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The Bronze Killer: Haemochromatosis and Diabetes

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Introduction

Haemochromatosis is one of the causes of diabetes. It leads to excess iron in the blood and more importantly in the tissues of the body. It is one of the most commonly inherited disorders. There is abnormally increased absorption of iron from the intestine, leading to deposition of excess iron in a wide range of organs. It is sometimes referred to as a 'silent killer' because iron overload often goes undetected for years, until the damage is done. Haemochromatosis has been called the 'Celtic curse' based on its higher prevalence in people from Ireland, Wales, Scotland, and Great Britain.

Types of Haemochromatosis

An overview of iron trafficking is shown below in Figure 1

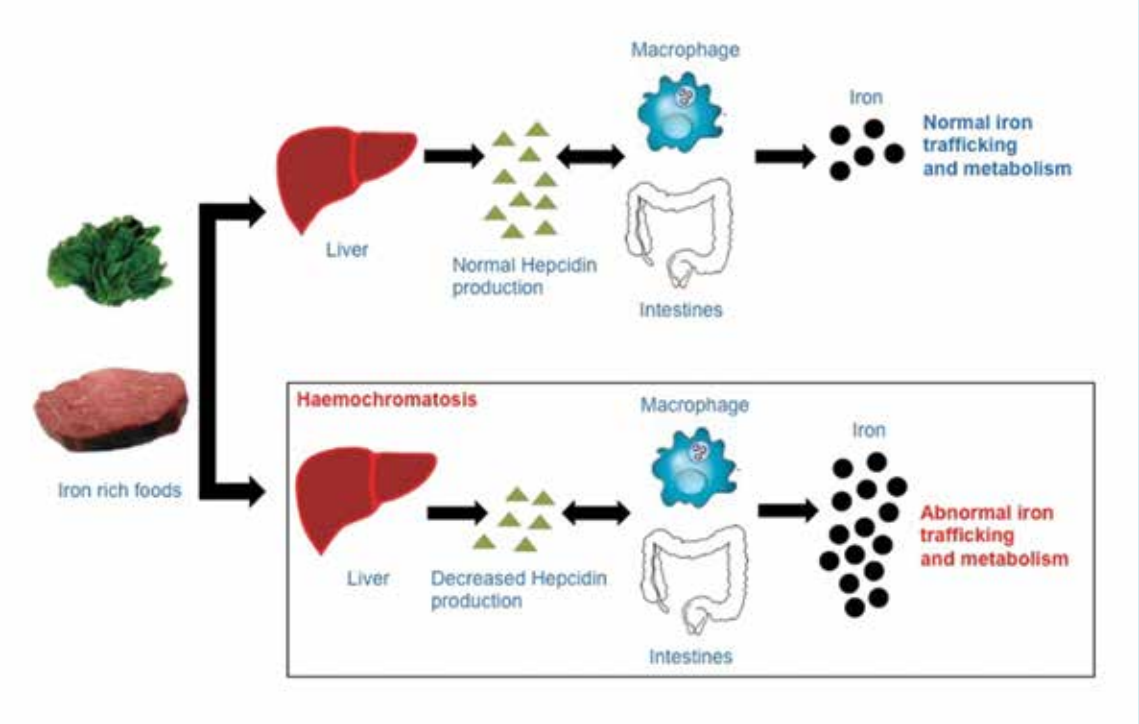

Figure 1 - Overview of iron trafficking and metabolism: Hepcidin is a regulator of iron trafficking. In normal individuals, circulatory iron received from daily food intake sets hepcidin synthesis by hepatocytes at a basal level. The amount of iron released from macrophages and intestine (enterocytes) is modified by serum hepcidin that contributes to the pool of circulatory iron in a regulatory feedback loop to keep the hepatic production of hepcidin under control. Hepcidin blocks ferroportin activity, which inhibits iron absorption from the intestine (duodenum) and iron recycling from macrophages. Hepcidin is synthesized in the liver, and its decreased production leads to excess accumulation of iron in enterocytes and macrophages. HFE, the product of the haemochromatosis gene, is required for hepcidin activation in response to the circulatory iron signal. Hence mutations in this gene (or in hepcidin) disrupt iron homeostasis and cause haemochromatosis.

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References and Acknowledgements:

There are a number of genes that when mutated lead to haemochromatosis. These genes include HAMP (hepcidin antimicrobial peptide), HFE (haemochromatosis), HFE2 (haemochromatosis type 2 (juvenile)), SLC40A1 (solute carrier family 40 (iron-regulated transporter), member 1), and TFR2 (transferrin receptor 2). A mutation in each type of gene causes a specific type of haemochromatosis[1]. The commonest by far is HFE, which is responsible for classic, or type 1 haemochromatosis. The different types of haemochromatosis and the gene mutation(s) responsible are listed in Table 1 below.

arthropathy affecting the 1st, 2nd and/or 3rd metacarpophalangeal joints may develop, which is a classic sign[3,4]. People with this pattern of arthritis, which spares other joints, who also have diabetes, should always be screened for haemochromatosis. Images of the hands of 2 normal individuals (Austrian origin) indicating the relevant joints is shown in Figure 2. A diagrammatic illustration of course of progression of haemochromatosis is shown in Figure 3. The classic bronze skin colour is usually a late symptom, as in the case of 'bronze diabetes'.

Table 1 – Different types of haemochromatosis

Haemochromatosis Type	Gene involved
Type 1 haemochromatosis or Classic haemochromatosis	HFE (haemochromatosis)
Type 2 haemochromatosis	HAMP (hepcidin antimicrobial peptide) or HFE2 (hemochromatosis type 2 (juvenile))
Type 3 haemochromatosis	TFR2 (transferrin receptor 2)
Type 4 haemochromatosis or Ferroportin disease	SLC40A1 (solute carrier family 40 (iron-regulated transporter), member 1)

In very rare cases, iron overload accumulates before birth. These cases are called neonatal haemochromatosis. It progresses rapidly and is characterized by liver damage that is apparent at birth or on the first day of life. The gene or genes causing neonatal haemochromatosis are not known[2].

Clinical Presentation/ Features/Expression/ Manifestations

There are no symptoms specific to haemochromatosis. Diagnosis can be missed even in advanced stages unless looked for specifically. Early diagnosis is difficult. Symptoms usually start between ages 30-50 in men, but may begin earlier in some patients and are usually later in women. Initial symptoms are non-specific and include fatigue, weakness, nonspecific abdominal problems and pseudogout. Later,

Prevalence

Haemochromatosis is more common in people of Northern European backgrounds with approximately 1 in 11 persons being heterozygous carriers and 1 in 200 being homozygous for C282Y mutations. The expression of the disease is affected by factors that include alcohol consumption, dietary iron intake, blood loss due to menstruation and pregnancy, and blood donation. Other contributing factors include blood transfusions, oral iron pills or iron injections, with or without supplemental vitamin C intake (vitamin C helps your body to absorb iron), hepatitis, or non-alcoholic steatohepatitis[5].

Haemochromatosis is much less common in Asia, the Middle East and most of Africa because of a lower prevalence of the genetic mutations in non-Caucasians.

Diagnosis

The first step in diagnosing an iron-overload disorder is to assess iron status. If the probability of haemochromatosis is thought to be low, a simple measurement of ferritin alone could be undertaken. However, ferritin is an acute phase reactant, so it goes up with any acute illness, including viruses, so it may be more useful to request "iron studies". These will include serum iron, transferrin, ferritin and either TIBC (total iron binding capacity) or transferrin saturation. Iron studies therefore allow assessment of iron status so long as there is not a severe illness at the time. If the iron studies suggest that the person has excess iron, with high transferrin saturation (or low TIBC) and high ferritin, then proceeding to genetic testing is indicated. Normal ranges vary between laboratories, but the 'normal' for ferritin in males is approximately 30-300 μg/L and for females is 10-200 μg/L[6,7].

Mutations in the HFE gene are identified by genetic testing (i.e. sequencing the gene). This is somewhat expensive, but more importantly, identifying genetic disorders in people comes with the crucial need for **pre-test** and **post-test** genetic counselling, so it must not be undertaken lightly. Since it is a genetic disease, if identified, it also has implications for testing of parents, siblings and children. These are the reasons why assessing iron status should be done as the first step except in the case of screening relatives of people with known haemochromatosis.

In patients who are positive for mutations, usually MRI (magnetic resonance imaging) of the liver is undertaken to assess hepatic iron loading, and a liver fibroscan (a special kind of ultrasound) is often done to assess fibrosis. These tests together assess liver risk and will usually, in combination with the serum iron studies, decide the

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Table 2 – Complications of haemochromatosis

Sign/Disease	Symptoms
Liver disease	Occurs in about 35-75% of the patients. Hepatomegaly. Chronic liver disease signs, such as cutaneous stigmata of liver disease (palmar erythema, spider angioma, or jaundice). Liver failure. Cirrhosis. Hepatocellular carcinoma develops in 30% of patients with cirrhosis (risk > 200-fold).
Diabetes	Up to 65% of patients. More likely to develop in those with a family history of diabetes. Prevented by early treatment. Early alteration of glucose intolerance and insulin resistance may partially be improved by phlebotomy treatment. Treatment after long-term diabetes is unlikely to reverse glucose intolerance.
Hyper-pigmentation or skin bronzing	Bronzing or metallic or slate grey skin coloration. Results from a combination of iron deposition and melanin in the dermis. Pigmentation is usually diffused and generalized, but may be more prominent on the face, neck, lower forearms, lower legs and genital regions.
Arthropathy	Arthropathy (abnormality of joints) develops in 25-50% of patients More commonly occurs after age 50. Non-inflammatory. Particularly involves the small joints of the hands, especially the first, second and/or third metacarpophalangeal joints (CLASSIC SIGN). Usually no warmth, redness, or deformity.
Heart disease	Congestive heart failure Abnormal heart rhythms (arrhythmias), which can cause symptoms of palpitations, chest pain and lightheadedness. Cardiomyopathy (enlarged heart muscle).
Pituitary disease	Pituitary dysfunction produces a plethora of endocrine disturbances. Reduced gonadotropin levels are seen commonly. Can also cause reductions in gonadal synthesis of sex steroids, which in turn delays sexual maturation in some children with transfusional iron overload. Infertility is also seen quite commonly.
Hypogonadism/ Infertility	Can occur in both males and females. Loss of libido, impotency, amenorrhea, testicular atrophy, sparse body hair. The production of gonadotropins is decreased due to impairment of hypothalamic-pituitary function by excess iron deposition. Adrenal insufficiency, hypothyroidism and hypoparathyroidism is seen in rare cases. Excess iron deposition in the hypothalamus and/or pituitary can affect production of hormones that are critical for reproductive function.

treatment offered.
These tests have largely removed the need for liver biopsy, except where hepatocellular carcinoma is suspected.

Treatment of Haemochromatosis

If treatment is required for haemochromatosis, it is normally phlebotomy or venesection to reduce iron load, as well as dietary changes. In people without significant iron overload, for example relatives who are diagnosed by genetic testing, they would be given dietary recommendations alone and be followed with iron studies over time. The goals of treatment are to normalize iron levels and to prevent further organ damage[8,9]. Table 2 shows a list of potential complications of haemochromatosis. Treatment prevents, delays, and may sometimes reverse complications

Figure 2 - Normal hands: male (left) and female (right), both of Austrian origin. The 1st, 2nd and 3rd metacarpophalangeal joints, indicated by the brown circles are the joints that develop arthropathy, in the classic pattern for haemochromatosis.

of the disease. People who are diagnosed and treated early have a normal life expectancy. Left untreated, haemochromatosis can lead to severe organ damage and even death in some cases.

Therapeutic Venesection

A therapeutic venesection is very similar to a regular blood donation except that it has been prescribed as a form of medical treatment. It is a safe, simple and relatively inexpensive form of medical treatment and is the standard treatment for people with iron overload and haemochromatosis. It carries the same possible risks as blood donation; nausea, vomiting, dizziness, fainting, seizures, local bruising discomfort and local infection. In the first stage of treatment, about 500ml of blood is removed once a week. After iron levels return to normal, phlebotomy treatments are carried out less frequently, perhaps 3-4 times yearly. When being carried out less frequently, in some countries, the patient can donate their blood for medical use if they have no other contra-indications. Details of the most current Australian Red Cross Blood Service Therapeutic Venesection arrangements (revised May 2013) can be found at: http://www.transfusion.com.au/high_ferritin

Iron Chelation Therapy

Chelation is the process of removing a heavy metal from the bloodstream by means of a chelator. This treatment is a good alternative for individuals who cannot tolerate routine blood removal, usually due to heart disease.

Diet Recommendations for Individuals with Haemochromatosis

Normally individuals absorb about 1 milligram of iron per day from their diets. Individuals with haemochromatosis can absorb as much as four times that amount. The body has no way of ridding itself of the extra iron. The two main types of iron found in the diet are: heme iron contained in red-meat and non-heme iron contained in plants and supplements. Calcium is the only known substance that can impair the absorption of both heme and non-heme iron. The various diet recommendations for individuals with haemochromatosis or at risk individuals are listed in Table 3 below. Diabetes educators and dietitians play an important role in this aspect of care for people with diabetes and haemochromatosis.

Gender Distinction

As an autosomal recessive condition, haemochromatosis affects men and women equally in regard to the inheritance. However, symptoms occur more frequently in males than females, with an estimated male-to-female ratio of 3:1 [6,8]. Men also tend to express the disease at a younger age. The decreased incidence of symptoms in females is partially attributed to blood loss with menses and pregnancy. Women more commonly present with fatigue and pigmentation, whereas men more often present with cirrhosis and diabetes[3,9].

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How is it Linked to Diabetes?

Patients with haemochromatosis have a higher incidence of diabetes[10,11]. Depending upon the iron study, up to 65% of patients diagnosed with haemochromatosis may develop diabetes. Development of diabetes in haemochromatosis is likely multifactorial. Selective β-cell damage by apoptosis due to excess iron leads to impaired insulin secretory capacity. Iron overload also associates with insulin resistance[12]. In addition, iron overload may cause insulin resistance through hepatic dysfunction (e.g. liver fibrosis) and this contributes to some patients requiring large amounts of insulin to obtain optimal blood glucose control. Therefore, it is likely that all three factors; β-cell damage, insulin resistance, and underlying genetic tendencies play a causal role in patients with haemochromatosis developing diabetes [7,13].

Screening Patients with Diabetes?

Various studies around the world have shown that people with diabetes do not need to be screened routinely for haemochromatosis as most patients with both conditions will have clinical features suggesting haemochromatosis[10]. There is insufficient evidence at the present time to recommend screening for haemochromatosis in all individuals with diabetes. We recommend screening individuals who have diabetes and one or more of the following: arthralgias, bronze hyperpigmentation, features of chronic liver disease, pituitary dysfunction, elevated liver enzymes, or Northern European ancestry[14,15]. Iron studies change during acute illness, so screening should be carried out when the patient is well.

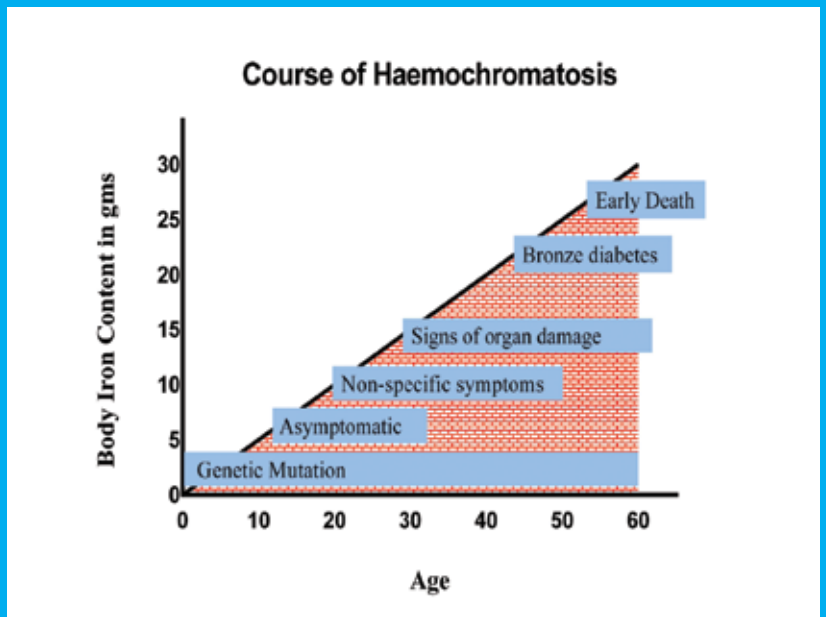

Figure 3 - Course of Haemochromatosis: Relationship between total body iron stores and clinical manifestations of haemochromatosis over time.

Impact of Haemochromatosis on Blood Glucose levels and HbA1c in Patients with Diabetes

Serum ferritin has a positive correlation with blood glucose levels and HbA1c in people with diabetes. This reflects a positive correlation between serum ferritin and glycaemia, both short term and long term[12]. It has been confirmed that patients with poorly controlled diabetes have hyper-ferritinaemia[7] but evidence suggests that there is no direct impact on the HbA1c levels.

However, iron deficiency artificially increases HbA1c levels[4,16], and this should be borne in mind if people are venesected resulting in temporary iron deficiency. An artificial increase in HbA1c levels is also relevant to people with iron deficiency that do not have haemochromatosis.

In people being venesected, red-cell life-span may be altered, artificially decreasing HbA1c. Therefore, fructosamine may be worth considering, but it is not rebated so may leave the patient 'out of pocket'. Fructosamine is also affected by other factors which can be altered in haemochromatosis so may also be unreliable. If the person is being venesected, and HbA1c is felt to be unreliable, patient self-monitoring of blood glucose levels should be relied upon, as always.

Diabetes Management in Haemochromatosis

The management of diabetes in patients with haemochromatosis is similar to that of normal diabetes. Treating the haemochromatosis itself though, is highly effective not only in slowing progression of all complications; it sometimes may improve or reverse glucose intolerance. Long-term complications can occur in any form of diabetes, but the risk of some complications may be increased in haemochromatosis[8,9].

Table 3 – Self-management options and dietary recommendations for Haemochromatosis.

Food item/type	Rationale
Harmful	
Excess red meat	Red meat contains the most easily absorbable form of iron (heme iron).
Foods high in fats	Fats (lipids) when in combination with unbound iron can generate free radical activity, which is destructive to cells and can damage DNA.
Vitamin C supplements	Vitamin C enhances iron absorption.
Excess alcohol (>20g/day for men, 10g/day for women)	Alcohol enhances the absorption of iron and increases liver damage.
Sugary foods and beverages	Sugar enhances the absorption of iron.
Vitamin supplements or tonics containing iron	Iron supplements increase iron available for absorption.
Breakfast cereals or bread fortified with iron	Supplemental iron is absorbed in people with haemochromatosis.
Raw shellfish (oysters, clams, mussels)	May be contaminated with vibrio vulnificus (a strain of bacteria) which thrives in an iron rich environment and can be fatal.
Beneficial	
Moderate tea or coffee	These beverages contain tannins, which inhibit the absorption of non-heme iron.
Nuts, grains, rice and beans	These foods are high in fibre, which impair the absorption of non-heme iron and promote healthy digestion of food.
Fruits and vegetables, including spinach	These foods contain fibre and antioxidants, which inhibit free radical production. Spinach contains oxalates, which impair absorption of iron contained in this plant.

Diabetes management in haemochromatosis, as a general rule, can follow the traditional sequence from diet and exercise to Metformin, increasing medications, and potentially eventually to insulin[7]. The authors have no experience using the SGLT2 inhibitors in haemochromatosis, but the mechanism of action suggests that they should also be effective.

If the patient with haemochromatosis has severe liver or heart disease, the use of Metformin should be avoided. Similarly the use of sulfonylureas should be avoided by pregnant and breast feeding women. These points should not be overlooked especially in patients with diabetes and haemochromatosis.

As outlined above, people with haemochromatosis may develop significant liver disease. In this setting, the use of Metformin and most sulfonylureas becomes contra-indicated. The DPP4 inhibitors Saxagliptin or Linagliptin may be used with hepatic impairment. There are, however, no clinical reports of the effects of DPP4 inhibitors or GLP-1 agonists in haemochromatosis. However, because many people have both pancreatic and liver damage, many of these people will require insulin for blood glucose control. In the setting of haemochromatosis coupled with significant liver damage and diabetes, we recommend specialist consultation for glycaemic management.

Discussion/Conclusions

Haemochromatosis is a common genetic disorder. Progression to multi-organ failure or hepatocellular carcinoma can be avoided with simple and effective treatment which should include dietary modification and avoiding excess alcohol. Haemochromatosis should be considered in any individual with unexplained liver, heart, or endocrine dysfunction, and of course with a family history of the condition. Because of the implications of genetic testing and the need for pre-test and post-test counselling, screening with iron studies should be the initial step. Genetic testing should be pursued if iron studies indicate iron overload.

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References

1. Griffiths, W.J., *Review article: the genetic basis of haemochromatosis.* Alimentary pharmacology & therapeutics, 2007. **26**(3): p. 331-42.
2. Hemochromatosis – Genetic Home Reference (http://ghr.nlm.nih.gov/condition/hemochromatosis)
3. Utzschneider, K.M. and K.V. Kowdley, *Hereditary hemochromatosis and diabetes mellitus: implications for clinical practice.* Nature reviews. Endocrinology, 2010. **6**(1): p. 26-33.
4. Manachino, D., et al., *Hemochromatosis and diabetes.* Mayo Clinic proceedings. Mayo Clinic, 1994. **69**(9): p. 913-4.
5. Rong, Y., et al., *Hemochromatosis gene (HFE) polymorphisms and risk of type 2 diabetes mellitus: a meta-analysis.* American journal of epidemiology, 2012. **176**(6): p. 461-72.
6. Longo D, Fauci A, Kasper D, Hauser S, Jameson J, Loscalzo J, **Harrison's Principles of Internal Medicine, Part 16. Endocrinology and Metabolism, Section 3, Chapter. 357.**

Hemochromatosis. 18th Edition, McGraw-Hill Medical Press, ISBN 13: 9780071748896 **ISBN 10:** 007174889X.

7. Pietrangelo, A., *Hereditary hemochromatosis: pathogenesis, diagnosis, and treatment.* Gastroenterology, 2010. **139**(2): p. 393-408, 408 e1-2.
8. Hereditary hemochromatosis: The Australian Handbook for General Practitioners by NHMRC Australia. (https://www.nhmrc.gov.au/_files_nhmrc/file/your_health/egenetics/practioners/gems/sections/13_hereditary_haemochromatosis.pdf)
9. Hemochromatosis (Iron Storage Disease) by Centers for Disease Control and Prevention, USA. (http://www.cdc.gov/ncbddd/hemochromatosis/index.html).
10. Henderson, P.C., P. Dowling, and R. Ozaki, *Should all patients with diabetes mellitus be screened for hemochromatosis?* The Western journal of medicine, 2002. **176**(2): p. 110-4.
11. Dubois-Laforgue, D., E. Larger, and J. Timsit, *Is diabetes mellitus a sufficient condition to suspect hemochromatosis?* Diabetes & metabolism, 2000. **26**(4): p. 318-21.
12. Barton, J.C., *Hemochromatosis and iron overload: from bench to clinic.* The American journal of the medical sciences, 2013. **346**(5): p. 403-12.
13. Brissot, P., *Hereditary hemochromatosis.* Hematology, 2013. **18**(6): p. 370-1.
14. Nadakkavukaran, I.M., E.K. Gan, and J.K. Olynyk, *Screening for hereditary haemochromatosis.* Pathology, 2012. **44**(2): p. 148-52.
15. Tanner, A.R. and R. Wright, *Haemochromatosis screening.* Lancet, 1988. **2**(8605): p. 286.

Lawrence, R.D., *Hemochromatosis and complications of diabetes.* Physician's bulletin, 1947. **12**(5): p. 34-7.