Hyperferritinemia

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Ferritin is one of the most frequently requested laboratory tests in primary and secondary care, and levels often deviate from reference ranges. Serving as an indirect marker for total body iron stores, low ferritin is highly specific for iron deficiency. Hyperferritinemia is, however, a non-specific finding, which is frequently overlooked in general practice. In routine medical practice, only 10% of cases are related to an iron overload, whilst the rest is seen as a result of acute phase reactions and reactive increases in ferritin due to underlying conditions. Differentiation of the presence or absence of an associated iron overload upon hyperferritinemia is essential, although often proves to be complex.

ferritin iron inflammation hemochromatosis

1. Introduction

Ferritin is one of the most commonly requested laboratory tests in general and secondary care, and levels deviating from reference ranges are a frequent finding [1]. Ascribed to its proportionality to total body iron stores, ferritin function is an indirect marker of iron status [2]. When concurrent inflammation is absent, ferritin has proven to be a highly specific and sensitive parameter for the diagnosis of iron deficiency [3][4]. High ferritin, hyperferritinemia, may indicate increased iron stores, but is more commonly seen upon acute phase reactions and as a result of ferritin being released from damaged cells such as hepatocytes in liver disease [5]. It may also be the result of increased synthesis and/or increased cellular secretion of ferritin upon various stimuli such as cytokines, oxidants, hypoxia, oncogenes, and growth factors [6].

Ferritin reference ranges may vary according to the analytical assay being used, although upper cut off is typically set to 200 µg/L in women and 300 µg/L in men [1][7]. In a prospective Danish population-based study, ferritin proved to be a strong predictor of premature death in the general population. Subjects with a baseline ferritin ≥200 µg/L were found to have increased risk of cause-specific mortality due to cancer, endocrinological disease, and cardiovascular disease, as well as increased total mortality compared to those with levels <200 µg/L. The study furthermore found a stepwise increase of this risk upon stepwise increases in ferritin, with the highest cumulative risk seen upon levels ≥600 µg/L [8].

Clinical interpretation of hyperferritinemia often proves to be complex, and ferritin >1000 µg/L is regarded as a non-specific marker of pathology. General practitioners seem somewhat unfamiliar with the appropriate management of hyperferritinemia, as >50% of primary care patients presenting with ferritin levels of such magnitude, and without any obvious clinical reason, are not referred to secondary care nor offered any further investigation [9]. Based on

the wide etiological spectrum, hyperferritinemia should prompt for further investigation through clinical examination and additional laboratory tests when the cause remains unknown [1][7].

2. Ferritin and Iron Homeostasis

Ferritin is mostly found as a cytosolic protein, where it plays an important role in the storage of intracellular iron, sequestering up to 4500 Fe^{3+} atoms per molecule. It is a 24-subunit molecule composed of two structurally distinct subunits, the light-chain (molecular weight 19 kilodalton) and the heavy-chain (molecular weight 21 kilodalton) [10]. Ferritin levels are upregulated and matched to intracellular iron levels through the activated translation of heavy- and light-chain mRNA upon high intracellular iron levels. The opposite is true upon low intracellular iron levels, resulting in prevented translation through specific sequences of heavy- and light-chain mRNA that block the recruitment of ribosomal subunits, as illustrated in Figure 1 [11].

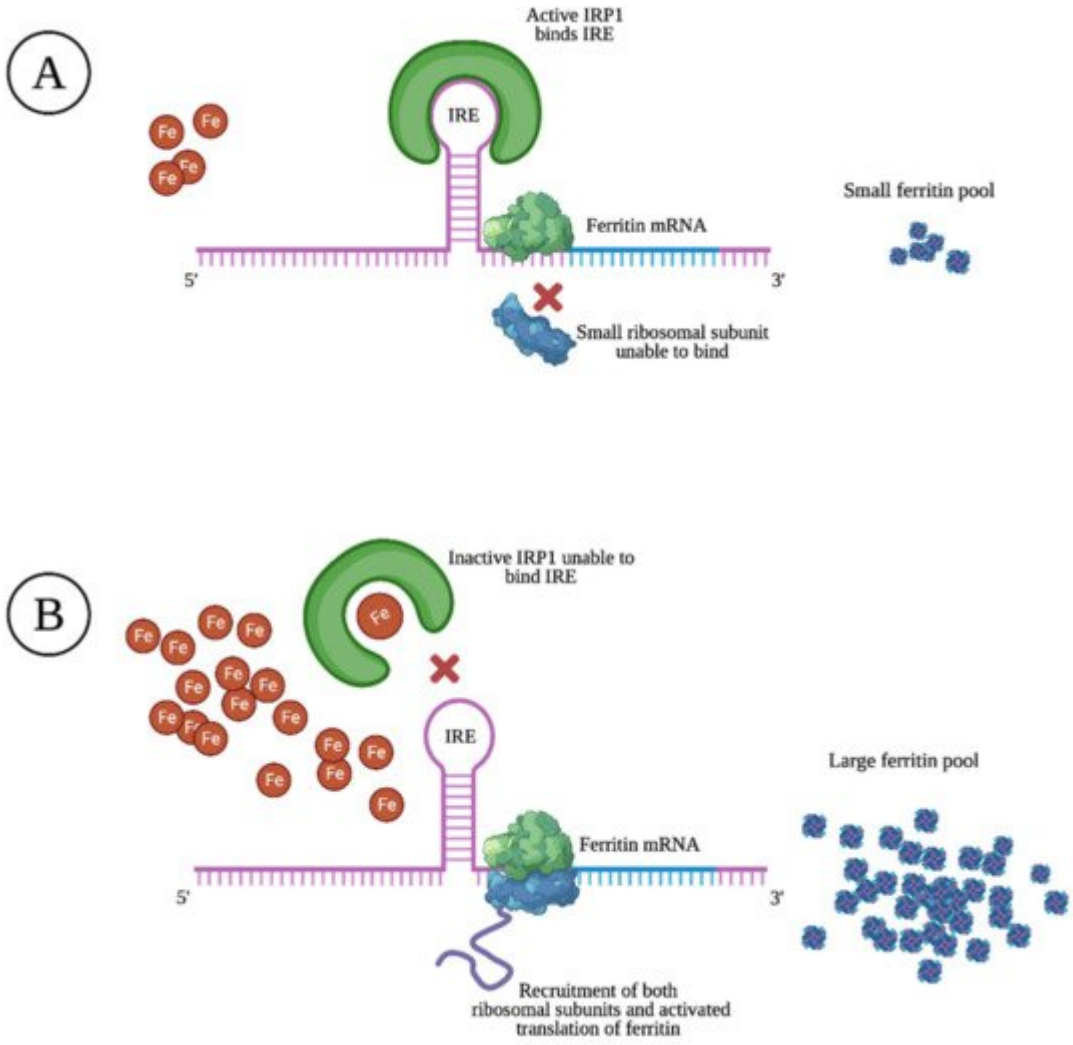

Figure 1. Schematic overview of regulated ferritin translation by the iron responsive element (IRE)/iron regulatory protein 1 (IRP1) system. Upon low intracellular iron levels (**A**), IRP1 binds to IRE, inhibiting the recruitment of the small ribosomal unit to mRNA, which results in a small ferritin pool. Upon high intracellular iron levels (**B**), iron

binds to IRP1, causing a transformational change that dissociates IRP1 from IRE. Both ribosomal subunits are now recruited to the mRNA and the translation of ferritin is activated. This coordinated IRP1/IRE binding with respect to iron levels stabilizes cellular iron through the synthesis of ferritin.

Within cells, limited amounts of free iron are found in a labile pool, which is biologically active in metabolism, although toxic if present in excess. By capturing and buffering iron, ferritin plays a key role in maintaining iron homeostasis [12]. Through its ferroxidase activity, heavy-chain ferritin subunits transform ferrous iron (Fe^{2+}) into the less toxic ferric state (Fe^{3+}). Homozygous murine knockouts of heavy-chain ferritin were found to be embryonically lethal, illustrating its importance in cellular defense, the detoxification of iron, and in maintaining iron bioavailability [13].

Through mechanisms that are not fully understood, small quantities of ferritin emerge into the serum. Controversial results regarding the subunit composition and iron content of ferritin found in serum are reported [14][15][16]. It is, however, assumed to be relatively iron-poor and almost entirely made up of light-chain subunits [6][17]. In the normal state, 50–80% of serum ferritin is glycosylated as a result of release from macrophages of the reticuloendothelial system (RES), and to some extent hepatocytes [1][18][19]. In certain hereditary hyperferritinemic states, glycosylation is almost 100% [20]. This supports a regulated release mechanism, whilst a higher percentage of non-glycosylated ferritin upon liver necrosis suggests hyperferritinemia to be the result of passive release, mainly due to cellular damage [1].

A schematic overview of the human iron metabolism is shown in Figure 2. The uptake of heme and non-heme iron takes place through the enterocytes of the proximal duodenum. Once inside the enterocyte, iron has two possible pathways—one portion remains intracellularly for use or for storage, while the rest is transported across the basolateral membrane through the iron exporter ferroportin, upon which it subsequently binds to transferrin. Effective efflux of iron through the basolateral membrane requires iron to be oxidized. This is mainly facilitated by the ferroxidase activity of plasma ceruloplasmin, which is synthesized in the liver, and its membrane-bound intestinal homolog hephaestin [21].

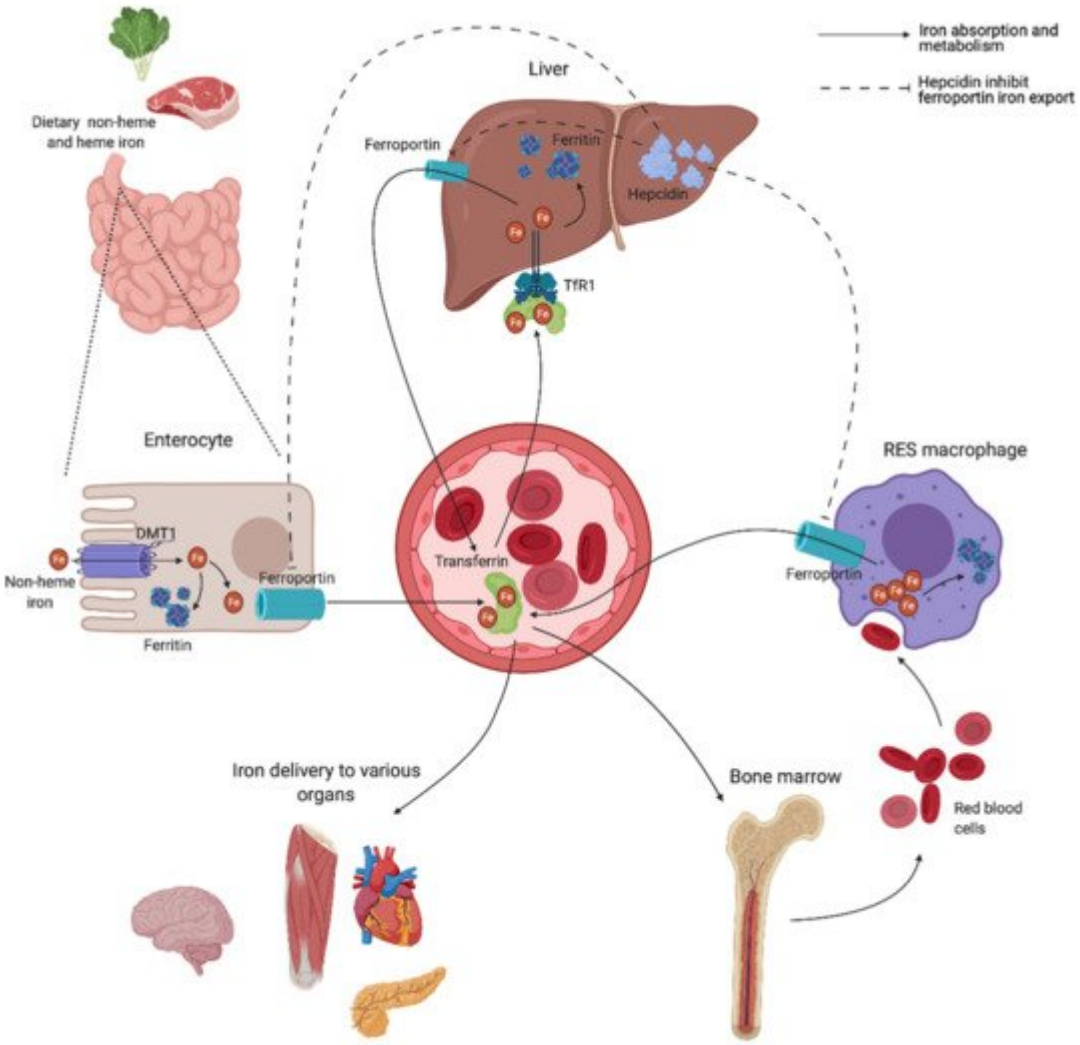

Figure 2. Body iron homeostasis and the hepcidin–ferroportin axis. Dietary non-heme is absorbed at the apical site of enterocytes of the jejunum through divalent metal transporter 1 (DMT1). One portion remains stored as ferritin inside the enterocyte, while the rest is transferred through the basolateral site via ferroportin. Iron subsequently binds transferrin and is further distributed throughout the body. Most iron is distributed to bone marrow for hemoglobin production. Senescent erythrocytes are phagocytosed by macrophages of the reticuloendothelial system (RES), and iron is catabolized from hemoglobin before subsequently re-entering circulation. Hepcidin produced in the liver regulates the systemic iron balance through binding to ferroporrtin. This binding facilitates the lysosomal degradation of the iron exporter, ultimately resulting in decreased serum iron concentrations.

Transferrin is capable of sequestering only two iron atoms, and is also predominantly synthesized in the liver [22]. It is the major serum iron-binding protein, keeping iron biologically accessible in an aqueous environment for delivery to cells through the transferrin receptor 1 (TfR1), allowing Fe^{2+} atoms to be internalized through receptor-mediated endocytosis. Almost all tissue and cells express TfR1. Cells with increased iron demand have a particularly high expression, including rapidly dividing cells such as activated lymphocytes, as well as erythroblasts, which depend on iron delivery for hemoglobin production in erythropoiesis [21][23].

Ferroportin is also expressed in macrophages of the RES, involved in the recycling of iron from the hemoglobin of old red blood cells (RBCs) [24]. Irrespective of levels, iron is eliminated at a basal rate through the desquamation of skin and intestinal epithelium, and through blood loss in fertile women [25]. Both intracellular ferritin and the intestinal absorption of iron are important regulators of iron homeostasis, due to a lack of active physiological iron excretion mechanisms. Systemic regulation of metabolism and the modulation of availability to meet iron needs are predominantly mediated through the peptide hormone hepcidin and the hepcidin–ferroportin axis (Figure 2).

Hepcidin is mainly synthesized by hepatocytes, and facilitates synchronized iron metabolism between various organs, protecting the body against iron overload [26]. It is considered a negative regulator of serum iron levels as it mediates ubiquitin-mediated degradation of ferroportin, which shuts off export of iron to plasma. Iron is consequently retained in the intestinal epithelium, while iron recovery from senescent RBCs is interrupted by inhibited release from RES macrophages [21]. Hepcidin also facilitates a reduction in iron uptake by enterocytes through inhibited transcription and increased degradation of the intestinal iron transporter divalent metal transporter 1 (DMT1) [27][28]. Dysregulation of the hepcidin–ferroportin axis, promoting uncontrolled intestinal absorption and uninhibited cellular export of iron, is a characteristic feature in various iron-loading conditions exhibiting high serum iron levels [29][30], and is later discussed.

Finally, whether hyperferritinemia caused by disease processes has a causal role or a role in cellular protection is not fully established yet. Apart from ferritin's iron-storing properties, the biological purpose of it remains partly unknown. Nevertheless, increasing evidence of ferritin subsuming additional physiological roles is emerging, and it is now suggested as molecule contributing to inflammation, iron delivery and angiogenesis, as well as cell signaling, proliferation and differentiation [18][21]. Increased understanding of these mechanisms might grant additional insight into the pathophysiology of iron overload, cancer, and inflammation, which may contribute to the development of novel therapeutic targets.

3. Etiology

Underlying conditions upon hyperferritinemia, with and without an associated iron overload, are summed up in Table 1. Transferrin saturation is a useful parameter for the distinction of the presence or absence of an iron overload upon hyperferritinemia. It is a calculated value reflecting the proportion of iron-binding sites on transferrin that are occupied [7]. Whilst a normal transferrin saturation usually excludes pathologically increased iron absorption, it does not necessarily exclude the presence of an iron overload [1][31][32][33]. Increases in transferrin saturation are not always equivalent to an iron overload either, and the interpretation of this parameter therefore requires careful considerations [29].

Table 1. Underlying conditions in hyperferritinemia with and without an associated iron overload.

Hyperferritinemia without iron overload	**Common causes**
	Cellular damage

	Metabolic syndrome and obesity
	Insulin resistance/diabetes mellitus
	Excessive alcohol consumption
	Inflammatory and infectious conditions (septic shock, COVID-19)
	Malignancy (solid and hematological)
	Rare causes
	Benign hyperferritinemia/HHCS
	Immune-mediated syndromes (primary and secondary HLH, adult-onset Still's disease) Gaucher disease
Hyperferritinemia with or without iron overload	**Common causes**
	Chronic liver disease (cirrhosis, alcoholic liver disease, NAFLD, viral hepatitis, porphyria cutanea tarda)
Hyperferritinemia with iron overload	**Common causes**
	HFE hemochromatosis
	Dysmetabolic iron overloading syndrome
	Iron-loading anemias (congenital or acquired)
	Iatrogenic iron overload (RBC transfusion, parenteral iron administration)
	African iron overload
	Rare causes
	Non-*HFE* hereditary hemochromatosis Ferroportin disease
	Aceruloplasminemia/hypoceruloplasminemia Atransferrinemia/hypotransferrinemia

This differentiation of hyperferritinemia is essential, as the management, treatment, and prognosis greatly differ for the two entities. Estimates show that only 10% of clinical cases of hyperferritinemia in routine medical practice are associated with an iron overload. For the rest, one of the following underlying causes attributing to a reactive increase are usually identified: inflammation, metabolic syndrome, chronic alcohol consumption, cellular damage, and malignancy [34][35][36].

COVID-19, coronavirus disease 2019; HHCS, hereditary hyperferritinemia cataract syndrome; HLH, hemophagocytic lymphohistiocytosis; NAFLD, non-alcoholic fatty liver disease; RBC, red blood cell.

3.1. Hyperferritinemia without Iron Overload

All forms of inflammation, regardless of its cause, may elevate ferritin levels, and are thus recognized as an acute phase reactant. Pro-inflammatory cytokines stimulate the synthesis of ferritin and hepcidin, leading to

hyperferritinemia, iron retention in macrophages, and less iron being available for erythropoiesis due to the redistribution of body iron from RBCs to tissue cells [37]. This is commonly known as anemia of inflammation, which is part of the innate immune defense against invading pathogens and tumor progression [38][39].

Prostaglandins involved in inflammatory and febrile responses, as well as viral replication, have also been demonstrated to induce light-chain ferritin synthesis [6]. Inflammation may induce apoptotic pathways through cytokines, contributing to cellular damage with the concurrent release of ferritin [40], and mechanisms of reactive increases in ferritin thus work synergistically and cannot solely explain the cause of hyperferritinemia. An example of this is seen in autoimmune diseases and cancer, with increased synthesis of ferritin due to inflammation as well as induced cellular damage with the release of ferritin [6][18][40].

If common clinical conditions can be excluded, clinicians must recognize hyperferritinemia as a clue to various autoimmune, inflammatory and genetic disorders. Rare immune-mediated conditions such as hemophagocytic lymphohistiocytosis (HLH), where monocytes and macrophages seem to play a vital role through the production and release of ferritin, may cause extremely elevated ferritin levels [41]. It has been proposed that these high levels are not only a product of inflammation, but also play a pathogenic role themselves, causing extreme expression of additional inflammatory mediators, known as a cytokine storm [41].

Trends in ferritin have proven to be a prognostic marker in pediatric HLH patients, as a decrease <50% within 10 weeks after diagnosis showed a 17 times higher mortality risk compared to those with a decrease ≥96% [42]. Ferritin >10,000 µg/L is highly specific and sensitive for the diagnosis of HLH in pediatric patients [43]. This is, however, not true in the adult patient population, as a variety of conditions such as chronic kidney disease, infection, and hematological malignancies may exhibit ferritin levels >50,000 µg/L [44].

Coronavirus disease 2019 (COVID-19) emerged as a pandemic in 2020 and is associated with a hyperactive immune response upon severe disease, which correlates with a high degree of morbidity and mortality. All patients with severe COVID-19 should be screened for hyperinflammation using laboratory parameters such as ferritin [45], which has proven to be a prognostic marker and an indicator of inflammation in these patients [46]. Extreme hyperferritinemia with a cytokine profile similar to that seen in secondary HLH is reported in a subgroup of patients. Serial measurements of ferritin may help monitor this hyperinflammatory state and treatment response, as well as predict worsening and mortality in hospitalized COVID-19 patients [47].

Hematological and various solid malignancies may also induce elevations in ferritin, thought to be the result of both inflammation and cytolysis [1][18], and ferritin levels >1000 µg/L are often seen upon metastatic cancer [48]. No studies have provided evidence of ferritin contributing to the etiology of cancer, rather than merely being a marker for the presence of it. However, several pro-oncogenic functions of ferritin are suggested, as free iron released from ferritin and hemosiderin may potentially catalyze the formation of powerful oxidizing agents capable of promoting lipid peroxidation, mutagenesis, DNA strand break, the activation of oncogenes, and inhibition of tumor suppressors [18].

Cellular damage may induce great rises in ferritin levels. With the liver being the major storage organ of iron, ferritin may reach >10,000 µg/L upon acute and chronic hepatopathy, including alcoholic liver disease and non-alcoholic fatty liver disease (NAFLD), and is partly as a result of cellular damage [7][49]. It should be noted that low serum transferrin due to the impaired synthetic function of the liver upon chronic liver disease may be misleading in the diagnostic workup, as this potentially results in an elevated transferrin saturation, even in the absence of an iron overload [7][50].

An isolated ferritin <1000 µg/L due to daily alcohol consumption is a common presentation [7], seen in up to 40–70% of chronic alcoholics [51]. Experimental models have shown that alcohol promotes the direct stimulation of ferritin synthesis and suppresses hepatic hepcidin expression [52][53], which may account for the linear correlation between alcohol intake and serum iron indices in alcoholics [54][55]. Clinical trials have furthermore shown increases in serum iron and ferritin to be greater upon beer consumption compared to the consumption of wine and spirits [56]. Functioning as both a diagnostic and therapeutic test for alcohol-induced hyperferritinemia, withdrawal results in a rapid decline in ferritin [57].

Liver steatosis and insulin resistance is a frequent finding in patients referred for suspected hemochromatosis on the basis of hyperferritinemia [58]. Insulin has been implicated to induce ferritin synthesis at mRNA level in experimental models, proposing a novel explanation for the hyperferritinemia commonly seen upon insulin resistance [6]. The association between ferritin and metabolic syndrome has been suggested being mainly mediated by undiagnosed NAFLD, which is considered to be the hepatic manifestation of metabolic syndrome.

Although subclinical inflammation commonly seen upon metabolic syndrome and NAFLD also influence the described association, C-reactive protein (CRP) did not correlate with ferritin levels in the general population or in patients with metabolic syndrome. Studies have also found ferritin in healthy individuals to remain positively correlated with blood glucose and insulin resistance after adjusting for CRP levels [59][60]. These results show that inflammation is unlikely to play a predominant role in determining ferritin levels in these patients [61][62][63][64], and that the pathogenesis is also related to steatosis, hyperinsulinemia, and cellular damage [65]. NAFLD and its association with perturbations of iron homeostasis is also becoming increasingly evident [64], and is discussed later.

Rare genetic causes of hyperferritinemia without an associated iron overload include hereditary hyperferritinemia cataract syndrome (HHCS), caused by variants in the ferritin light-chain gene (*FTL* gene). After common causes have been ruled out, such genetic variants may help explain rare clinical cases of unexpected and isolated hyperferritinemia. HHCS is characterized by an unleashed ferritin light-chain synthesis, ultimately causing bilateral cataracts at an early age due to the deposition of ferritin in the ocular lenses [66]. Variants in the *FTL* gene causing an isolated hyperferritinemia without any symptoms are also reported and are referred to as benign hyperferritinemia [20][67].

Another rare genetic cause related to hyperferritinemia with a normal transferrin saturation is Gaucher disease. It is the most common lysosomal storage disorder and is frequently underdiagnosed, even when all clinical symptoms

are present. Gaucher disease should be considered when patients present with unexplained cytopenia and hepatosplenomegaly [68][69].

3.2. Hyperferritinemia with Iron Overload

Iron overloading diseases are classified as (1) primary when caused by an inherited defect in the regulation of iron balance and (2) secondary when acquired as a result of underlying congenital or acquired conditions [70]. During iron-loading conditions where the iron binding capacity of transferrin is exceeded and a high transferrin saturation is observed, non-transferrin bound iron (NTBI) enters circulation. NTBI predominantly enters hepatocytes, but also the parenchymal cells of the heart, pancreas, thyroid, and central nervous system. This diffuse distribution of iron is associated with organ dysfunction through cell death and complications such as fibrosis, atherosclerosis, and carcinogenesis [23][30][71].

3.2.1. Primary Iron Overload

Primary iron overload, synonymous with hereditary hemochromatosis (HH), is, for all practical purposes, the leading cause of severe iron overload. HH is frequently unrecognized in primary care due to a preclinical phase of years [72]. Associated complications such as liver fibrosis and endocrinological disease are serious and potentially preventable, making timely diagnosis and treatment important [8][33]. HH is a result of the previously mentioned dysfunction of the hepcidin–ferroportin regulatory axis, leading to increased serum iron, iron depleted macrophages, accelerated dietary iron absorption, and, finally, parenchymal iron overload in the majority of cases [73]. A schematic overview of the molecular basis of HH due to impaired hepcidin synthesis is shown in Figure 3.

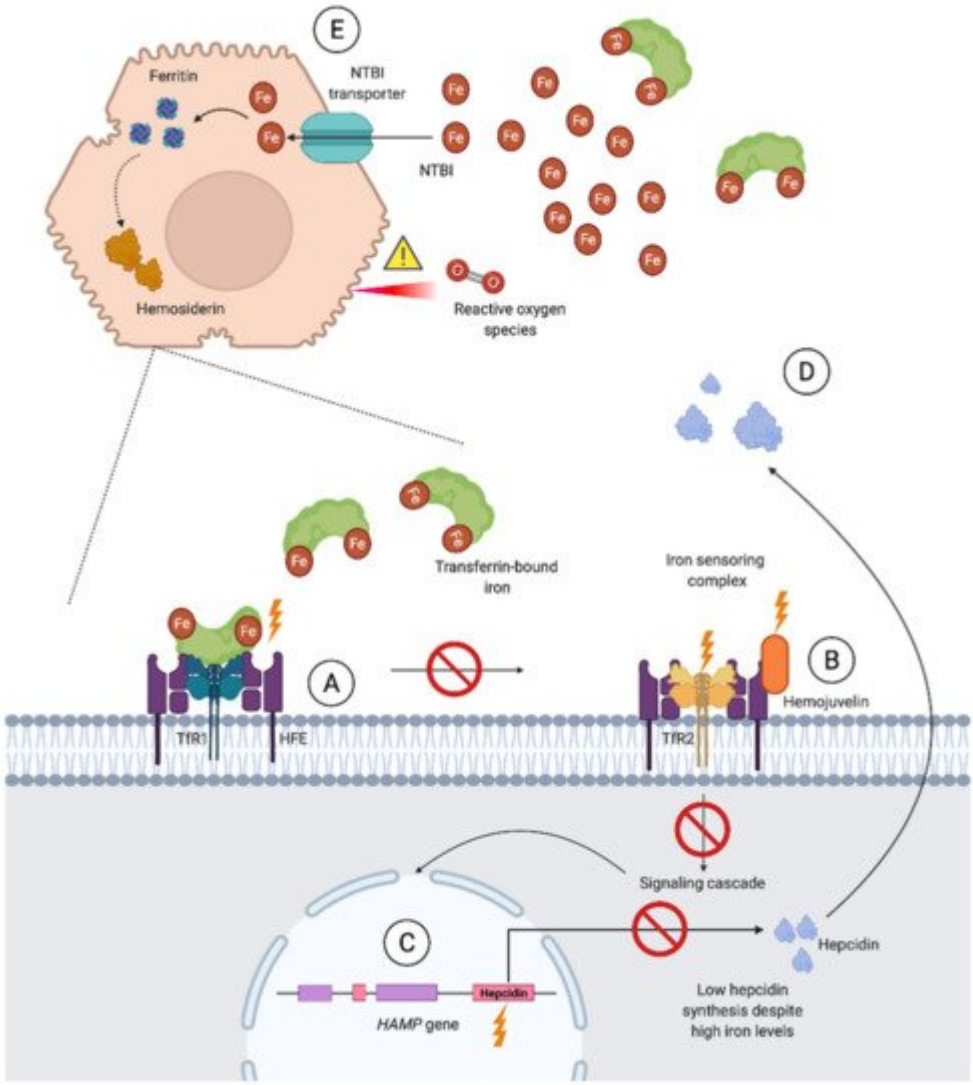

Figure 3. Schematic overview of hereditary hemochromatosis (HH) associated with impaired hepcidin expression. *HFE* disease-associated variants (type 1 HH) cause impaired assembly of the iron sensing complex (**A**), as transferrin binding to transferrin receptor 1 (TfR1) normally competes with and releases HFE to interact with transferrin receptor 2 (TfR2). Disease-associated variants of the *HJV* (type 2A HH) and *TFR2* (type 3 HH) genes, encoding subunits of the iron sensing complex, cause impaired function of this complex which normally regulates hepcidin transcription through a signaling cascade (**B**). Disease-associated variants of the *HAMP* (hepcidin) gene (type 2B HH) cause reduced hepcidin levels, despite a functioning iron sensing complex (**C**). An impaired hepcidin–ferroportin axis (**D**) results in uncontrolled intestinal iron absorption and the release of iron stores from macrophages and parenchymal cells, and, accordingly, high serum iron levels. When transferrin saturation is highly elevated, the transferrin iron-binding capacity is exceeded and non-transferrin bound iron (NTBI) enters circulation. NTBI is a more toxic form than transferrin-bound iron, capable of producing reactive oxygen species, which are involved in the cellular damage seen upon iron-loading conditions, for example, liver fibrosis and cirrhosis. NTBI is eliminated from circulation through transporters mainly expressed on hepatocytes (**E**). Here, it is subsequently stored in iron-storing complexes such as ferritin and hemosiderin to limit cellular damage.

Approximately 82–90% of clinical disease in Caucasian HH patients is related to homozygosity for the missense variant C282Y of the homeostatic iron regulator gene (*HFE* gene), referred to as hemochromatosis type 1 or *HFE* hemochromatosis [23][29][74][75]. It is the most common monogenic disorder in northern European populations, with a prevalence of 0.5% [31][35]. *HFE* hemochromatosis is, however, far less common, and practically absent, among individuals of Asian and Hispanic heritage [32][33]. Penetrance is incomplete, with phenotypic expression in the form of elevated ferritin levels occurring in 80% of male and 50% of female C282Y homozygotes. Furthermore, proportion of C282Y homozygotes with definite disease manifestations such as liver disease or arthritis greatly varies between genders, and is significantly lower in women (1%) than in men (28%) [1][76].

While C282Y is considered the “major” *HFE* hemochromatosis-associated variant, H63D is considered to be the “minor” variant, which seldom causes significant iron overload, even when it is present in compound heterozygosity with C282Y [31]. Phenotypic penetrance in C282Y/H63D compound heterozygotes is approximately 2–5% [77], although only 0.5–2% of these develop clinical signs of iron overload [35][78][79]. This overall low disease penetrance of *HFE* hemochromatosis is partly the rationale for recommendations stating that general population screening for *HFE* hemochromatosis through genetic testing is *not* recommended [31][36][80].

Iron overload may be related to the C282Y or H63D variant in compound heterozygosity with rarer *HFE* variants. It is suggested that these variants are the most frequent cause of iron overload in cases of non-C282Y homozygous *HFE* hemochromatosis [81]. When such rare *HFE* variants are not involved, accompanied environmental or host risk factors are identified in practically all cases of iron overload in patients with *HFE* hemochromatosis related to C282Y or H63D heterozygosity, C282Y/H63D compound heterozygosity, or H63D homozygosity.

This includes comorbidities such as metabolic syndrome, hepatopathy, diabetes, or chronic alcohol abuse, ultimately contributing to iron homeostasis dysfunction more than the genetic abnormality itself [1][3][31][77][80]. When an unexpected severe iron overload is detected in these patients, further investigation for possible digenic inheritance or variants in other contributing genes might be of interest [1][29], as this may affect phenotypic and clinical expression [31][82]. It should also be noted that transferrin saturation predicts hepatic iron overload (HIO) better in C282Y homozygotes than in non-C282Y homozygotes and non-*HFE* iron overload (type 2–4 HH). Accordingly, iron overload may be proven in patients with elevated ferritin, despite them having normal transferrin saturation [7][31].

In areas such as Southern Europe and Asia, non-*HFE* HH represents a larger proportion of clinical HH cases [83]. This is a heterogenous group caused by genetic variants unrelated to the *HFE* gene, and genetic testing for these is largely unavailable [31]. Type 2 HH, known as juvenile hemochromatosis, is caused by variants of the hepcidin (*HAMP*) and hemojuvelin (*HJV*) genes, while type 3 HH is related to variants of the TfR2 (*TFR2*) gene.

Finally, type 4 HH is seen as a result of ferroportin 1 (*FPN1*) genetic variants [84]. It is distinct from type 1-3 HH as it is not related to the impaired synthesis of hepcidin, but rather the impaired function of ferroportin (type 4A HH), known as ferroportin disease, or ferroportin being resistant to hepcidin stimulus (type 4B HH). While the latter

results in a clinical phenotype similar to that of *HFE* hemochromatosis, a more distinct clinical picture is seen in ferroportin disease, with iron retention mainly being localized to the macrophages of the spleen, liver, and spine, with marginal delivery of iron to circulating transferrin, resulting in a normal or low transferrin saturation (Figure 4). Such a triad of iron retention, shown by abdominal magnetic resonance imaging (MRI), enables the characterization and diagnosis of ferroportin disease. It should also be noted that the clinical expression of ferroportin disease tends to be milder than that of other forms of HH. A non-aggressive phlebotomy regimen is thus recommended in these patients due to the risk of anemia [85]. When anemia occurs during repeated phlebotomies in patients with primary iron overload, ferroportin disease should be considered [86].

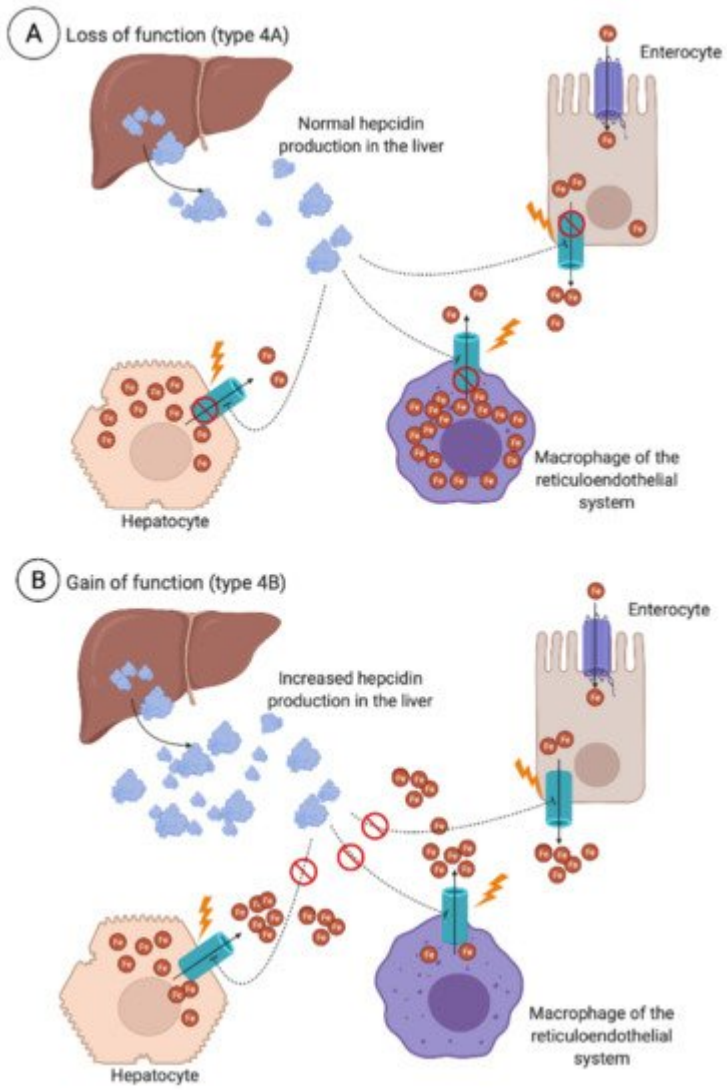

Figure 4. Variants of the *FPN1* (SLC40A1) gene encoding the iron exporter ferroportin involved in type 4 hereditary hemochromatosis (HH). Loss-of-function variants (**A**) impair the iron-export capability or expression of ferroportin, leading to iron accumulation mainly in cells such as tissue macrophages and discrete accumulation in parenchymal cells, decreased iron delivery to circulating transferrin causing an inappropriately low transferrin saturation, and decreased iron delivery for hemoglobin production. This is referred to as ferroportin disease, or type 4A HH. Gain-of-function variants (**B**), however, make ferroportin resistant to hepcidin-induced degradation, which normally inhibits the export of iron. This results in a similar impairment of the hepcidin–ferroportin axis, as seen in type 1-3

HH, with high serum iron concentrations and transferrin saturation, and iron mainly accumulating in parenchymal cells and hepatocytes. This is often referred to as type 4B HH.

Type 4A HH is highly prevalent in African populations, making *FPN1* the gene most frequently associated with hereditary hyperferritinemia in this area. Numerous variants associated with ferroportin disease have also been identified in people of Thai, Japanese, European, and French-Canadian heritage [85].

Extremely rare causes of primary iron overload include genetic defects of the iron metabolism caused by variants in the ceruloplasmin and transferrin gene. When ceruloplasmin activity is impaired (hypoceruloplasminemia) or absent (aceruloplasminemia) due to such genetic variants, marked iron overload ultimately develops as a result of cellular iron retention. Brain iron accumulation in aceruloplasminemia, which causes progressive neurological symptoms, makes this disorder unique among other systemic iron overload syndromes [87]. Hypotransferrinemia with low transferrin concentrations also causes systemic iron overload and is characterized by impaired erythropoiesis and microcytic anemia due to the marked reduction in iron delivery to bone marrow, which, in turn, increases iron absorption. Only a dozen cases of atransferrinemia with the complete absence of plasma transferrin have been reported [88].

Finally, oral iron ingestion does not cause iron overload except in patients with ineffective erythropoiesis and in genetically predisposed individuals [31]. African iron overload, which is seen in up to 10% of adults in rural societies in Sub-Saharan Africa, was thought to be exclusively caused by increased dietary iron through the consumption of a traditional beer containing high amounts of dissolved iron from its preparation in iron drums [89]. Recent studies of pedigrees, however, suggest that, in addition to a high dietary iron content, the disorder does, in fact, have a genetic component caused by variants in genes distinct from the *HFE* gene [90], although the putative has not yet been identified.

3.2.2. Secondary Iron Overload

Secondary iron overload occurs in individuals who absorb or store excessive amounts of iron as a result of underlying diseases other than those previously mentioned or due to iatrogenic iron overload through frequent RBC transfusions or parenteral iron administration. Owing to the liver's major role in iron homeostasis, hyperferritinemia in liver diseases may also be associated with an iron overload. Reduced liver function in chronic liver diseases is associated with impaired hepcidin and transferrin synthesis, hepatic iron overload (HIO), as well as increased levels of circulating NTBI [50][91]. Consequently, iron overload has been proposed as a cofactor in these conditions, but its exact role remains unclear [92]. While HH may cause severe iron overload if left untreated, secondary iron overload due to chronic liver diseases usually remains minimal to modest [93].

HIO is present in up to 50% of patients with alcoholic liver disease [50]. Cirrhosis due to chronic hepatitis C contributes to hepatic iron accumulation [50], and *HFE* variants such as C282Y heterozygosity have shown to accelerate hepatic fibrosis and HIO in these patients [94]. Porphyria cutanea tarda should be considered when hyperferritinemia is seen with a photosensitive rash and liver dysfunction. This is an acquired liver disease in 80%

of clinical cases, and exogenous factors (e.g., alcohol, smoking, and hepatitis C) are a prerequisite for inducing HIO in these patients [1][48][95].

One third of patients with NAFLD and metabolic syndrome have increased body iron stores, known as dysmetabolic iron overload syndrome—a much more common condition than clinically recognized by physicians. These patients most often exhibit a normal transferrin saturation and have been found to have increased hepcidin concentrations with a mixed pattern of iron retention in both hepatocytes and macrophages [96]. Studies suggest this to be the result of hepcidin-resistance and a compensatory mechanism to prevent and counteract iron accumulation [96][97][98].

Although iron deficiency anemia affects nearly all chronic kidney disease and long term hemodialysis patients as the disease progress [99], iatrogenic iron overload attributed to RBCs transfusions due to hypoproliferative erythroid marrow and intravenous iron to ensure sufficient available iron during therapy is also recognized as a complication in some of these patients. Mild to severe HIO measured by MRI was observed in 84% of hemodialysis patients treated with erythropoietin and regular intravenous iron supplementation, in keeping with guidelines, although transferrin saturation was normal for all [100]. Hyperferritinemia seen in chronic kidney disease patients on hemodialysis is also partly a result of systemic inflammation, with ferritin levels correlating positively with the severity of it [101].

Prolonged parenteral administration of iron or the transfusion of RBCs in patients with chronic anemia such as thalassemias or dyserythropoietic, aplastic, sideroblastic, and hemolytic anemias will also most often result in iron overload. Tissue deposition becomes significant when more than 40 units of RBCs are transfused [23]. Iron is deposited in the macrophages of the RES prior to the iron-loading of the liver and heart parenchyma, ultimately leading to progressive heart and liver failure if left untreated [91].

Even in the absence of transfusions, a variety of blood cell disorders such as myelodysplastic syndrome, thalassemias, and other iron-loading anemias are associated with increased iron absorption. Hepcidin is down-regulated by signaling molecules associated with anemia and hypoxia upon these conditions [30]. Ineffective erythropoiesis, therefore, leads to low hepcidin levels, and, subsequently, increased intestinal iron absorption. The hormone erythroferrone, secreted by erythroid precursors, suppresses hepcidin and increases the amount of iron available for hemoglobin synthesis [102]. Loss of this hormone in thalassemic knock out mice led to the full restoration of hepcidin mRNA expression and a significant reduction in the iron content of the liver and spleen [103], making erythroferrone a potential therapeutic target upon secondary iron overload in anemias and other blood cell disorders.

References

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