54]. The most frequently reported mutation is p.G320V, although additional variants including p.I222N, p.I281T, p.C321X, p.D249H, and p.Q312X have been described in different populations [28, 55-57].

HAMP-related HC is caused by mutations in the *HAMP*. Reported variants include a frameshift mutation (93delG), a nonsense mutation (p.R56X), and a missense mutation (p.C70R), all of which impair functional hepcidin production. *HAMP* mutations are relatively rare, and heterozygosity may act as a modifier of the *HFE* phenotype [3, 27, 58, 59].

Clinically, *HJV*-related or *HAMP*-related HC classically presents in the second or third decades of life and shows similar penetrance in both sexes [60, 61]. It is associated with severe iron hyperabsorption and more pronounced clinical manifestations than *HFE*-related HC, frequently including cardiac and endocrine involvement. Although traditionally defined as an early-onset phenotype linked to *HJV* or *HAMP* variants, some overlap in age at diagnosis among molecular subtypes has been reported, and early severe phenotypes may also occur in defects involving other iron-related genes [5, 62].

TFR2-related HC is caused by mutations in the transferrin receptor 2 (*TFR2*) located on chromosome 7. The *TFR2* spans approximately 20 kB and numerous mutations and polymorphisms have been identified. Although it was initially thought that *HFE* formed dimers with *TFR2* in the duodenum, *TFR2* is now recognized as an independent regulator of hepcidin in hepatocytes [63, 64].

Clinically, *TFR2*-related HC is described as intermediate in presentation between *HFE*-related HC and *HJV*-related HC. In some cases, *TFR2* mutations may produce a phenotype resembling *HJV*-related or *HAMP*-related HC [65, 66].

The first pathogenic *TFR2* mutations were identified in two unrelated Sicilian families with HC but without p.C282Y mutations. Linkage mapping excluding *HFE* and *HJV* demonstrated homozygosity in the *TFR2* region on chromosome 7. Microsatellite analysis confirmed a cytosine to guanine substitution in exon 6, resulting in a nonsense mutation (p.Y250X). Subsequently, a second mutation was identified in a consanguineous family: Insertion of a cytosine in exon 2, leading to a nonsense mutation at amino acid position 60 (p.E60X) [25, 67].

SLC40A1-related HC results from mutations in the *SLC40A1* encoding FPN and follows an autosomal dominant pattern of inheritance. This form is distinct from other types of non-*HFE*-related HC and has been referred to as FPN disease [33, 68].

One type of *SLC40A1*-related HC, historically classified as HC but increasingly recognized as a distinct IO syndrome, is caused by loss of function variants in *SLC40A1* that reduce FPN expression or impair its iron export capability at the cell surface [33, 68]. Common genotypes include p.A77D and p.V162del [26, 69]. This condition is characterized by normal to low TS, iron retention in splenic and hepatic macrophages, and sometimes poor tolerance to standard phlebotomies. Iron becomes trapped within iron-recycling macrophages, particularly in the spleen, leading to reduced circulating iron, a tendency to iron-restricted erythropoiesis, and occasionally mild anemia following phlebotomy. Because of its distinctive clinical, biochemical, and pathological features, many authors have suggested adopting the term FPN disease [33, 68].

Another type of *SLC40A1*-related HC is also caused by mutations in *SLC40A1* but results from gain of function variants. In this form, FPN becomes resistant to hepcidin-induced internalization and degradation. The cysteine residue at position 326 plays a critical role in the interaction between hepcidin and FPN, and alterations at this site markedly reduce hepcidin-mediated internalization [70-72]. Very rare gain of function variants leads to FPN resistance to hepcidin and produces IO conditions that are phenotypically and biochemically indistinguishable from hepcidin-deficient HC [73]. Clinically, these two types of *SLC40A1*-related HC can be differentiated by TS levels [69].

Given their distinct molecular mechanisms and autosomal dominant inheritance pattern, FPN-related disorders are increasingly described according to functional variants [5].

6.3. Digenic Hemochromatosis (DI)

Digenic inheritance (DI) refers to pathologies representing the simplest form of multigenic etiology, involving more than one gene (and possibly environmental factors) [74]. True DI occurs when biallelic or even triallelic mutations in two distinct genes, in cis or in trans, are necessary and sufficient to cause a defined pathological condition. In true DI, a heterozygous mutation in each of the two genes alone is not associated with a recognizable phenotype [74].

In HC, some cases exhibit a "digenic" inheritance pattern resulting from the combination of pathogenic variants in two different genes involved in iron metabolism. Examples include single p.Cys282Tyr heterozygous variants occurring together with pathogenic variants in *HJV*, *HAMP*, or *TFR2* [75-77]. Although only a limited number of cases have been reported, digenic inheritance should be considered when the *HFE* genotype alone does not fully explain the clinical presentation, such as in patients with p.Cys282Tyr homozygosity and very early or severe IO [5].

6.4. Molecularly Undefined Hemochromatosis (Provisional Diagnosis)

Molecularly undefined HC refers to cases in which molecular characterization is not available after sequencing of the known genes and is therefore considered a provisional diagnosis. If an appropriately investigated patient presents with an unequivocal HC phenotype without cofactors but is not a p.Cys282Tyr homozygote -including cases of compound p.Cys282Tyr/p.His63Asp heterozygosity or p.His63Asp homozygosity- a provisional diagnosis of molecularly undefined HC can be established, and phlebotomy may be initiated [5].

7. Clinical Features

The clinical presentation of HC is heterogeneous and depends on the extent and duration of iron accumulation. Fatigue and joint pain are the most common early symptoms of the disease. Most HC patients develop a typical arthropathy, as described by Schumacher in 1964, affecting the metacarpophalangeal and proximal interphalangeal joints [78]. There are no specific clinical markers or radiological findings that reliably differentiate HC-related arthropathy from primary ankle osteoarthritis; therefore, diagnosis is mostly based on the patient's history [79].

Liver damage most frequently occurs in *HFE*-related HC [80]. The clinical presentation is diverse and includes asymptomatic increases in alanine aminotransferase and aspartate transaminase activity, followed by non-specific right upper quadrant or epigastric pain, and eventually signs of end-stage liver disease. SF level below 1000 ng/mL at the time of HC diagnosis identifies individuals who are at low risk of advanced liver fibrosis. Risk factors associated with advanced liver disease include the presence of comorbidities (i.e., diabetes and arthropathy), alcohol misuse, high ferritin levels, increased liver iron concentration, and phlebotomy [81].

Cardiac involvement in HC may manifest as cardiomyopathy (dilated or restrictive), arrhythmias including sinus node dysfunction and atrial fibrillation, and heart failure. Cardiac hypertrophy or dilation, systolic or diastolic dysfunction, and arrhythmias may occur as manifestations of cardiac HC [82]. When symptoms of heart failure appear, prognosis becomes poor. Cardiomyopathy is the second most common cause of death in patients with HC, making early prevention of cardiac complications crucial [83].

Diabetes in HC develop because of pancreatic islet damage due to IO and insulin resistance secondary to liver injury [84, 85]. Increased iron content raises

the risk of diabetes by reducing insulin secretion, promoting insulin resistance, and increasing hepatic gluconeogenesis [86].

Hypogonadism remains the second most prevalent endocrine complication in HC. It results from selective iron deposition in the pituitary gland, leading to alterations in hormonal secretion, and occurs most often in adolescent HC. Men may present with loss of libido, impotence, and osteoporosis, whereas women may experience amenorrhea or premature menopause [87].

8. Diagnosis and Treatment

Since clinical signs of overt IO in homozygotes usually develop in adult life, testing in children is not recommended before the age of 18 [81, 88]. In current practice, HC is typically suspected in individuals with no or minimal symptoms, increased SF without an alternative explanation, high TS, and evidence of increased liver iron stores on magnetic resonance imaging [1]. Considering the variety of clinical manifestations, diagnosis may be demanding, and a common initial presentation is an asymptomatic patient with mildly elevated liver enzymes [89]. Iron accumulation is slow and often asymptomatic; patients may remain symptom-free until the age of 30 despite having already accumulated 10-20 g of iron, mainly in the liver, heart, and endocrine glands [90].

The first step in the diagnostic approach in patients with suspected HC is the assessment of TS and SF [42]. TS is calculated as the ratio of serum iron to total iron-binding capacity or to transferrin concentration (multiplied by a correction factor) and expressed as a percentage. Normal TS values range between 20% and 45% [91]. A persistently elevated TS above 45% represents the earliest and most consistent biochemical indicator of HC across all subtypes and often precedes an increase in SF levels [6, 92].

When elevated TS and ferritin levels are detected, testing for *HFE* mutations remains the standard confirmatory step. Demonstration of p.Cys282Tyr homozygosity together with elevated SF and TS is considered sufficient for diagnosis. *HFE*-related HC most commonly results from p.C282Y homozygosity or compound heterozygosity (p.C282Y/p.H63D), with p.C282Y homozygosity present in more than 80% of overt cases [1, 81, 93]. In Caucasian populations, *HFE* genetic testing is indicated when high TS is confirmed, irrespective of parenchymal IO demonstration, although clinical penetrance is variable [18, 31, 94].

Liver biopsy is currently reserved mainly for prognostic purposes in patients with SF levels repeatedly above 1000 mg/L, to identify advanced fibrosis or subclinical cirrhosis [1]. Due to its invasiveness, biopsy has largely been replaced by noninvasive methods. Magnetic resonance imaging is now widely used to assess liver iron concentration, although there is no consensus regarding the optimal protocol [95-97]. Hepatic transient elastography is a reliable noninvasive tool for detecting liver fibrosis and reduces the need for biopsy to cases with indeterminate findings [98].

Treatment aims at preventing IO in early stages and removing excess iron from established disease. As humans have no specific pathway for iron excretion, therapeutic phlebotomy remains the first-line treatment [81, 99]. Treatment should begin once IO is confirmed, typically when TS exceeds 45% and ferritin is above 200 μg/L in females or when TS exceeds 50% and ferritin is above 300 μg/L in males and postmenopausal women. According to European Association for the Study of the Liver guidelines, ferritin targets are below 50 μg/L during the induction phase and below 100 μg/L during maintenance [81].

Erythrocytapheresis is an alternative extracorporeal procedure that selectively removes red blood cells and returns the remaining components to circulation [100]. Compared to phlebotomy, erythrocytapheresis reduces IO more efficiently and may require fewer procedures, particularly during induction therapy. Personalized erythrocytapheresis may be preferred in selected patients with adequate venous access and preserved cardiac function [99, 101, 102].

Iron chelation therapy is reserved for selected cases, such as patients with severe IO who cannot tolerate phlebotomy, severe non-*HFE* forms, poor venous access, anemia, or cardiac complications [93, 103]. Chelators can be administered orally, subcutaneously, or intravenously to promote iron excretion via urine or bile. In Europe, available agents include deferoxamine, deferiprone, and deferasirox, all approved by the United States Food and Drug Administration, each with specific advantages and limitations [104].

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