Detailed Study Notes

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Introduction to this Episode

Iron deficiency is a prevalent issue. Worldwide, it is the leading nutritional deficiency. And although there is lower prevalence in high-income countries, a significant number of people are still affected.

Iron deficiency may be a result of too little iron coming in (i.e., via diet choices or low absorption), or from excess losses (e.g., commonly from blood losses). Understanding how these can impact iron status is crucial for both accurate diagnosis and treatment.

In relation to dietary iron, the source of iron is a common talking point, as there are two forms of iron that we can consume. Heme iron is found in meat, fish, and poultry, while non-heme iron is found in plant foods. It is known that heme iron is more readily absorbed than non-heme iron. However, there is much more to this story that makes things complicated.

Some of the nuances of iron bioavailability, absorption, and metabolism, were covered in this episode with leading expert in the area Professor Paul Sharp of King's College London.

Prof. Sharp discusses crucial aspects of dietary iron sources, bioavailability, supplementation, and impacts in the body.

Connection to Previous Episodes

#465: Diagnosing & Treating Iron Deficiency & Excess – Austin Baraki, MD

- This episode of the podcast was the previous episode in this 3-part series on iron.
- In the episode, Dr. Austin Baraki discussed some of the clinical aspects of iron status, including the impacts of both deficiency and excess.
- The discussion also emphasized how crucial both accurate diagnosis and explanation of the deficiency is.
- Some aspects covered include:
    - Iron homeostasis
    - Biomarkers and testing
    - Consequences of iron deficiency and excess
    - Crucial aspects of accurate diagnosis
    - Correcting deficiencies
- You can find the episode page here.

#342: Are Vegan Diets Superior for Health?

- The discussion of heme vs. non-heme iron commonly arises in relation to vegan vs. omnivorous diets.
- In episode 342, Alan and I discussed the question of whether evidence supports the claim that vegan diets are superior for health.
- You can find the episode page here.

SNP #1: Quack Asylum – "Don't Eat Vegetables"

- One of the claims made by those recommending plant foods are "bad", related to the point that many of the nutrients present in vegetables can be obtained from animal foods. And beyond that, these nutrients are more bioavailable when coming from animal sources.
- We addressed this idea, among others in this podcast episode.
- You can find the episode page here.

Functions of Iron

- The molecule **heme** contains iron.
  - Adequate heme supply is essential for several functions including oxygen transport and storage, energy production and drug metabolism.
  - So the primary role of iron relates to **oxygen transport and delivery**.
- Iron is a constitutive element of numerous proteins, such as **hemoproteins** or in **iron–sulfur clusters**.
- There are some important hemoproteins:
  - **Hemoglobin**
    - Found in red blood cells (RBCs)
    - Most of the iron in our body is contained in red blood cell hemoglobin
  - **Myoglobin**
    - Myoglobin performs similar functions to hemoglobin, but specifically in muscle tissues
  - **Cytochromes**
    - Part of the electron transport chain
      - ETC: Converting metabolism of macronutrients to ATP
    - Involved in oxido-reductive reactions
    - So in addition to oxygen transport, we need iron also for **energy production**.

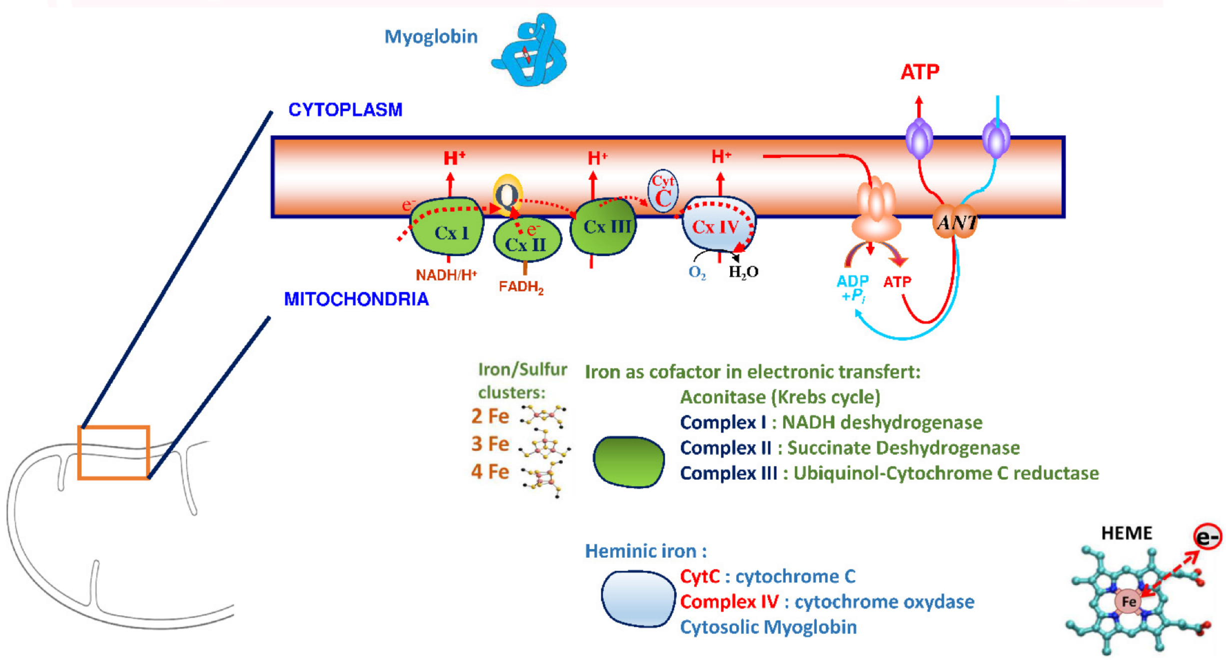

Image from: [Manceau et al., Nutrients 2022, 14, 3214]

Iron Homeostasis

- Iron is an essential mineral for many processes and overall function. But, it is highly toxic to cells and tissues if present in elevated levels.
    - Therefore, maintaining appropriate iron levels is crucial.
- However, there are **no excretory mechanisms** to get rid of excess iron from the body.
    - So the control of iron homeostasis really takes place at the level of the intestine in the amount that we absorb from diet.
- Normally, absorption of dietary iron may be around 10% of consumed iron (although this will go up and down based on many factors).
    - So absorption from the diet contributes only:
        - ~ 1 mg/d in an iron-sufficient adult man.
        - ~ 2.0 - 3.5 mg/d for pre-menopausal women
- About 0.5 - 2.0 mg/d of iron will be lost due to blood loss and turnover of cells

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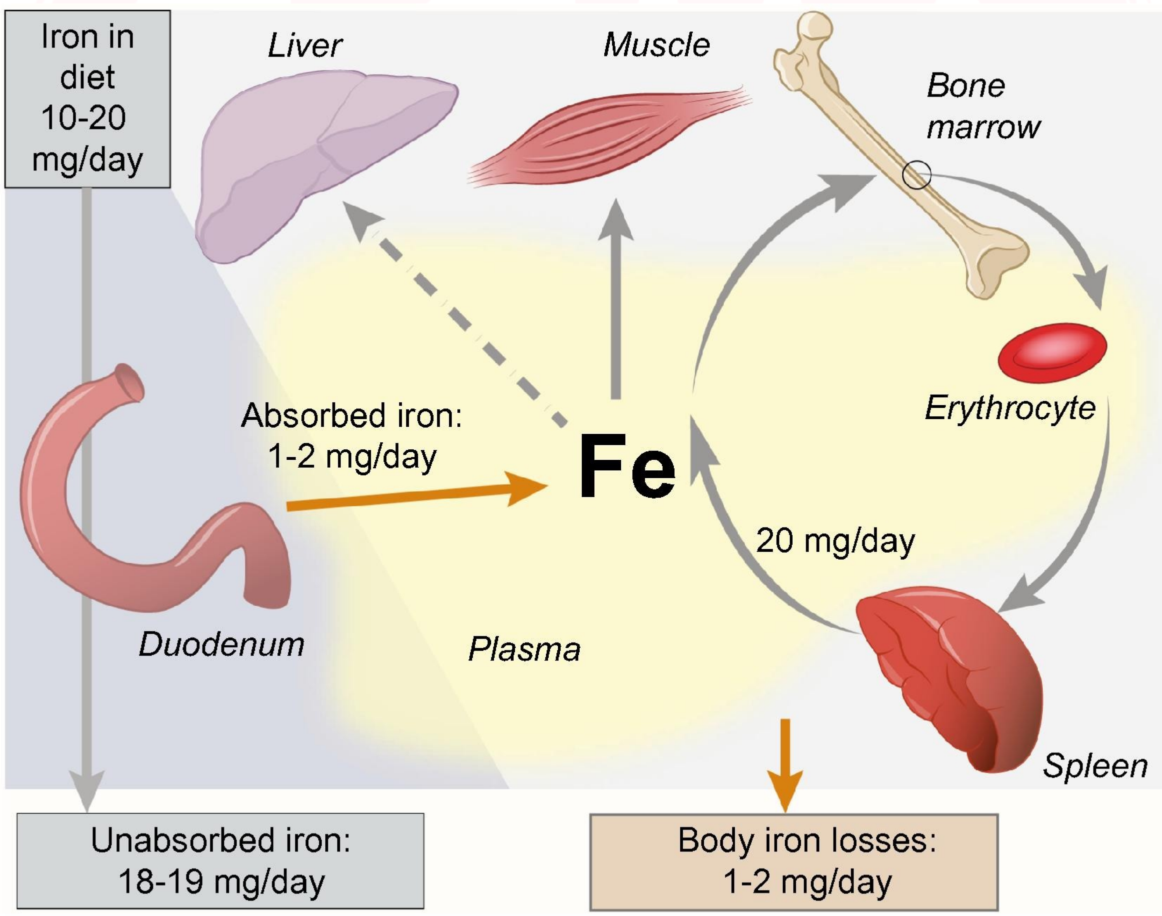


Image from: [Brissot & Loréal, J Hepatol. 2016 Feb;64(2):505-515](#).

Iron Absorption

- **Ferritin**:
    - A protein that stores up to 4,500 atoms of iron.
    - It's the main storage protein in all cells; in plants and in animals.
    - And we can release the iron from ferritin and we can absorb that in the intestine through a transporter that is known as the **divalent metal transporter or DMT-1**.
- DMT-1:
    - Sits on the luminal membrane of the enterocytes in the duodenum (the first part of the small intestine).
    - One of the features of DMT-1 is that it is a proton coupled transporter. So it needs acid to drive the absorption of iron.
    - It's receiving the acidic outflow from the stomach.
    - Acid makes iron more soluble.
- That first part of the duodenum is the only section of the intestine in which we absorb iron efficiently.
- When it comes to the non-heme iron, we can only absorb it in its *reduced form*.
    - So one of the main biological functions of iron is that it can exchange its oxidation state very readily between its oxidized form, which is Fe3 or Ferric iron, and the reduced state, which is Fe2 or ferrous iron.
    - And we can only efficiently absorb the ferrous iron. So we have to reduce the iron before we can absorb it in the intestine.

Iron transport in the enterocyte. Notice DMT-1, ferritin, and reduction of non-heme iron to Fe^{2+}

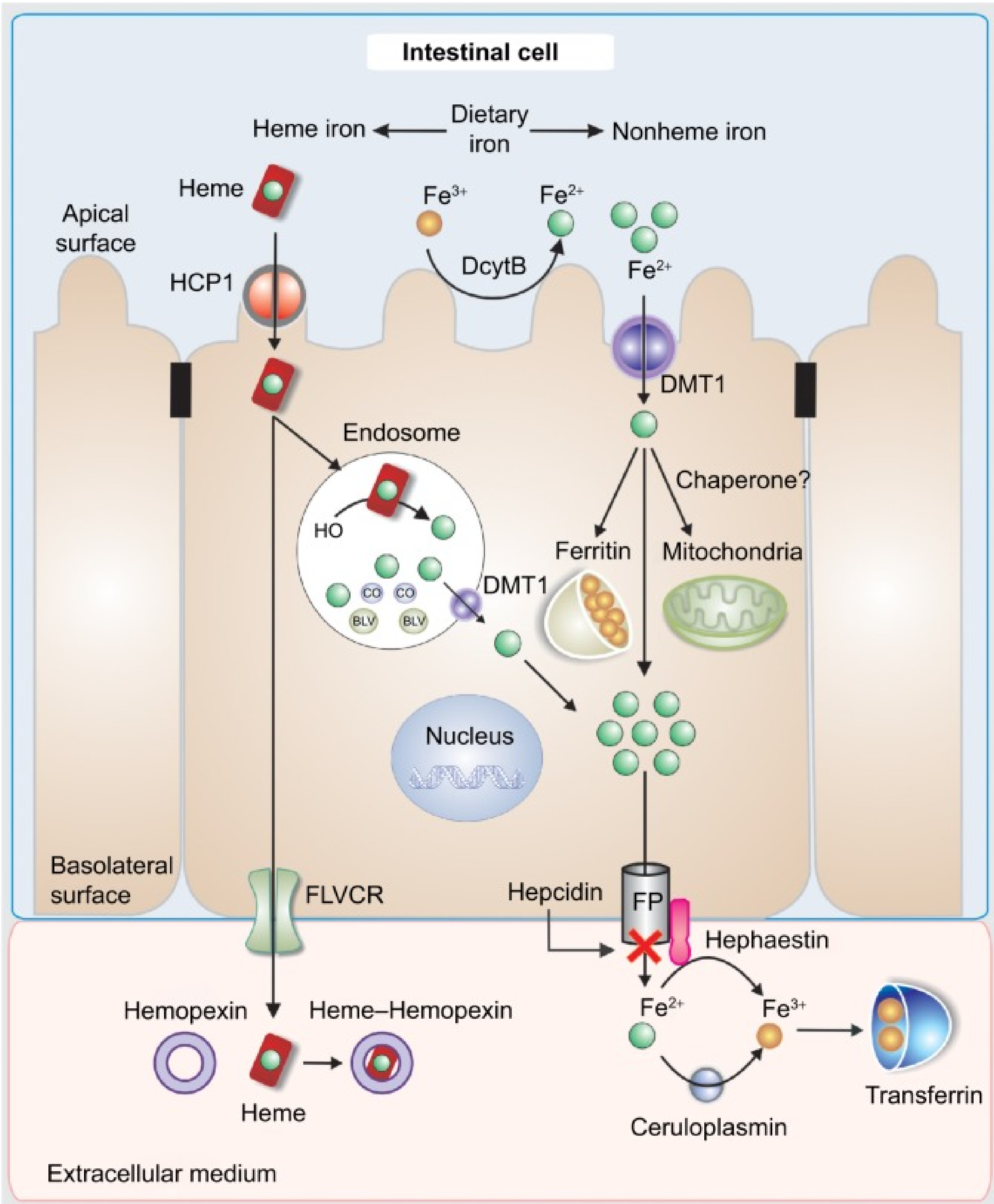
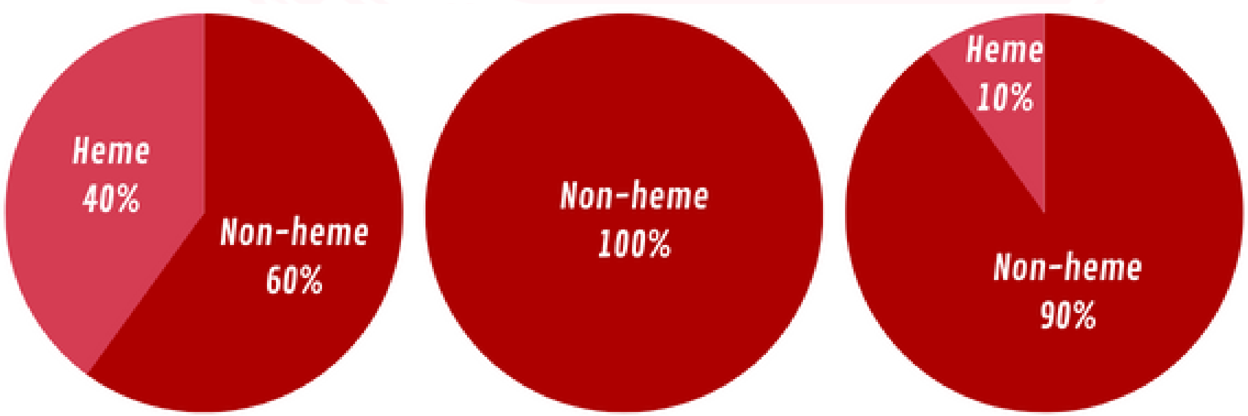


Image from: [Toblli and Angerosa, Drug Des Devel Ther. 2014 Dec 11;8:2475-91](#).

Dietary Sources - Heme vs. Non-heme

- Dietary iron occurs in two main forms:
  - Non-heme iron
  - Heme iron
- Heme is found in animal tissue, while non-heme iron is found in a variety of plants.
- Therefore, animal sources are the only direct source of heme iron.
- And heme iron has long been known to be more bioavailable than non-heme iron.
- And it's true if you look on a like-for-like basis that heme iron is more bioavailable; it's more readily absorbed than non-heme iron.
- But even in people who eat meat on a regular basis, heme is still only a relatively small amount of their dietary intake.
  - So it accounts for maybe 5 - 10% of the total amount of iron that an omnivore is eating.
  - Also, Prof. Sharp highlighted one of the things that's often overlooked: *"people often think that all of the iron that's present in meat is heme iron. And actually more than 50% of the iron that's present in meat is non-heme. It's in proteins like ferritin. So a relatively small amount of our total iron intake comes from heme even if you are a very regular meat eater."*
  - So the vast majority of the iron in everybody's diet comes from non-heme.
  - For example, meat and poultry was observed to contribute between 4.3% and 14.2% of the total iron intake in a multi-ethnic USA cohort (Sharma, Sheehy, & Kolonel, 2013).

Image showing heme and non-heme iron in foods: (a) foods of animal origin; (b) foods of plant origin; (c) dietary iron intake from all foods, daily average.



Adapted from image originally in: Introduction to Human Nutrition, Wiley-Blackwell

How Much Do We Need?

Iron needs are a function of three components:

1. **Growth**
    a. We need iron for growth of all cells and organisms.
2. **Iron losses**
    a. Cells that line the gut, line the urinary tract, skin cells, and hair cells all contain small amounts of iron.
    b. We turnover or shed these cells daily and so need to replace that lost iron.
3. **Menstruation**
    a. Menstruating women need to cover the iron lost via menstrual blood loss.

Recall that absorption from the diet is typically only 10-15%. And remember we need to absorb about:

- ~ 1 mg/d in an iron-sufficient adult man.
- As high as 3.5 mg/d for a pre-menopausal woman.

Reference Nutrient Intake (RNI)

- The amount that should satisfy the metabolic requirements of about 95% of the population.
- Adult males = 8.7 milligrams of food iron per day
- Adult females = 14.8 milligrams of food iron per day

Dietary Inhibitors of Iron Absorption

Dietary factors that can inhibit non-heme iron include:

1. Phytic acid (phytate)
2. Oxalic acid (oxalate)
3. Polyphenols
4. Calcium

- The main inhibitory factor that can limit the amount of iron that we absorb the amount of non-heme iron that we absorb is a molecule called **phytic acid**.
  - Phytic acid is abundant in cereals and cereal products.
  - So we've got this paradox where cereal grains are the main dietary source of iron in the population, yet also contain the most potent inhibitor of iron absorption.
- **Oxalates** are another group of organic acids that will readily bind iron and other divalent metals, so will stop the absorption of that.
- Some **polyphenols**, which are present in coffee and various fruits and vegetables, are also very good at binding iron and stopping it being absorbed.
- There's some evidence that calcium might be involved in the inhibition of iron absorption.

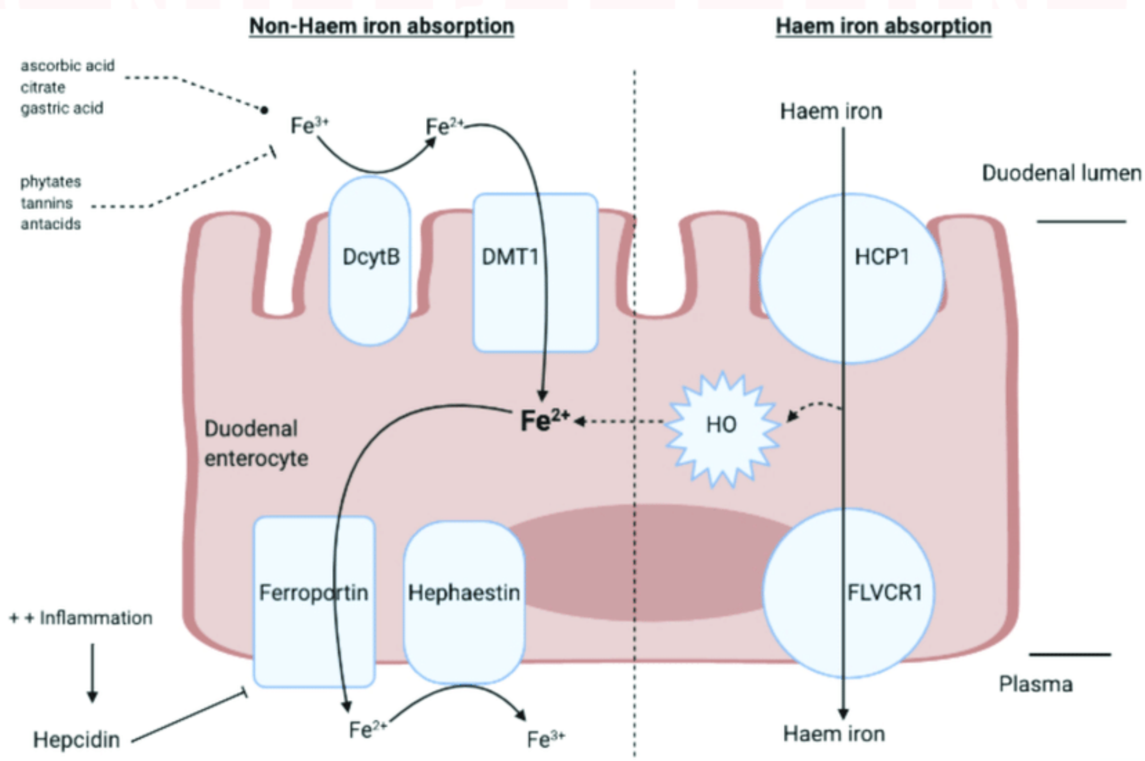


Image from: [Kumar & Brooks, Nutrients. 2020 Nov 12;12(11):3478.]

Dietary Enhancers of Iron Absorption

- The factors that increase the absorption of iron tend to be factors that will favor the reduced iron state, so will favor iron being in its ferrous form.
- The most powerful of those agents is ascorbic acid or vitamin C
- Ascorbic acid is a very potent reducing agent and it very readily reduces the oxidized iron (ferric iron) into the reduced form, ferrous iron.
- To a much lesser extent, there are also effects from other small organic acids.
    - E.g. malic acid or citric acid, found in fruits and vegetables.

Vitamin C (Ascorbic Acid)

- A study by Collings et al. (2013) showed that the addition of ascorbic acid (from citrus fruit) to each meal resulted in a significant increase in absorption rate to across a range of baseline ferritin levels:

From: Collings et al., American Journ Clin Nutr, Vol 98, Iss 1, 2013, pg 65–81

	Absorption	
Serum Ferritin	Standard Diet	With Enhancer
6 µg/L	17.9%	23.0%
12 µg/L	10.8%	13.9%
15 µg/L	9.2%	11.8%
40 µg/L	4.5%	5.8%

- ***Note:*** Notice how iron absorption increases with lower iron status (and conversely decreases as iron status is higher). This shows the body's regulation of absorption in order to maintain homeostasis.

Single-Meal Studies vs. Whole Diet Interventions (Mechanisms & Outcomes)

- Many acute, mechanistic studies (e.g. isotope absorption studies) have shown there are many compounds that can impact iron absorption, studies looking at an exposure of the whole diet, or on outcomes of iron status, don't always support the single meal studies.
- This may be explained by the compensatory mechanisms we have for maintaining iron homeostasis
- A good example of this (mentioned in the 'Key Ideas' segment), is shown in the results of a study by Hoppe et al. (2019):
    - For 12 weeks, Swedish females consumed either:
        - 200 g/d dephytinized wholegrain rye bread
        - High phytate bread
    - The only significant effect observed was a small but significant reduction in iron status in the ***low phytate*** group.
    - So this result contradicts what one might suspect "should" happen on the basis of the known mechanism by which phytate inhibits iron absorption.
- Therefore we shouldn't be relying on using results from single meal studies to come to strong conclusions on how diet will affect iron status, or what strategies will help improve iron status.

Iron Supplementation

- People should be prescribed them by a medical practitioner.
    - See the previous episode with Dr. Austin Baraki for an explanation why someone taking supplements by their own decision after getting a blood test is a bad (and potentially fatal) mistake.
- They are prescribed in cases of anemia.
- The gold standard supplement typically used is **ferrous sulfate**.
    - It's relatively soluble and it's quite readily absorbed.
- There are others: e.g. iron salts like ferrous fumarates. Or various conjugations with amino acids; e.g., a ferrous bisglycinate compound that's used.
- They're all essentially serving the same purpose: They're trying to deliver iron in a bioavailable form that would be readily absorbed by the intestine.
- Typically a *clinically- prescribed* supplement has **65 milligrams** of iron
    - That is a huge amount of iron. If we think about that in terms of diet, that is a week's worth of iron in one go. We've only got a finite capacity to absorb it.
- So a lot is just going to pass straight from the small intestine and into the colon.
    - There are species of bacteria in the colon that are specifically target iron. They're **iron sulfur bacteria**.
    - Side effects = nausea, gut pain, black tarry stools.
        - Directly due to the production of iron sulfide by these ion sulfur bacteria.
        - So actually the compliance with these very high dose iron supplements is limited.
- Alternative dosing regimens have been proposed.
    - Higher doses of iron lead to lower absorption rate
        - So absolute absorption is higher, but as dose increases a smaller percentage is absorbed. Plus high doses come with side effects.
        - Options: give lower doses and/or more infrequently (e.g. alternate days)
        - High doses can lead to “mucosal block”.
            - Transporters are swamped and so will down-regulate.
            - Can take up to 24 to 36 hours for those transporters to move back towards their normal position.
    - In addition, high dose iron supplements increase **hepcidin**.
        - Hepcidin binds to the ferroportin transporter and blocks the efflux of iron out of cells and back into the circulation.
        - So high hepcidin basically locks iron up inside cells.