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Iron Chelators in The Management of Hereditary Hemochromatosis

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Abstract

Hereditary Hemochromatosis (HH) is a genetic disorder characterized by abnormal iron metabolism, leading to excessive iron absorption and deposition in various organs. This iron overload can result in severe complications, including liver cirrhosis, diabetes, and cardiomyopathy. Traditional treatment approaches for HH primarily involve therapeutic phlebotomy to reduce iron levels; however, the emergence of iron chelators has expanded therapeutic options. This review explores the role of iron chelators in the management of Hereditary Hemochromatosis. We delve into the mechanisms of iron chelation, discussing how these agents bind and eliminate excess iron, preventing its accumulation in vital organs. Various iron chelators, including deferoxamine, deferiprone, and deferasirox, are scrutinized for their efficacy, safety profiles, and potential side effects. While therapeutic phlebotomy remains a cornerstone in HH management, the integration of iron chelators as adjunctive or alternative therapies presents a promising avenue.

Keywords*: Iron Chelators, Management, Hereditary Hemochromatosis*

Introduction

The goal of therapy in patients with iron overload disorders is to remove the iron before it can produce irreversible parenchymal damage. This is achieved via chelation therapy or Venesection, depending on the underlying cause(1). A Cochrane data base review of interventions for hereditary haemochromatosis found that phlebotomy remained the treatment of choice in hereditary haemochromatosis that required bloodletting, but no data from randomized trials provided evidence of benefit from any form of bloodletting in these patients (2). In patients with haemochromatosis and heart disease, anemia, or poor venous access, treatment with iron chelation agents is recommended (1) because secondary haemochromatosis is due to hereditary or acquired anemia, phlebotomy is not a suitable means of removing excess iron in this situation. Rather, the treatment is based on the targeted elimination of iron by means of iron chelators (3). The main

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purpose of chelation therapy is the entire elimination and prevention of iron overload. Chelation can clear away the surplus iron load and keep iron at natural levels. Treatment of patients with iron chelators can decrease the toxic effect of iron overload. Iron chelators enter cells, bind free iron, and remove it from the body. In young patients with severe chronic anemia, iron chelation therapy is highly accepted; however, for older patients suffering from the same illness, the same treatment is doubtful due to myelodysplastic syndromes (3). Some aspects of haematological disorders, such as the stimulation of platelet production, inhibition of leukemic cell proliferation, and induction of their differentiation, can also be benefited with iron chelator activity (4,5).

Iron is a vital component of the human body, and its concentration is strictly regulated. While iron is essential for life, it can also be toxic to the cells (6). Iron overload is associated with multiple organ damage due to a lack of ways to protect cells from iron overload and iron function in the production of free radicals. Free radicals production due to iron overload causes serious complicated and side effects such as mental retardation, early neurological diseases (Alzheimer's, multiple sclerosis, Huntington), delays in sexual maturity, impotence and infertility, cardiac dysfunction (arrhythmia, cardiomyopathy, haemosiderosis), liver cirrhosis, liver cancer and hepatitis and metabolism dysfunction (diabetes, hypogonadism, thyroid disorders, parathyroid and less level of adrenal glands). The side effects and other complications include arthritis, chronic fatigue, depression, hair loss, skin color changing, abdominal pain, splenomegaly, infection with HIV, venous thrombosis and osteoporosis (7).

Iron overload is iron deposition in multiple organs along with serum ferritin value over 1000 µg/L (4). Iron overload, either genetically or acquired, among genetic disorders that causes iron overload including hereditary haemochromatosis (all types), African iron overload, sickle cell disease, major betathalassemia, sideroblastic anemia, enzyme deficiency (pyruvate kinase, G6PD) and rare disorders of transporting proteins (Atransferrinemia, Aceruloplasminemia), hereditary haemochromatosis is the most common genetic causes of iron overload where Small intestine absorbs high level iron that accumulates in liver, pancreas and some parts of brain which results to impair vital function (1,4).

Prevalence of Hereditary Haemochromatosis

Type 1 haemochromatosis is one of the most common genetic disorders in the United States, affecting about 1 million people. It most often affects people of Northern European descent. The other types of haemochromatosis are considered rare and have been studied in only a small number of families worldwide (8). Among most populations of northern European ancestry, the prevalence of individuals homozygous for HFEp.Cys282Tyr is 2:1,000 to 5:1,000. In non-Hispanic whites in North America, the prevalence of p.Cys282Tyr homozygotes is 1:200 to 1:400. Among African Americans, p.Cys282Tyr homozygotes are rare (1:6,781). The prevalence of heterozygotes is 1:775. Among Asians, p.Cys282Tyr homozygotes are very rare (1:25,000) with prevalence of heterozygotes as 1:1,000. Among Hispanics, the prevalence of p.Cys282Tyr homozygotes and heterozygotes is 0.027% and 3.0%, respectively. Heterozygosity for p.His63Asp is common in most populations (northern Europeans: 25%; Hispanics: 18%; African Americans: 6%; Asians: 8.5%). Approximately one third of northern European whites are heterozygous for either p.Cys282Tyr or p.His63Asp (9).

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History of Hereditary Haemochromatosis and Iron Chelation Therapy

The disease was first described in 1865 by Armand Trousseau in a report on diabetes in patients presenting with a bronze pigmentation of their skin (10). Two years later, Perls developed the first practical method for the analysis of iron in tissue. Despite Trousseau not associating diabetes with iron accumulation, the recognition that infiltration of the pancreas with iron might disrupt endocrine function resulting in diabetes was made by History Friedrich Daniel von Recklinghausen in 1890 (11). In 1935, English gerontologist Joseph Sheldon described the cases of haemochromatosis. He established this as the name of the disorder and his detailed monograph. Despite lacking the modern molecular techniques accessible today, he came to accurate conclusions that describe haemochromatosis disease as an inborn error of metabolism where this inherited disorder can increase the absorption of iron and thus cause tissue damage due to iron deposition. Moreover, he rejected theories that alcohol, drug, and other factors contribute to the disorder (12). The clinical case series from 1935 to 1955 indicated that haemochromatosis was more common than had been acknowledged. During the 1960s, MacDonald, a pathologist at Boston City Hospital, diverted attention away from the true cause of haemochromatosis. He believed that haemochromatosis was a nutritional condition because he observed many drunken patients of Irish ancestry. During this period of time, other investigators reported additional evidence suggesting that a genetic factor could play a central role in the absorption of iron in people with haemochromatosis. However, alcohol consumption is known to increase the risk of liver injury in haemochromatosis. This finding is consistent with the concept that excess iron metabolism is a primary cause of haemochromatosis disease (13). Finally, in 1976, Marcel Simon and his collaborators confirmed that haemochromatosis is an autosomal recessive disorder that has a link to the human leukocyte antigen (HLA) region of the genome. It took 20 years for researchers at Mercator Genetics to effectively identify and clone the haemochromatosis genes using a positional cloning approach (14). In 1996, Feder and associates identified HFE, which is a major histocompatibility complex (MHC) gene. They found that 83% of patients have homozygosity for a missense mutation (C282Y) in the HFE gene (15). Finally, several groups reported their findings in a series of patients with haemochromatosis where they discovered the existence of the C282Y mutation in about 85-90% of the cases (16).

The history of chelation therapy goes back to early 1930s when Ferdinand Munz worked out on synthesis of ethylene diamine tetra-acetic acid (EDTA). Afterwards, researchers found that EDTA is effective in treatment of lead poisoning (17). From 1970s, chelation therapy replaced phlebotomy to remove excess iron in patients with haemochromatosis. Chelators are able to bind metal ions for drastic reduction in their reactivity, the ultimate complex is water soluble which can enter bloodstream and be excrete without any damages (18). However, there was cardiac arrest during treatment with EDTA-chelation due to hypocalcemia. Nowadays, using EDTA in not common for children (19). Deferoxamine was the first iron chelator which gets FDA approval in 1968. Deferoxamine significantly reduces iron burden and prevents a large portion of life-threatening iron overload complications. The first clinical use of oral Deferoxamine therapy in

human began in 1987 (3). In September 2006, the oral iron chelator deferasirox was approved for use in Europe(4, 7).

Hereditary Haemochromatosis

The term "haemochromatosis" refers to an excess of iron in the body (20). Hereditary haemochromatosis e.g HFE-associated haemochromatosis is a type of haemochromatosis caused by an alteration (sometimes called a variant or mutation) in one of the genes that control Controls the absorption of iron from food in the gastrointestinal tract (20). This disorder causes the body to absorb too much iron from the diet, leading to a pathological increase in total iron stores in the body (1,7). Excess iron is stored in the body's tissues and organs, including the skin, heart, liver, pancreas, and joints. Since excess iron cannot be eliminated, iron overload can eventually damage tissues and organs. For this reason, hereditary haemochromatosis is also known as iron overload disorder (21). Hereditary haemochromatosis is a primary disease with a genetic component. When haemochromatosis has a genetic cause, it is called "hereditary haemochromatosis" because the genetic changes are usually hereditary (16). Other mutations cause disorders similar to haemochromatosis type 2 (sometimes called juvenile haemochromatosis); Tissue haemochromatosis type 3 (also known as transferrin receptor 2 [TFR2]) mutation; Haemochromatosis type 4 (also called ferroportin disease). Although the types of haemochromatosis vary depending on the age at which it occurs, the symptoms and complications of iron overload are the same in everyone (8). People can also have secondary haemochromatosis, which develops as a result of another disease or condition (4).

Types of Haemochromatosis

There are four types of haemochromatosis, which are classified depending on the age of onset and other factors such as genetic cause and mode of inheritance as Type 1; Type 2; Type 3 and Type 4 (8).

Classification Based on Age of Onset

Type 1, the most common form, and type 4 (also called ferroportin disease) appear in adulthood. Men with type 1 or type 4 haemochromatosis typically develop symptoms between the ages of 40 and 60, and women typically develop symptoms after menopause (8).

Type 2 haemochromatosis is known as a juvenile-onset disorder because symptoms usually appear in childhood. By the age of 20, the accumulation of iron leads to a decrease or loss of the ability to secrete sex hormones. Affected women usually start having normal periods but stop after a few years. Men may experience delayed puberty or symptoms related to a lack of sex hormones. If type 2 haemochromatosis is left untreated, life-threatening heart disease becomes apparent by age 30. The onset of type 3 haemochromatosis is usually intermediate between type 1 and type 2, with symptoms usually starting before age 30 (8).

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Classification Based on Causes

Haemochromatosis can be caused by mutations in several genes. Mutations in the HFE gene cause type 1 haemochromatosis, while mutations in the HJV or HAMP genes cause type 2 haemochromatosis. Type 3 haemochromatosis is caused by mutations in the TFR2 gene, while type 4 haemochromatosis is caused by mutations in the SLC40A1 gene (8).

Classification Based on Mode of Inheritance

Types 1, 2, and 3 haemochromatosis are inherited in an autosomal recessive pattern, which means that mutations occur in both copies of the gene in each cell. Typically, the parents of a person with an autosomal recessive condition each have one copy of the mutated gene but do not have the condition. The autosomal dominant inheritance pattern of type 4 haemochromatosis distinguishes it. One copy of the altered gene in each cell is enough to cause the disorder in this type of inheritance. In most cases, an affected person has one affected parent (8).

Hereditary Haemochromatosis Causes

Haemochromatosis (iron overload) can be caused by changes (also called "variants") in one of the genes that control how the body absorbs iron from food. A gene named HFE is most often mentioned ("H" stands for genetic or tall; "Fe" is the chemical symbol for iron). The HFE variant most commonly associated with haemochromatosis is known as "C282Y". There are also variants in other genes that can (very rarely) cause hereditary haemochromatosis. Alterations in the HFE gene that can lead to hereditary haemochromatosis are seen in about 10% of people of European ancestry, but having a single copy of the C282Y variant (inherited from the father or mother) rarely causes iron overload, unless there is another cause of iron deficiency such as liver disease. In fact, most people do not develop iron overload if they carry the HFEC282Y variant, especially if it is inherited only from one parent and even if it is inherited from both parents. The reason why some people get iron overload and others don't is still being studied. In general, men with iron overload tend to develop the disease at a younger age than women because women lose iron during menstruation and during pregnancy (20).

Genetics of Hereditary Haemochromatosis

On chromosome 6, there is a gene that codes for hepcidin, a protein that helps to regulate iron absorption. The HFE gene has three frequently observed genetic variants: rs1799945, c.187C>G, p.His63Asp (H63D); rs1800562, c.845G>A, p. Cys282Tyr (C282Y); and rs1800730, c.193A>T, p.Ser65Cys (S65C) (22, 23). The C282Y allele is a guanine-to-adenine transition point mutation at nucleotide 845 in HFE, resulting in a missense mutation that replaces the cysteine residue at position 282 with the amino acid tyrosine (24). Heterozygotes for either allele may exhibit clinical iron overload if they have two alleles. This makes them heterozygous for hemochromatosis and puts them at risk of storing excess iron in their bodies (25). Homozygous for the C282Y genetic variant is the most common genotype responsible for clinical iron accumulation, although heterozygosity for the C282Y/H63D variants is termed compound heterozygosity, leading to clinically apparent iron overload (26). Most men homozygous for HFE C282Y exhibit at least one manifestation of iron storage disease in middle age. Individuals with related genetic variants may never develop iron overload (27). Phenotypic expression was present in 70% of C282Y

homozygotes and less than 10% with severe iron overload and organ damage. The H63D variant is only a genetic polymorphism and in the absence of other alterations it may not be of clinical significance (28).

Each patient with a susceptible genotype will accumulate iron at different rates depending on the amount of iron absorbed, the exact nature of the genetic variation, and the presence of other harmful effects on the liver, such as alcohol and viral diseases. As such, the extent of involvement of the liver and other organs varies widely and depends on these factors and their comorbidities, as well as the age at which they are studied for disease manifestations (29).

Pathophysiology or Mechanism of Hereditary Haemochromatosis

Normally, HFE facilitates the binding of transferrin, a protein that transports iron in the blood. Transferrin levels are often high during iron deficiency (low ferritin stimulates transferrin release from the liver). When transferrin is elevated, HFE increases the release of iron into the bloodstream from the intestines. When HFE is mutated, the gut repeatedly interprets a strong transferrin signal as if the body is iron deficient. This leads to maximal absorption of iron from food and iron overload in tissues. However, HFE is partly the determining factor, as many patients with mutant HFE do not exhibit clinical iron overload and some patients with iron overload have a normal HFE genotype. One possible explanation is that HFE often plays a role in liver production of hepcidin, a function that is impaired by HFE mutations (30). People with an abnormal iron regulatory gene do not have a decreased ability to absorb iron in response to increased iron levels in the body. As a result, the body's iron stores increase; as they increase, iron originally stored as ferritin accumulates in the organs as haemosiderin, which is toxic to tissues, possibly at least in part by inducing oxidative stress (31). Thus, haemochromatosis has common symptoms eg, cirrhosis and dyskinesia symptoms with other "pro-oxidative" diseases such as Wilson's disease, chronic manganese poisoning, and other "pro-oxidant" diseases, hyperuricemia syndrome (31).

Signs and Symptoms of Hereditary Haemochromatosis

Haemochromatosis symptoms typically appear in adults after the body has accumulated a significant amount of excess iron. Symptoms usually appear after the age of 40 in men, and even later in women. Prior to genetic testing for hereditary haemochromatosis, iron overload was frequently not diagnosed until the person noticed symptoms and sought medical attention. Most people with hereditary haemochromatosis are diagnosed in their early twenties because they are tested after a family member is diagnosed. As a result, approximately three-fourths of people with hereditary haemochromatosis are diagnosed before symptoms appear, and the majority of people do not have complications at the time of diagnosis (20).

- Liver disease: The liver is one of the primary organs where iron is stored. Iron accumulation in the liver can result in abnormal liver function, liver fibrosis (scarring), and cirrhosis; approximately three-fourths of people with symptoms at the time of diagnosis have abnormal liver function. Cirrhosis can lead to a variety of complications, including liver failure or death; however, this is usually limited to people who have had significant iron accumulation over a long period of time. Cirrhotic patients are also more likely to develop liver cancer. Liver disease is often worse in people with hereditary haemochromatosis who

also have chronic hepatitis B or C or who drink excessively, so it is critical to identify and treat these conditions as soon as possible.

- Weakness and lethargy: The majority of people who have symptoms at the time of diagnosis have weakness and lethargy (a feeling of mental and physical sluggishness).
- Infections: Haemochromatosis can increase the risk of infection with certain types of bacteria. Iron accumulation in immune cells impairs their ability to fight off certain bacteria, and certain bacteria thrive in an iron-rich environment.
- Darkening of the skin: Iron in the skin, along with the pigment melanin, can darken the skin and give a person a tanned appearance, or it can sometimes cause kintolookgrey.
- Joint pain: The cause of joint pain in haemochromatosis patients is unknown. One theory is that excess iron causes calcium crystals to form in the joints. These crystals can cause joint pain and, in time, joint deformity. The joints of the hands, particularly the knuckles and third fingers, are the most commonly affected.
- Osteoporosis: Some people can develop osteoporosis or osteopenia (bone weakening), which can lead to fractures.
- Diabetes mellitus: An accumulation of iron in the pancreas can interfere with insulin production and result in diabetes mellitus.
- Reproductive issues: Iron accumulation in the pituitary gland in the brain can interfere with the pituitary's control of sex hormones. Pituitary damage in men can result in impotence and/or a loss of libido (sex drive). Pituitary damage in women can cause menstruation to stop or become irregular.
- Heart disease: Iron buildup in the heart can cause enlargement and interfere with the heart's normal electrical conduction system, affecting heart rhythm. Heart failure can develop in severe cases. Heart disease is rarely the first symptom of haemochromatosis.
- Thyroid disease: An accumulation of iron in the thyroid gland can result in hypothyroidism (reduced thyroid function) (20).

Some of these problems get better with treatment, especially if treatment is started early and sufficient iron is removed from the body. However, some of these complications may not be reversible (20).

Hereditary Haemochromatosis Laboratory Investigation And Diagnosis

It is critical to detect hereditary haemochromatosis early in the disease's progression because early treatment can help prevent complications. Diagnostic tests can help distinguish hereditary haemochromatosis from other conditions that cause symptoms similar to hereditary haemochromatosis, such as alcoholic liver disease. The severity of haemochromatosis and its complications can also be determined using tests (20).

- Blood tests: To determine the amount of excess iron in the body, two blood tests are usually recommended. These tests could be part of "iron studies panel."
- Saturation of transferrin: Transferrin is a protein that binds iron and transports it throughout the body. Transferrin saturation (also known as TSAT) is a measurement of the amount of iron bound to transferrin, which increases as the body's iron stores increase. This is one of

the most sensitive tests for early haemochromatosis detection. TSATs greater than 45 percent should be investigated further. Total iron binding capacity (TIBC) is a test used in some laboratories that essentially measures the same thing.

- Ferritin levels: Ferritin is a protein that represents the body's iron stores. Blood ferritin levels rise when the body's iron stores rise; however, ferritin levels typically do not rise until iron stores are high. As a result, early in the course of haemochromatosis, the results of this test may be normal. Ferritin levels greater than 300ng/mL in men and greater than 200ng/mL in women support a diagnosis of haemochromatosis. However, ferritin levels can be raised by conditions other than haemochromatosis.

➢ Other blood tests routinely performed include blood count, renal function, liver enzymes, electrolytes, and glucose (and/or an oral glucose tolerance test).
➢ Genetic tests: Genetic testing can reveal the HFEC282Y variant associated with hereditary haemochromatosis. H63D is another variant seen in some people with hereditary haemochromatosis; however, its relevance to hemochromatosis is more limited and controversial.
➢ Liver biopsy: A liver biopsy involves taking a sample of tissue from the liver with a thin needle; smear is made and stained with cytochemical stain such as Perl's Prussian blue. The amount of iron in the sample is then quantified and compared to normal, and evidence of liver damage, particularly cirrhosis, is measured microscopically. Previously, this was the only way to confirm a diagnosis of haemochromatosis, but measurements of transferrin and ferritin, along with a history, are now considered adequate in determining the presence of the disease (20, 22).
➢ Magnetic resonance imaging (MRI): MRI testing is a noninvasive and accurate method of determining liver iron concentrations (32).
➢ Other types of imaging the disease may be clinically silent, but characteristic radiological features may point to the diagnosis. Increased iron stores in the organs involved, particularly the liver and pancreas, cause characteristic findings on unenhanced CT and a decrease in signal intensity in MRI scans (32).

Management of Hereditory Haemochromatosis

Reduction therapy is used to treat iron overload. This is most commonly accomplished through therapeutic phlebotomy (33). In patients with an acceptable hemoglobin level, phlebotomy can be prescribed every 1 to 2 weeks until serum ferritin levels are acceptable. Then, based on serum ferritin levels, a schedule of periodic phlebotomy can be maintained, typically every 2 to 3 months. Patients with mildly elevated serum ferritin levels are frequently advised to donate blood on a regular basis (20, 34). Iron chelation therapy becomes another option in patients with low hemoglobin levels who do not tolerate therapeutic phlebotomy (34). Deferoxamine is an iron chelation therapy that is currently in use (33).

Iron Chelators

Phlebotomy is the most effective method of removing iron from the body. However, people with secondary hemochromatosis have congenital or acquired anemia and cannot usually be treated this

way (4). Chelating agents provide another way to negatively balance iron in the body and achieve acceptable iron levels, and can also neutralize harmful none transferrin bound iron (NTBI) (3, 4). It is important to remember that only a small fraction of the body's iron can be accessed by chelator molecules, as the majority of iron ions are tightly bound to suitable storage or transport molecules (4). It follows, therefore, that the chelator should be present continuously or as close as possible(4). Iron chelators must meet chemical needs. To meet this requirement, the chelator should be selective for iron and not be converted to non-chelated metabolites once inside the organism. A rapid iron exchange must occur between the chelator and the endogenous ligand. Complexes formed from chelating agents and iron should have better redox and higher stability than complexes of iron and endogenous ligands. In addition, biomedical requirements such as low toxicity of the formed complex and chelator, good absorption in the abdomen, and high bioavailability of the chelator upon entering target cells must also be satisfied (35). Three iron chelators are now available for clinical use: deferoxamine, deferiprone, and deferasirox (4).

Mechanism of Action

The mechanism of action of deferoxamine, deferiprone, and deferasirox in the treatment of iron overload is that deferoxamine binds to nontransferrin bound iron or iron found in ferritin, forming an iron complex molecule that is then excreted via the kidney. Deferoxamine also promotes the degradation of ferretin in lysomsomes. Cytosolic labile iron is chelated by deferiprone and deferasirox. Furthermore, deferasirox can raise hepcidin levels, which leads to ferroportin degradation (3)

Deferoxamine

Deferoxamine (DFO or Desferal) is a non-toxic iron chelator that has been shown in clinical trials to be effective for long-term iron chelation therapy in beta-thalassemia and other cases of iron overload. DFO has a remarkable effect on serum ferritin and hepatic iron levels, which increases longevity (36). Despite DFO's oral absorption ability, the pharmacokinetics of chelators in oral form is not optimal. The ineffectiveness of its intramuscular injection has also been demonstrated. As a result, it should not be administered orally or intravenously, but rather through continuous intravenous or subcutaneous infusion (37). The main mechanism of iron deposition by deferoxamine includes (38):

1. DFO is a hexadentate chelator, binding iron at a 1:1 molar ratio.

2. Old RBC iron storage will be released by reticuloendothelial system macrophages and precipitated by DFO and rapidly excreted through urine.

3. Non-bonded DFO will be internalized by liver parenchymal cells and attached to excess hepatic iron and excreted via bile.

4. DFO can directly absorb iron accumulation in cardiac muscle cells.

Deferoxamine's dose-dependent side effects include visual and auditory neurotoxicity from chronic treatment, as well as acute effects such as abdominal pain, diarrhea, nausea, vomiting, and

Figure 2. Mechanism Of action of Iron Chelators. TFR, Transferin Receptor (3)

hypotension. As a result, optometrists and audiometerists recommend annual testing (38). Fortunately, most toxicity can be reversed by discontinuing DFO treatment. Treatment with high doses of DFO is associated with an increase in pulmonary blood pressure (39). Deferoxamine therapy raises the risk of mucormycosis, vibrio, and yersinia infection. It should be noted that other iron chelators, such as Deferasirox and Deferiprone, cannot be seen because they do not function as siderophores (7).

Deferiprone

Deferiprone (DFP), an oral iron chelator that chelates iron in a 3:1 ratio, is a good option for patients who did not respond well to prior chelation therapy such as Deferasirox and Deferoxamin (40). The most common side effects are elevated liver enzymes, gastrointestinal problems, and arthralgia. The most serious side effects of DFP are agranulocytosis and neutropenia, which occur at a rate of 0.2 and 2.8 per 100 patients over one year, respectively, and are reversible after stopping therapy (40). Deferiprone is resorbed in the gastrointestinal tract. To achieve a negative iron balance, it must be administered in a total dose of 75 mg/kg/day; due to the drug's short half-life, this amount must be administered in three divided doses (41).

In essence, deferiprone therapy would be intolerable in iron overload conditions such as hereditary haemochromatosis. In addition, transfusion-dependent patients with severe conflict cardiac require more serious chelation therapy than regular chelation therapy patients. In such cases, a combination of subcutaneous or intravenous deferoxamine and oral deferipronem is advised. This combination therapy will greatly improve severe cardiac siderosis or left ventricular dysfunction (7).

Deferasirox

The tridentate iron chelating agent Deferasirox (DFX) binds iron in a 2:1 ratio. This combination has a strong affinity for iron but a weak affinity for copper and zinc (42). Abdominal pain, nausea, vomiting, diarrhea, skin rashes, and ophthalmic complications are the most common DFX side effects. These reactions are more common in older patients who are predisposed to myelodysplastic syndrome, have renal or hepatic disease, or have low platelet counts (43). Serum creatinine, transaminases, bilirubin, and complete blood counts (CBC) should all be checked on a regular basis. One of the most troublesome aspects of Deferasirox therapy is proximal renal tubular dysfunction, as well as other complications such as severe metabolic acidosis, hypophosphatemia, and hypokalemia (7). In one study, Deferasirox withdrawal and replacement therapy resulted in normal electrolyte balance in four patients with similar conditions. It is important to note that in order to avoid these complications, patients should avoid using aluminum-containing antacids such as Maalox and Mylanta while on Deferasirox therapy (7, 44).

Combined Therapy with More Than One Chelator

Combined therapy is an alternative method of adjusting iron levels in patients who did not respond completely to monotherapy (45). Treatment of iron overload with more than one iron chelator has a number of advantages, including improved access to various iron pools, better control of non-

transferrin bound to iron, better tolerability, improved compliance, reduced myocardial iron, and improved cardiac dysfunction in iron-overload cardiomyopathy. By reducing the dosage of both chelators, not only will the adverse effects of these chelators be reduced, but they will also exhibit high chelation efficiency. It was also discovered that the amount of iron removed through combined therapy was greater than the total iron eliminated individually by each chelator (46).

Deferoxamine with Deferasirox

Because their toxicity profiles do not overlap and they can reach the intracellular iron pool quickly, the combination of DFO and DFX may produce better results. Furthermore, both have a low molecular weight (47). A case study found that combining DFX and DFO in beta-thalassemia Major patients had a positive effect on liver and heart haemosiderosis. The treatment was well tolerated, with no side effects reported (39). Furthermore, a combination of DFX and DFO was associated with higher serum ferritin levels than DFO, DFX, DFO plus silymarin, and DFP plus DFO monotherapy (48).

Deferoxamine with Deferiprone

According to long-term experience, chelating DFP and DFO together reduces serum ferritin, liver iron, and myocardial siderosis, improves cardiac function, reverses and avoids endocrine disorders, lowers cardiac mortality, and improves survival (49). This combination therapy also resulted in a higher left ventricular ejection fraction, a lower risk of adverse events and mortality, and lower serum ferritin levels than DFO therapy alone (48). DFO binds iron more efficiently in the liver, resulting in biliary iron excretion; however, DFP binds iron more broadly in the parenchyma (50). Some studies have been evaluated to assess the impact of combined therapy in patients with various diseases, and patients with homeostatic iron regulator haemochromatosis and low erythrocytapheresis tolerance benefit from the addition of iron chelators. Synergistic effects were observed in a significant number of patients, implying that the total amount of iron removed in combined therapy was greater than the sum of the amounts removed individually by each chelator (51). According to the findings, the DFO and DFP combination is one of the most effective medications that have been used for chelation therapy in various illnesses (3).

Deferasirox with Deferiprone

Among the three iron chelators currently in use, DFP is thought to be the most effective at reducing cardiac iron overload, while DFX is thought to be the most effective total body iron chelator. As a result, the DFX and DFP combination may be advantageous in making chelation agents cautiously available in the in-patient blood circulation. This combination also increases iron excretion while decreasing free labile iron. Another advantage is that the toxicity profiles of these two agents are distinct. The hypothesis is that using DFP three times a day and DFX once a day will ensure that iron chelator agents are exposed and toxic iron species are suppressed. As a result, end-organ damage will be limited (3). In terms of frequency, one study found that a combined therapy of DFP every day and DFX 2-4 days per week was the most effective way to reduce serum ferritin and liver iron levels in patients chelated on DFX or DFP alone (52).

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Other Treatment Methods

Phlembotomy

Once diagnosed, haemochromatosis is treated with phlebotomy to remove excess iron from the body while maintaining normal iron stores. Phlebotomy is still the only recommended treatment for hereditary haemochromatosis, and it should be done on a case-by-case basis Regular phlebotomies should be performed indefinitely, and the frequency of maintenance therapy should be determined by serum ferritin levels. Phlebotomy therapy is divided into two stages: induction and maintenance (28).

During the induction phase, blood is removed at a rate of 7mL/kg per phlebotomy (not to exceed 550Ml per phlebotomy). The efficacy of treatment is monitored by measuring ferritin levels in plasma once a month until they remain below the upper limits of normal (300mcg/L in men and 200mcg/L in women). Before each procedure, the hemoglobin level must be checked; the normal range is 12-13 g/dL. Following that, ferritin concentration should be measured bimonthly until it falls below 50mcg/L (53).

Phlebotomy should be done every 2-4 months during the maintenance phase. The interval between procedures is determined by the ferritin level, which should be less than 50cg/m (53). Most patients require maintenance phlebotomy, which involves removing one unit of blood every 2-3 months (1). Some of the manifestations and complications of the disease, such as fatigue, elevated liver enzymes, hepatomegaly, abdominal pain, arthralgias, and hyperpigmentation, may be improved or even cured by therapeutic phlebotomy. Other complications usually show little or no improvement after phlebotomy. Avoid excessive phlebotomy and the risk of hypovolemia and dehydration (1).

Dietary therapy

Diet can be a powerful but underutilized tool in the prevention of iron overload. It is very common for people to eat more than the Recommended Dietary Allowance of even in a single meal, especially in the Western world where many foods are fortified and animal protein is relatively convenient and inexpensive. For example, one serving of several popular cereals contains more than twice the dietary reference intake (RDA) of iron for a man or non-menstruating woman. Menstruating women have roughly twice the iron requirements of a man or non-menstruating woman due to monthly blood loss. Limiting your intake of alcoholic beverages, iron-fortified foods such as certain cereals and supplements, and vitamin C (increases iron absorption in the gut), red meat (high in iron), and potential causes of food poisoning (shellfish, raw seafood) (54).

Increasing intake of iron-inhibiting substances such as high tannin tea, calcium, and foods containing oxalic and phytic acids such as collard greens, which must be consumed concurrently with iron-containing foods to be effective. Maintenance therapy with polymeric chelators is a novel experimental approach to the treatment of hereditary haemochromatosis. These polymers or particles have negligible or no systemic biological availability and are designed to form stable complexes with Fe^{2+} and Fe^{3+} in the GIT, limiting uptake and long-term accumulation of these ions. Although this method has only a limited efficacy, unlike small-molecular chelators, such an approach has virtually no side effects in sub-chronic studies. Interestingly, the simultaneous chelation of Fe^{2+} and Fe^{3+} increases the treatment efficacy (55). Treatment of organ damage such as heart failure with diuretics and Angiontensin converting enzyme (ACE) inhibitor therapy is

another option. In patients with liver failure, hepatic transplantation can alleviate many symptoms and complications (54)

Future Perspective

New synthetic or natural iron chelators that inhibit iron absorption may also be developed and considered for future hereditary haemochromatosis treatments. These chelators are expected to bind iron in the GI tract and prevent it from being transferred or stored in the body. Chelators with a high affinity for iron that are not orally absorbed and chelators that form insoluble iron complexes could be considered for such treatments. Similarly, DMT1 inhibitors could be used to reduce iron absorption. Combinations of chelators and chelators combined with DMT1 inhibitors could be considered for reducing increased iron absorption and associated iron overload (56).

Since, Iron is also needed for tumor cell growth; the multiplication of cancerous cells will be difficult in the absence of this crucial ingredient. As a result, the potential function of chelation therapy in cancer treatment and management will be studied in the near future (7).

Future management of hereditary haemochromatosis and related conditions may include the use of low and less absorbable forms of iron in selected diets, chelation therapies to inhibit iron absorption, chelation therapies to increase iron excretion, inhibitors of DMT1 and other iron metabolism proteins involved in iron transport, and a combination of some of these treatment methods (56-80).

Conclusion

Knowledge and understanding of the pathophysiology of iron metabolic disorders and toxicity and the mechanisms of iron chelation may promote the development of improved therapeutic strategies. Several factors, such as the severity of iron overload, treatment duration, final treatment costs, and the findings of recent studies, must be considered when deciding on the best chelation therapy for a specific clinical situation.

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