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Bronze Diabetes: A Common Genetic Disorder Due to Systemic Iron Overload

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Abstract

In medical science, hemochromatosis is a genetic disorder that is commonly known as bronze diabetes, which is due to continuously over-absorbed of excess iron from the gastrointestinal tract for hepcidin deficiency, and deposited in the liver, pancreas, heart, skin, gonads, pituitary gland, and other organs. Hepcidin regulates the activity of ferroportin, the only identified cellular iron exporter. Hemochromatosis is a relatively new term to common people, and it is named bronze diabetes because of the brown color of the skin due to the accumulation of huge iron in the body. Symptoms and expressions of this disease are hepatic fibrosis, fatigue, arthralgia, cirrhosis, diabetes mellitus, arthropathy, pigmentation, cardiomyopathy, and hepatomegaly. Hemochromatosis is more prevalence among Northern European populations, and five to ten times more common among males than females. Phlebotomy is the popular treatment of this disease to remove iron, and ensures normal survival if applied early, and has been shown recently to reverse hepatic fibrosis but not cirrhosis.

Keywords: Bronze diabetes, hemochromatosis, phlebotomy, hepcidin deficiency

1. Introduction

In modern science, hemochromatosis is a genetic condition that is caused by hepcidin deficiency, commonly referred to as bronze diabetes. It restricts iron transport into plasma (Brissot et al., 2018). It is characterized by a dangerous medical condition, which can occur as a complication of frequent blood transfusions, and decreased activity of hepcidin-ferroportin binding. The hepcidin hormone is a key iron modulator for the controlling of the ferroportin, an iron exporter protein in the cells (Cancado et al., 2022; Sharma et al., 2022). It regulates small intestinal iron absorption, plasma iron concentrations, and tissue iron distribution by inducing inactivation and ubiquitination of ferroportin (Qiao et al., 2012). There are mainly two types of hemochromatosis: i) primary hemochromatosis, and ii) secondary hemochromatosis. Primary hemochromatosis is a hereditary disorder and caused by a genetic mutation. On the other hand, secondary hemochromatosis is transfusion related (Sharma et al., 2022).

Iron is an essential element of the body that is involved in regulating the differentiation and growth of living cells, and participates in electron transfer between cells (Liu et al., 2020). It also combines and transports oxygen to various parts of the body, and participates in many metabolic processes essential for life. Total iron content in human body is about 3-5g with the majority contained in hemoglobin and myoglobin (Mitchell & McClain, 2014). Our body regulates the amount of iron mainly through absorption from the foods we eat. When iron is deficient or excessive, it causes dysfunction of the body (Liu et al., 2020).

Normally an individual absorbs about 1 milligram of iron per day from their diets, but hemochromatosis patients can absorb as much as four times of that amount. Among these patients there is an abnormal deposition of iron in

specific organs. A single gene mutation causes extra iron to be absorbed from food in the intestine (Maduranga et al., 2022). Over time, overload iron often stores in various vital organs of the body, mainly in the liver, and the pancreas; and later stores in other organs, such as in kidneys, heart, pituitary glands, and skin, etc., which remain undetected for several years, until the damage is done. Also excess iron in the pancreas can lead to diabetes mellitus. Hemochromatosis is a fatal disease and undetected for a long-time; that is why it is called "*silent killer*" (Wieringa & Rankin, 2010; Barton & Acton, 2017).

It is found that 1 in 5 men and 1 in 10 women with the human homeostatic iron regulator protein (HFE) mutations developed additional hemochromatosis as they got older compared to those without the genes (Allen et al., 2008). At least 50% of men and 25% of women with the disease are likely to develop life-threatening complications. Individuals who take iron supplements or vitamin C, and people who consume high-iron diets, such as red meat, may experience symptoms of homeostatic earlier (Mccarthy et al., 2002).

2. Literature Review

The literature review section is an introductory unit of research, which displays the works of previous researchers in the same field within the existing knowledge (Polit & Hungler, 2013). It helps the researchers to understand the subject, and it serves as an indicator of the subject that has been carried out before (Creswell, 2007). Jenny E. Gunton and Amit Lalwani indicate that Hemochromatosis is one of the causes of diabetes that leads to excess iron in the blood and more importantly in the tissues of the body (Gunton & Lalwani, 2014). K. Maduranga and his coworkers studied a case of 39-year-old female who presented with diabetes mellitus, secondary amenorrhea and dilated cardiomyopathy with Mobitz type II heart block from previously unrecognized Juvenile Haemochromatosis (JH). They realized that JH is a form of hereditary hemochromatosis that presents with endocrine, cardiac, and liver involvement at a young age (Maduranga et al., 2022).

Geraldine M. Mccarthy and her coworkers show that early diagnosis and phlebotomy to reduce iron stores for preventing complications and providing normal life expectancy. They also realized that genetic testing of relatives of patients with hemochromatosis is warranted in some circumstances (Mccarthy et al., 2002). W. J. H. Griffiths has described novel genes and iron overload phenotypes with potential insights into the molecular pathophysiology of human iron metabolism. He has observed that the impact of HFE mutation analysis on the management of hemochromatosis is significant and allows early accurate diagnosis (Griffiths, 2007).

Rodolfo D. Cancado and his coworkers wanted to show updates on hemochromatosis and to report a practical set of therapeutic recommendations for the human factors engineering protein (HFE) hemochromatosis for the p.Cys282Tyr (C282Y/C282Y) homozygous genotype, elaborated by the Haemochromatosis International Taskforce (Cancado et al., 2022). Luke C Pilling and his coworkers have tried to compare prevalent and incident morbidity and mortality between those with the HFE p.C282Y genetic variant and those with no p.C282Y mutations. They have found that HFE p.C282Y homozygosity is associated with substantial prevalent and incident clinically diagnosed morbidity in both men and women (Pilling et al., 2019).

Pierre Brissot and his coworkers have described that the most common form of hemochromatosis is due to homozygous mutations (specifically, the C282Y mutation) in HFE, which encodes hereditary hemochromatosis protein. Non-HFE forms of hemochromatosis due to mutations in HAMP, HJV or TFR2 are much rarer. Mutations in SLC40A1 (also known as FPN1; encoding ferroportin) that prevent hepcidin-ferroportin binding also cause hemochromatosis. Cellular iron excess in HFE and non-HFE forms of hemochromatosis is caused by increased concentrations of plasma iron, which can lead to the accumulation of iron in parenchymal cells, particularly hepatocytes, pancreatic cells and cardiomyocytes (Brissot et al., 2018).

Karan V. Sharma and his coauthors studied a 26-year-old male who is presented with a complaint of darkening skin, joint pain, and fever. The patient was a known case of thalassemia major and was undergoing blood transfusions three times a week. He was managed with chelation therapy and phlebotomy and his symptoms improved after adequate treatment (Sharma et al., 2022). Hiang Leng Tan and his coauthors have observed that diabetes affects 30% to 60% of patients with hereditary hemochromatosis (Tan et al., 2014).

3. Research Methodology of the Study

Research is the procedures of systematic investigations that requires collection, interpretation and refinement of data, and ultimately prepare an acceptable article, working paper, book chapter or a thesis by the appropriate use of human knowledge (Pandey & Pandey, 2015). Methodology is a guideline to perform of a good research (Kothari, 2008). Therefore, research methodology is the specific procedures that are used to identify, select, process, and analyze materials related to the topics (Somekh & Lewin, 2005). The research design is the plan of the researchers to develop research area that is underpinned by philosophy, methodology and method (Tie et al., 2019).

We start the main portion of the research through the discussion of types and causes of Hemochromatosis. Then we have briefly analyzed the symptoms and prevalence of bronze diabetes. Finally, we have highlighted the

prevention and treatment of hemochromatosis. In this study we have depended on the hemochromatosis related secondary data sources (Mohajan, 2018a, 2020). We have studied the published and unpublished research papers, books and handbooks of renowned authors, various research reports, internet, websites, etc. to enrich this paper (Mohajan, 2018b).

4. Objective of the Study

The chief objective of this study is to discuss aspects of hemochromatosis. Some other minor objectives are as follows:

- to give the basic idea of causes the hemochromatosis,
- to highlight the symptom and prevalence of bronze diabetes, and
- to provide the prevention and treatment of hemochromatosis.

5. Types of Hemochromatosis

There are four types of hemochromatosis: i) Type 1 hemochromatosis (hemojuvelin mutation), ii) Type 2 hemochromatosis (hepcidin mutation), iii) Type 3 hemochromatosis (mutated transferrin receptor 2 TFR2), and iv) Type 4 hemochromatosis (mutated ferroprotein 1 gene, SLC40A1) (D'Alessio et al., 2012). Type 1 hemochromatosis is also called classic hemochromatosis, which is involved with HFE. Type 2 hemochromatosis is related to hepcidin antimicrobial peptide (HAMP) or hemochromatosis type 2 (HFE2). Type 3 hemochromatosis is related to transferrin receptor 2 (TFR2). Type 4 hemochromatosis is related to solute carrier family 40 iron-regulated to transporter, member 1(SLC40A1) (Pietrangelo, 2004; Maduranga et al, 2022).

There are two main types of iron found in the diet we eat everyday: i) heme iron that is found in red-meat and fish, and ii) non-heme iron that is found in in vegetables, cereals and other foods; and our body can absorb both of them. But heme iron is absorbed more readily than non-heme iron (Lombardi-Boccia et al., 2002). There is a close connection between hemochromatosis and diabetes mellitus. Hemochromatosis patients have a higher risk of diabetes, because β-cells damage by apoptosis due to excess iron that impaired insulin secretory capacity (Dubois-Laforgue et al., 2000).

6. Causes of Bronze Diabetes

Among hemochromatosis patients, ferroportin activity is very high in the enterocytes due to lower hepcidin, and consequently, leads to high uptake and iron overload (Santos et al., 2012a). To develop hemochromatosis an individual must possess two sets of mutations in the gene known as human homeostatic iron regulator protein (HFE) gene, and people who have a point mutation called p.C282Y codes for a protein regulating iron absorption in much smaller quantities (Feder et al., 1996; Merryweather-Clarke et al., 2000). Very smaller proportion of patients has a different mutation, called H63D that also causes hemochromatosis (Burke et al., 1998). Hereditary hemochromatosis type 1 is predominantly attributable to two HFE gene mutations, with 95% of affected people having the p.C282Y (p.Cyst282Tyr) mutation and 4% having the p.C282Y/p.Hist63Asp compound heterozygote genotype (Adams, 2015; Adams et al., 2018; Pilling et al., 2019).

Non-HFE forms of hemochromatosis due to mutations in HAMP, HJV or TFR2 very rarely seen. Mutations in SLC40A1 or FPN1 that prevent hepcidin-ferroportin binding also develop hemochromatosis (Brissot et al., 2021). If a people have only one set of the faulty gene will not develop hemochromatosis. But this gene can pass on children if his/her partner is also a carrier of the faulty gene. Heavy alcohol use by individuals with hemochromatosis increases the risk of cirrhosis (Allen et al., 2008).

7. Symptoms of Bronze Diabetes

There are no specific symptoms to hemochromatosis. Symptoms typically develop over time as iron builds up in the system. Initial symptoms are non-specific and usually start between ages 30-50 in men, but may begin earlier in some patients, and are usually later in women (Gunton & Lalwani, 2014). The disease often shows no symptoms until middle age. Hemochromatosis is a genetic condition that the body absorbs excessive amounts of iron. This excess iron is not eliminated through waste, but deposited in the organs, mainly in the liver, but sometimes in the heart, pancreas, endocrine glands, and joints (Brissot & Loreal, 2016). For the store of huge iron in areas which are subject to sun exposure, for example, in skin; the body looks grey or brown/bronze color and consequently the disease is called bronze diabetes (Liu et al., 2003).

Non-specific symptoms of HFE hemochromatosis patients are chronic fatigue, abdominal pain, skin hyperpigmentation, arthropathies, diabetes mellitus, hepatomegaly and cirrhosis, when the serum ferritin is >1,000mg/l (Fonseca et al., 2018). Non-HFE hemochromatosis patients, who are usually younger and aged 20 to 30 years, have specific symptoms, such as heart failure, diabetes, and hypogonadism (Santos et al., 2012b). Severe iron overload in p.C282Y homozygotes may develop primary liver cancer, cirrhosis, diabetes, endocrinopathies, and cardiomyopathy (Barton et al., 2010).

Due to hemochromatosis it may result in enlargement of the liver, irreversible liver damage (cirrhosis), skin pigmentation, hepatomegaly, diabetes mellitus, impotence, arthritis, cardiomyopathy, arrhythmia, heart failure, reproductive and sexual issues, thyroid disease, and general malaise (Barton et al., 1998). It creates higher risk of diabetes mellitus, and chronic pain; sometimes liver cancer may develop among some patients (Rong et al., 2012).

Common symptoms of hemochromatosis are severe fatigue, joint pain, bronze color of the skin, erectile dysfunction, arthritis, loss of body hair, diabetes, excessive thirst, increase of urination, weakening of the heart, cardiomegaly, jaundice, cirrhotic liver and missed periods of women (Pilling et al., 2019). The most common cardiac symptoms associated with hemochromatosis are arrhythmias with palpitations, lower muscle strength, light headedness, chest pain, etc. (Tamosauskaite et al., 2019).

8. Prevalence of Bronze Diabetes

The disease bronze diabetes is higher prevalence in some countries and regions among Caucasians of Northern Europe, such as in Ireland, Wales, and Scotland. It is much less common in Asia, especially in the Middle East, and in the most region of Africa, because of a lower prevalence of the genetic mutations in non-Caucasians (Gunton & Lalwani, 2014). It affects as many as 8 per 1,000 persons of northern European descent. Point mutation p.C282Y homozygosity is high prevalence and the frequency of it is similar between men and women (Mccarthy et al., 2002).

The incidence of the p.C282Y mutation of the HFE gene to be higher in people with type 2 diabetes than it is in the general population (Tan et al., 2014). The disease is affected by many factors, such as alcohol consumption, dietary iron intake, blood loss due to menstruation and pregnancy, and blood donation, blood transfusions, consumption of oral iron pills, supplemental vitamin C intake, hepatitis, etc. (Rong, et al., 2012). Previously it is thought that hemochromatosis to be a low-level health risk disease; actually it is quadruples risk of liver disease and doubles the risk of arthritis and frailty in older people (Pigeon et al., 2001).

9. Prevention, Tests, and Treatment of Hemochromatosis

The goal of treatment of hemochromatosis is to normalize iron levels and to prevent further organ damage. Treatment is beneficial for the patients that delays, prevents, and sometimes reverse complications of hemochromatosis. Early treatment increases life expectancy or provides normal life expectancy. If the disease is untreated for long-time, vital organs may be damaged and even death may happen in some cases (Niederau et al., 1996).

Serum ferritin (SF) and transferrin saturation (TS) laboratory tests are routinely used to investigate biochemical evidence of iron overload. Patients with iron overload carrying the HFE p.Cys282Tyr/p.His63Asp compound heterozygous or p.His63Asp homozygous genotypes are frequently identified in some cohort studies on hemochromatosis (EASL, 2010; Santos et al., 2010). The SF is a highly sensitive test to measure iron overload, and SF values >300mg/l in males and postmenopausal females, and >200mg/l in premenopausal females (Wood et al., 2017). SF level of blood is checked at least once a year. The patient must keep the iron level within the normal range to avoid the serious problems caused by too much iron (Tavill, 2001). The TS is the ratio between serum iron and total iron-binding capacity (TIBC), and it can be a helpful biomarker of iron overload when the values are ≥ 45% (Bardou-Jacquet et al., 2017).

Blood donation, physiologic blood loss through menstruation, pregnancy, etc., which decrease hepatic iron stores, may delay the development of the disease (Mccarthy et al., 2002). Non-HFE hemochromatosis specifies very rare forms, related with mutations in the HJV, HAMP, TFR2 and SLC40A1 genes. Therefore, genetic investigation for the non-HFE hemochromatosis is necessary when the result for the p.Cys282Tyr homozygosity is negative (Santos et al., 2012b).

First attempt of this disease is to reduce iron load, and the needs to dietary changes. Phlebotomy (venesection) blood treatment is the gold standard therapy treatment for hemochromatosis patients. It is very effective to prevent hemochromatosis damages, safe, and has a low cost (Bring et al., 2008). It is frequently used to treat hemochromatosis that significantly reduces morbidity and mortality. One phlebotomy of 450ml removes about 225mg of iron from the body (Vanclooster et al., 2015). It is done in two phases through i) an iron reduction phase, and ii) a long-term maintenance phase. It can be detected through medical tests and treated by blood withdrawals (Rombout-Sestrienkova et al., 2016).

Erythrocytapheresis have been used to treat hemochromatosis patients, but is more expensive and less available than phlebotomy (Adams et al., 2018). Some elderly patients with comorbidities and/or poor vein conditions do not tolerate the "*standard phlebotomy regimen*". A modified phlebotomy regimen, such as a higher ferritin level of 200 to 400 mg/l may be required to avoid anemia and the discomfort due to the phlebotomies for them (Cancado et al., 2015). Sometimes iron chelators is an alternative treatment in severe iron overload without efficacy with phlebotomies, poor vein conditions and severe non-HFE hemochromatosis (Brissot et al., 2018).

10. Conclusions

In this study we have observed that hemochromatosis is a fatal disease. The increased awareness of the scope of the diseases hemochromatosis can help lead to increased testing and treatment that improves the quality of life and reduce frailty and disability rates of infected individuals. Bronze diabetes patients need regular monitoring of iron store to prevent various complications of life-threating. Early treatment with regular venesection and iron chelation can reduce the complications of iron overload and improve prognosis. Hemochromatosis patients never stop of checking their iron parameters and should be followed lifelong treatment on an out-patient basis.

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