Hereditary haemochromatosis and diabetes

Erica Jennison, Patrick Wainwright

Hereditary haemochromatosis (HH) is one of the most common hereditary conditions in people of European ancestry. If left untreated, it results in diabetes due to iron accumulation in beta-cells and the development of insulin resistance. HH is often underdiagnosed, so it is important that it be considered in all people with diabetes, especially those with a family history or when other organs are involved. A simple diagnostic algorithm can be used when there is clinical suspicion. Treatment is simple and involves regular venesection until iron levels return to normal values. Many secondary complications of HH are reversible if treatment is initiated early; however, even when organ damage is established treatment is still beneficial. Managing diabetes secondary to HH is not unlike managing diabetes of other causes; however, certain pitfalls exist, such as the inaccuracy of HbA$_{1c}$ monitoring and the early need for insulin therapy compared to people with type 2 diabetes.

Hereditary haemochromatosis (HH) is an autosomal recessive disorder of iron metabolism. Although previously considered a rare condition, classically manifested by "bronze diabetes" (insulin deficiency combined with darkening of the skin), HH is now recognised to be one the most common hereditary diseases. Within people of northern European ancestry, it has a prevalence of up to one in 100 (Merryweather-Clarke et al, 2000)

The condition is classified as a heterogeneous group of disorders that result from a number of possible mutations in genes involved in iron metabolism. The majority of cases (80–90%) are caused by a C282Y mutation in the *HFE* gene, which codes for the HFE protein located within intestinal enterocytes (Feder et al, 1996). Other rarer mutations can be found at different locations in the *HFE* gene or in other genes such as hepcidin or transferrin receptor 2.

The mutations all result in excessive and inappropriately regulated intestinal iron absorption. The clinical manifestations are related to excessive iron deposition in tissues, leading to oxidative damage and fibrosis. The organs most affected include the pancreas, liver, heart and skin, leading to the classic tetrad of diabetes, cirrhosis, cardiac failure and hyperpigmented skin.

The pathogenesis of diabetes secondary to HH is primarily due to the loss of insulin secretory capacity. Within the endocrine pancreas, iron deposits are usually restricted to beta-cells, resulting in decreased beta-cell mass. Alpha-cells tend to be spared, as evidenced by increased serum glucagon levels similar to those seen in type 1 diabetes (Nelson et al, 1979). Additionally, people who develop cirrhosis are at increased risk of having insulin resistance and hyperglucagonaemia, which contribute to the development of diabetes (Barton and Edwards, 2000).

Article points

1. Nursing practice can play an important role in diagnosing hereditary haemochromatosis (HH) through identifying those at risk, whether it be through family history, organ involvement or biochemical findings.

2. Diabetes is a late complication of HH; however, it is present in approximately 50% of people who present with symptoms.

3. Treatment of HH involves therapeutic venesection, which can slow the progression of beta-cell loss and reverse some glucose intolerance if initiated early.

4. As a general rule, diabetes management in people with HH follows the traditional sequence from diet and exercise to medications and, finally, to insulin. The majority of people will eventually require insulin, often earlier than in typical type 2 diabetes, due to beta-cell loss.

Key words
- Comorbidities
- Hereditary haemochromatosis

Authors
Author details can be found on page 2.

Table 1. Symptoms and signs of hereditary haemochromatosis.

Organ involved	Symptoms and signs

Pancreas	• Insulin deficiency
	• Insulin resistance
	• Diabetes
	  – Fatigue, polyuria, polydipsia, weight loss, recurrent infections
	  – Diabetic emergencies

Liver	• Deranged liver function tests
	• Hepatomegaly
	  – Abdominal pain
	• Chronic liver disease/cirrhosis
	  – Palmar erythema, spider naevi, jaundice
	• Liver failure
	  – Encephalopathy, jaundice, ascites
	• Hepatocellular carcinoma

Skin	• Bronze/metallic/slate-grey skin colouration • Caused by an increase in melanin production rather than iron deposition • More prominent on face, neck, forearms and genital regions

Heart	• Cardiomyopathy/congestive heart failure
	  – Shortness of breath, oedema, lethargy
	• Arrhythmias
	  – Palpitations, collapse
	• Due to iron deposition within the myocardium

Joints	• Often involves the small joints of the hands, especially the first, second and third metacarpophalangeal joints • Usually no warmth, redness or deformity

Pituitary gland	• Hypogonadism (most common pituitary dysfunction)
	  – Infertility
	  – Loss of libido
	  – Amenorrhoea
	• Adrenal insufficiency
	• Hypothyroidism
	• Hypoparathyroidism

Signs and symptoms of HH

The clinical manifestations of HH depend on the degree of parenchymal iron accumulation. On average, men develop symptoms at age 30–50 years. Symptoms normally develop later in women, as menstrual blood loss protects from excess iron accumulation. Today, new diagnoses are most often made incidentally or through family screening, and therefore patients are often asymptomatic (Bacon and Sadiq, 1997). As a result of earlier diagnosis and more readily available treatments, the prevalence of the more serious late complications is decreasing (O'Sullivan et al, 2008).

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Clinical manifestations of HH are diverse. *Table 1* summarises the organs involved and the common symptoms and signs associated with the disease. The classic tetrad of diabetes, cirrhosis, cardiac failure and hyperpigmented skin are late features and normally only occur when the total body iron content has reached 20 g (greater than five-times normal). Initial symptoms are often vague and include fatigue, weakness, abdominal pain and arthralgia.

Diabetes is present in approximately 50% of people with HH who present with symptoms. However, as this is a late complication, it is normally accompanied by other clinical signs and symptoms, such as skin pigmentation and those of chronic liver disease. It is more likely to develop if other risk factors for diabetes are present. Interestingly, heterozygotes for HH are also at increased risk of developing diabetes (Salonen et al, 2000).

The liver is usually the first organ to be affected, and hepatomegaly and deranged liver function tests are two of the most frequent findings at clinical presentation (Adams and Valberg, 1996). In more advanced disease, cirrhosis occurs. Such individuals have a 20% risk of developing hepatocellular carcinoma, which accounts for a significant proportion of deaths in people with HH (Beaton and Adams, 2006).

Diagnosis of HH

It is crucial to diagnose HH before the onset of complications; however, despite its prevalence and the availability of simple diagnostic tests, HH is often underdiagnosed and, therefore, untreated. It is recommended that all high-risk groups be screened for the disease (European Association for the Study of the Liver, 2010). This includes those with a family history, particularly in first-degree relatives; however, given that the inheritance is autosomal recessive, it should be remembered that the disease may skip generations, and in many cases there may be no clear family history. Screening is also recommended when organ involvement is suspected or when biochemical or radiological abnormalities suggestive of iron overload are detected incidentally. A diagnostic algorithm for HH is shown in *Figure 1*.

Diagnosis is based on identifying increased iron

stores, demonstrated by elevated serum ferritin and serum transferrin saturation. Importantly, ferritin is an acute-phase reactant and will, therefore, non-specifically increase with any illness or with hyperglycaemia (Barton, 2013). Additionally, serum iron concentrations have marked diurnal variation, and any abnormal transferrin saturation result should be followed up with a repeat fasted early-morning sample. Molecular genetic testing is often used to confirm the diagnosis, although this is expensive and requires preceding genetic counselling.

There is an argument that all people with diabetes should be screened for HH. Recent studies have shown that the prevalence of HH is five- to six-times higher in those with diabetes (both type 1 and type 2) compared with the general population (Conte et al, 1998; Ellervik et al, 2001). However, disease penetrance is an important issue when screening for HH is performed, as a significant proportion of individuals found to be homozygous for the disease have no evidence of iron overload, either at the time of screening or after many years of follow-up (Andersen et al, 2004). Routine screening for all people with diabetes would have economic, psychological and social implications; therefore, screening is not currently

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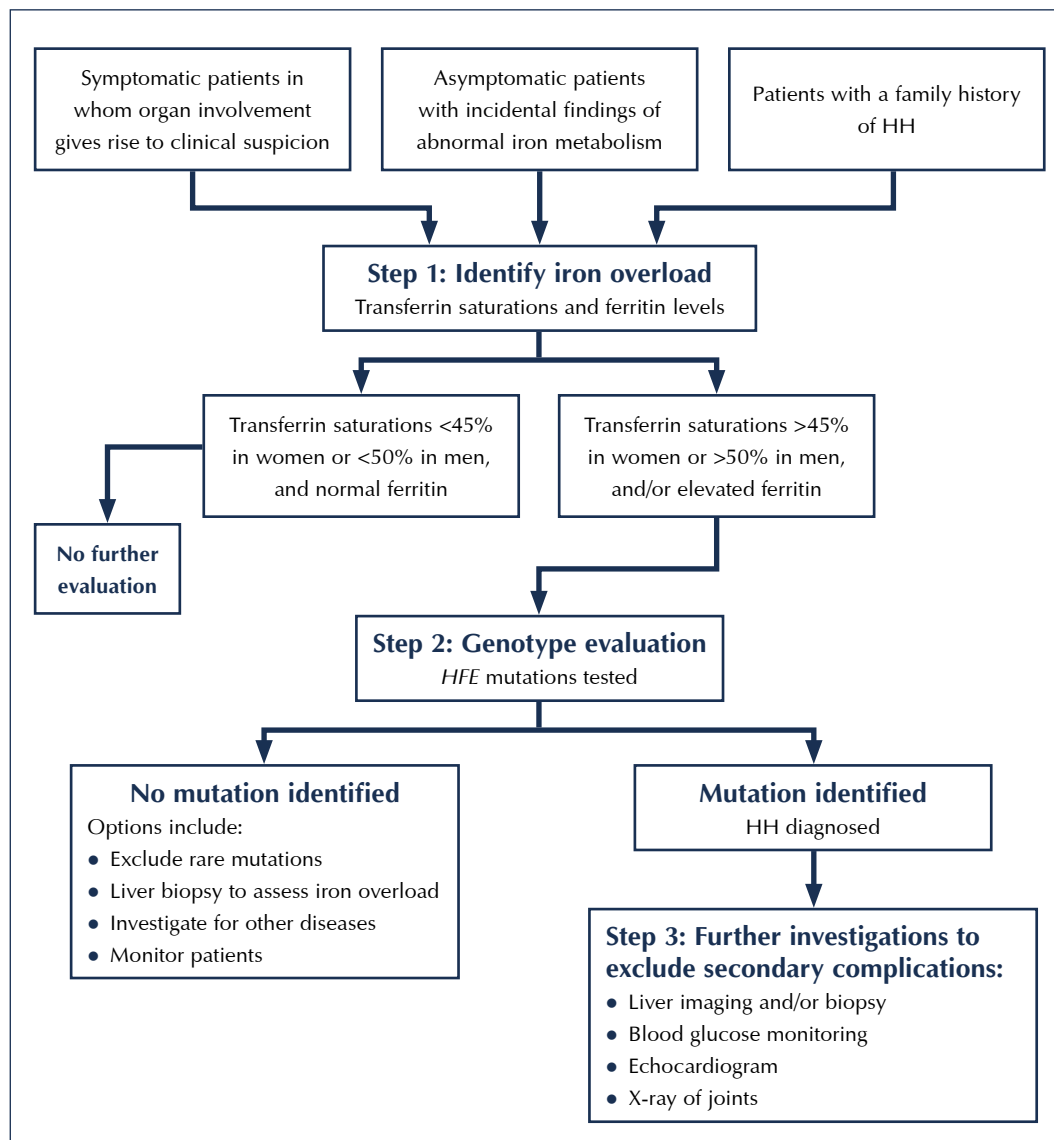

Figure 1. Diagnostic algorithm for hereditary haemochromatosis (HH).

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recommended unless there is a clinical suspicion of HH.

Once HH is diagnosed, further investigations are used to screen for associated complications. Given that cirrhosis has a significant prognostic effect, imaging – or in some cases liver biopsy – is performed to identify liver fibrosis. Other investigations include blood tests to diagnose diabetes and hypopituitarism, imaging to assess for arthropathy and echocardiograms to detect cardiac dysfunction.

Treatment of HH

Effective treatment can prevent, improve or even reverse some complications associated with HH and has been shown to prolong survival. Treatment involves therapeutic venesection, in which 500 mL of blood is removed regularly for several weeks to deplete the patient's accumulated iron stores. It is safe, inexpensive and effective. It is usually initiated in those who are symptomatic or when serum ferritin concentrations indicate excess accumulation of iron stores. These biochemical markers are also used to monitor the response to venesection.

Treatment usually resolves non-specific symptoms such as fatigue and weakness. It improves liver function and can reverse the severity of cirrhosis. Skin pigmentation and cardiomyopathy normally improve. The less reversible complications include diabetes; however, if treatment is initiated early it often reduces insulin requirements (Hramiak et al, 1997). Once established, hypogonadism and arthralgia are unlikely to improve with treatment.

Management of diabetes secondary to HH

There are some considerations to be made when treating diabetes secondary to HH. The main difference is the role of venesection to slow the progression of beta-cell loss and, possibly, reverse some glucose intolerance. Monitoring for micro- and macrovascular complications of diabetes plays the same important role, and the risk of developing these complications is similar in those with and without HH (Barton and Edwards, 2000). As a general rule, diabetes management in people with HH follows the traditional sequence from diet and exercise to medications and, finally, to insulin.

People with diabetes should be supported and encouraged to reverse modifiable risk factors such as obesity, poor diet and physical inactivity. Regarding dietary advice, there is no evidence that reducing oral iron intake is of any benefit; however, iron supplements should be avoided. Medical therapy with insulin sensitisers and secretagogues can have some benefit. However, the use of medical therapy can sometimes be contraindicated by other complications of HH; for example, metformin should not be used if severe liver or heart disease are also present. The majority of people will eventually require insulin, and often at an earlier stage than in type 2 diabetes, given that the major underlying pathogenesis is loss of beta-cells and not insulin resistance.

An important pitfall in managing diabetes secondary to HH is the inaccuracy of HbA_{1c} in monitoring glycaemic control. Continuous venesection reduces the lifespan of red blood cells, artificially decreasing HbA_{1c}. Fructosamine offers an alternative measure of glycaemic control; however, there are many issues with this, including inconsistent assay standardisation, poor access to the test and an unknown association with diabetes outcomes. Accurate recording of self-monitored daily blood glucose is, therefore, vitally important in managing these people.

Conclusion

HH is a common genetic disorder that is often underdiagnosed and undertreated. Nursing practice can play an important role in diagnosis through identifying those at risk, whether it be through family history, organ involvement or biochemical findings. This enables a simple treatment to be undertaken that can prevent or improve secondary complications such as diabetes. Once the disease is established, it is important that nurses and physicians incorporate subtle changes into their normal practice. In the case of diabetes, the early use of insulin and accurate recording of self-monitored daily blood glucose are crucial for the optimal management of these people. ∎