

# Hereditary Hemochromatosis: Dispelling the Myths

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# Conflict of Interest Declaration

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I have no conflicts to declare

# Agenda

- ▶ Learning objectives
- ▶ To develop and understanding/awareness of:
  - ▶ what hereditary hemochromatosis is
  - ▶ how one inherits hereditary hemochromatosis & who it typically affects
  - ▶ what iron overload is and what its consequences are
  - ▶ how hereditary hemochromatosis is diagnosed
  - ▶ how iron overload is treated
  - ▶ how pharmacists can support patients with hereditary hemochromatosis

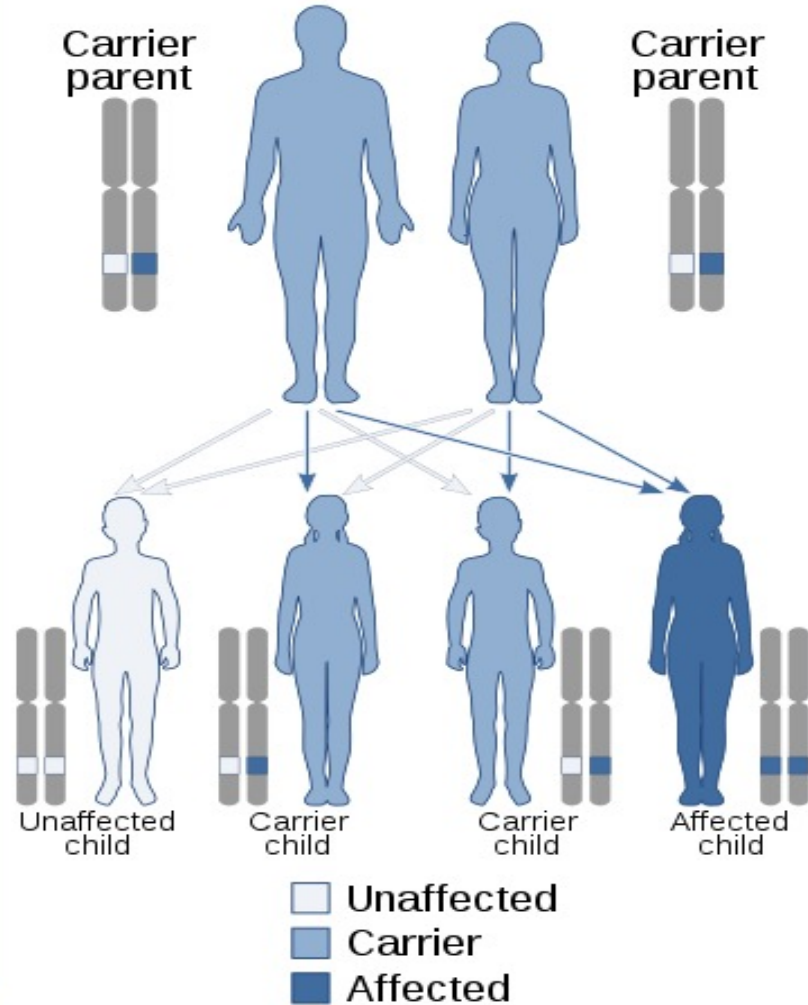
## Myth 1:

Hereditary Hemochromatosis is really rare

# What is it?

- ▶ Hereditary hemochromatosis (HHC) is a genetic, metabolic disorder that results in iron overload
  - ▶ It is the most common genetic disorder in the western world, affecting an estimated 1 in 300 Canadians.
  - ▶ In individuals of Northern European descent, the prevalence as high as 1 in 227
    - ▶ Ireland and France have the highest prevalence of the disorder
    - ▶ French, English, Welsh, Irish, Scottish
- ▶ Also called “Celtic Curse” or “Bronze Diabetes”

## Autosomal recessive



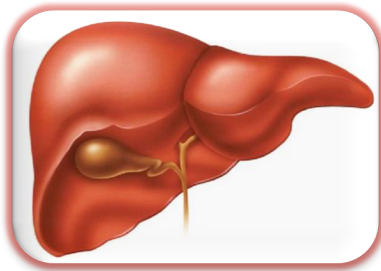
## A genetics refresher

- ▶ HHC is an autosomal recessive disorder - estimated that about 10% of the Caucasian population are carriers.
- ▶ Classic HHC is caused by mutations of the *HFE* gene.
- ▶ Mutations of the *HFE* gene result in low levels of functional hepcidin - a protein that regulated iron absorption in the body- which in turn leads to excess absorption of iron in the gastrointestinal tract.

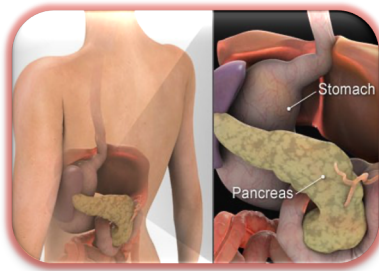
# So what if there is extra iron absorption?

- ▶ Normally - The body has about 4,000 mg (4 grams) of iron
  - ▶ ~3,000 mg is contained in hemoglobin
  - ▶ ~500 mg is bound to the storage protein ferritin
  - ▶ ~300 mg is stored in the liver.
- ▶ With HHC
  - ▶ The gut absorbs iron at 2-4 times the normal rate, despite the body already being overloaded with iron.
  - ▶ The level of ferritin increases to try to contain excess iron.
  - ▶ A person suffering from iron overload typically can have 15-60 grams of iron upon diagnosis

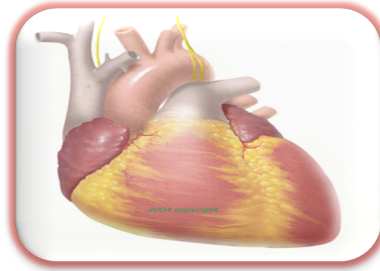
# Where does all this excess iron go?



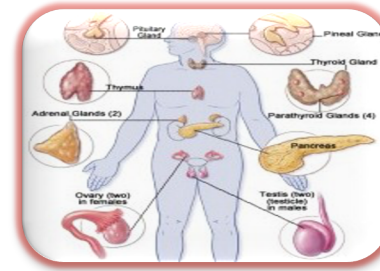
Liver



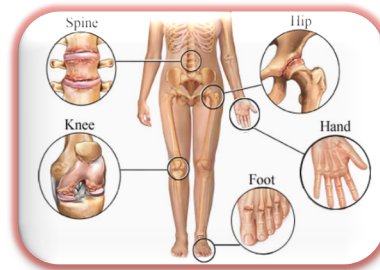
Pancreas



Heart



Endocrine  
glands



Joints

## Myth 2:

Hereditary hemochromatosis is readily identifiable and easy to diagnose

# How does a typical patient with iron overload due to HHC present?



- ▶ Mr. P.
- ▶ 33-year old male
- ▶ Physician refers him to purchase a splint for his wrist(s); complaining of joint pain in thumbs and index finger.
- ▶ Mr. P. mentions he might want to purchase medication for pain as well.
- ▶ Medication profile indicates that he is a healthy male, no allergies.
- ▶ Has had three antibiotics prescribed over the last 10 years; nothing in the last two years.
- ▶ You provide him with the required splint and advise that he can take acetaminophen as directed, as needed.

# Who does it usually affect?

- ▶ Primarily people of Northern European descent
- ▶ Too often, diagnosis does not come until signs or symptoms become severe
- ▶ In men, accumulation of iron generally does not begin presenting itself until late 20s or early 30s
- ▶ Women, naturally protected by menstruation, may not show effects until about 10-15 years after they stop having a period due to menopause, birth control pills or hysterectomy (BUT NOT ALWAYS)
- ▶ Diagnosis of one individual should lead to additional diagnosis within the immediate family

# Another interaction with Mr. P.



- ▶ Mr. P. and his wife come in looking for OTC vitamins.
- ▶ Mr. P.'s Wife is looking for pre-natal vitamins and while you are helping her select some, he mentions that he has been feeling tired in the last little while
- ▶ He is looking for iron supplements specifically
- ▶ You re-acquaint yourself with his profile and ask some additional questions.
- ▶ Refer him to his primary care physician

# Signs and Symptoms

- ▶ Symptoms often attributed to other causes
- ▶ Symptoms of HHC do not necessarily appear in a particular order, and importantly, not all hemochromatosis sufferers will have every symptom
  - ▶ Arthritis, especially in their hands, in particular, knuckles of first and second finger and thumb
  - ▶ Chronic fatigue
  - ▶ Loss of sex drive (libido) or impotence
  - ▶ Amenorrhea
  - ▶ Abdominal pain
  - ▶ High blood sugar levels
  - ▶ Hypothyroidism
  - ▶ Abnormal liver function tests, even if no other symptoms are present

# Iron-related Proteins

## ▶ Serum Ferritin (SF)

- ▶ protein that stores unused iron
- ▶ acute phase reactant
- ▶ Normal Men: 50-300 ng/mL; women 20-250 ng/mL
  - ▶ Elevated 300-999 ng/mL
  - ▶ Abnormal >1000 ng/mL

## ▶ Transferrin Saturation (TS)

- ▶ protein that carries iron between organs, transfers iron to cells and bone marrow
- ▶ 25-40% is normal; >45% saturation is high

# Genetic Testing

- ▶ Genetic testing is definitive -
- ▶ The HFE gene has three known mutations which cause hemochromatosis
  - ▶ C282Y mutation (most common)
  - ▶ H63D mutation
  - ▶ S65C mutation.
- ▶ Genetic counselling is a good idea
- ▶ ALL FIRST-DEGREE RELATIVES of individuals who have a clinical diagnosis of hereditary hemochromatosis would benefit from having a genetic test

## Myth 3:

Hereditary Hemochromatosis isn't a big deal

# What are the long-term complications of HHC

- ▶ It depends.....
- ▶ Assessment of potential end-organ damage
  - ▶ For example - The liver:
    - ▶ Liver enzymes
    - ▶ Radiological imaging of liver (MRI)
      - ▶ primary liver cancer (hepatoma), a complication that occurs in about 25 % of patients with cirrhosis resulting from HHC.

# Six months later - Mr. P. visits the pharmacy



- ▶ Insurance blood work showed elevated liver enzymes - denied coverage
- ▶ Family practitioner: Enlarged spleen, liver and abdominal lymph nodes; negative for Hepatitis A and B
- ▶ Referred to gastroenterologist: tested ferritin ( $>9000\text{ng/mL}$ ); HHC? Leukemia?
- ▶ Referred to hematologist: confirmed HHC with genetic testing
- ▶ Additional testing occurring to assess end organ damage - echocardiogram, MRI

## Myth 4:

There are several efficacious medications used to treat the disorder

# How is iron overload treated?

- ▶ Gold standard is phlebotomy
  - ▶ Each unit of blood contains 225 mg of iron within hemoglobin
  - ▶ Phlebotomy once-twice a week until iron reaches 105 g/L-110 g/L.
  - ▶ Iron mobilizes out of organs and into the bone marrow for manufacturing of more red blood cells
  - ▶ Some clinicians monitor ferritin levels during de-ironing, moving to maintenance when ferritin levels drop below 50 ng/ml

# Maintenance Phlebotomies

## ► Goal:

- Transferrin saturation between 30-40% while maintaining a normal hemoglobin (normal hemoglobin range is 140-180 g/L for men and 120-160 g/L for women).
- Phlebotomy every 3-4 months; FOR LIFE
- If a person with hemochromatosis is otherwise eligible, he/she can become a regular donor at Canadian Blood Services (CBS).

# Other interventions

- ▶ Limit intake:
  - ▶ Avoid taking iron, including iron pills, iron injections, or multivitamins that contain iron.
  - ▶ Limit vitamin C intake, as it enhances iron absorption
  - ▶ Avoid uncooked fish and shellfish (esp oysters and clams). Some fish and shellfish contain *Vibrio vulnificus* bacteria that can cause infections in people who have chronic diseases, such as hemochromatosis.
  - ▶ Limit alcohol intake
- ▶ Ensure vaccinations up to date
  - ▶ Especially for Hepatitis A & B

# Chelating Agents

- ▶ Very rarely used
- ▶ Mechanism of action: Essentially bind metal ions so that they are water soluble and can be excreted in kidneys
  - ▶ Desferoxamine
  - ▶ Deferasirox
- ▶ NOT efficient
- ▶ Concerns regarding toxicity

## Myth 5:

Pharmacists don't have a role in supporting patients with hereditary hemochromatosis

# What can the pharmacist do?

- ▶ Be aware of signs and symptoms of iron overload
  - ▶ Often patients will self-treat and products that one may typically recommend are not ideal for patients with iron overload due to HHC.
  - ▶ Is the person of Celtic or Northern European descent?
  - ▶ Is there a history of severe liver disease, diabetes and/or arthritis in the family?
  - ▶ Look to serum ferritin and transferrin saturation tests - not typically standard

# What can the pharmacist do?

- ▶ Offer information & support:
  - ▶ for treatment of end organ disease,
  - ▶ management of medications pending which organs affected,
  - ▶ awareness of iron containing products
  - ▶ vaccinations
- ▶ Iron Tracker app - for phlebotomies  
<http://www.irontracker.ca/>

# Mr. P. comes in to provide an update

- ▶ After 80 phlebotomies over 2.5 years, Mr. P. has successfully de-ironed and is on maintenance phlebotomies - every 56 days now as a blood donation
- ▶ He and his wife decided to get genetic counselling prior to starting a family.
- ▶ His 2 siblings have been tested and do not have HHC, some deceased relatives ?HHC
- ▶ He continues to have joint pain, which is a bit more involved - wrist
- ▶ His liver enzymes have normalized but his liver remains enlarged, he and his specialist have elected not to do a liver biopsy
- ▶ Still not taking regular prescriptions, you ensure that he is up to date on vaccinations,





# Resources and References

- ▶ The Canadian Hemochromatosis Society  
<https://www.toomuchiron.ca/>
- ▶ Classic Hereditary Hemochromatosis: NORD  
<https://rarediseases.org/rare-diseases/classic-hereditary-hemochromatosis/>
- ▶ National Institutes of Health: National Heart, Lung and Blood Institute  
<https://www.nhlbi.nih.gov/health-topics/hemochromatosis>
- ▶ Diagram for autosomal recessive disorders  
[https://en.wikipedia.org/wiki/Dominance\\_\(genetics\)](https://en.wikipedia.org/wiki/Dominance_(genetics))
- ▶ <https://cphm.ca/wp-content/uploads/Resource-Library/Practice-Directions-Standards/Test-Orders.pdf>
- ▶ <https://www.haemochromatosis.org.uk/Handlers/Download.ashx?IDMF=0c5d81b6-146c-4885-9ec0-91ab59b320e2>
- ▶ Thanks to Mr. P. for permitting his story to be used as an illustration in this presentation