Detailed Study Notes

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Introduction to this Episode

Iron is an important nutrient for athletes, given that it is used for oxygen transport and energy production.

However, research on athletes often reports a relatively high prevalence of iron deficiency. Common symptoms of low iron status like lethargy, fatigue and negative mood states are naturally of concern to athletes. But there is also the potential for low iron to directly impact work capacity. Therefore, maintaining adequate iron status (and knowing the signs of iron deficiency) is crucial for athlete health and performance.

In this episode, Professor Pete Peeling of the University of Western Australia discusses the role of iron in performance, iron deficiency in athletes, the impact of exercise-induced inflammation, and other important issues.

Connection to Previous Episodes

#240: Exercise-Associated Anemia, Hepcidin Activity & Implications for Athletes

- In this episode registered dietitian Erica Goldstein was on the podcast to discuss issues related to iron-deficiency, especially in the context of athletes.
- We discussed the symptoms of iron-deficiency anemia, why iron is so crucial for athlete performance, and the role of hepcidin, among other things.
- You can find the episode page here.

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

- This episode was the 1st 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.
- You can find the episode page here.

#466: Iron Absorption from Foods & Supplements - Prof. Paul Sharp

- This episode was the 2nd in this 3-part series on iron.
- 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.
- You can find the episode page here.

Endurance Sport Episodes

In the current episode with Prof. Peeling, he references two of his many collaborators that do work related to endurance sport nutrition and physiology; **Dr. Trent Stellingwerff** and **Dr. Louise Burke**. You can listen to episodes with them:

- #185: Trent Stellingwerff, PhD – Nutrition Strategies for Endurance Sports
- #282: Louise Burke, PhD – Project Supernova: The Science of Fuelling Elite Athletes

Background Context

- Iron is a mineral used for oxygen transport and energy production, processes that are crucial in athletic performance.
    - So iron status and utilization is of vital importance to athletes.
- ~15–35% of female athletes and ~3–11% of male athletes are reported to have iron deficiency, although some cohorts have shown much higher rates of deficiency (Sim et al., 2019).
    - Female athletes have higher iron deficiency rates, likely due to iron losses via menstruation.
- Common symptoms of low iron status like lethargy, fatigue and negative mood states can of course impact sports performance.
- However, there is also a risk of more direct effects on work capacity when iron status is particularly compromised.

Stages of Iron Deficiency

There are typically three stages described for the development of iron-deficiency anemia:

1. **Iron depletion**
    a. The levels of storage iron are reduced
    b. Typically assessed by serum ferritin concentration
2. **Iron-deficient erythropoiesis**
    a. There is a restricted iron supply to the bone marrow leading to mild tissue deficiency
    b. Reduced transferrin saturation and increased soluble transferrin receptor and erythrocyte protoporphyrin are often used here
3. **Iron deficiency anemia**
    a. The production of functional iron containing compounds is compromised (low Hb).
    b. In situations of chronic disease, anemia can develop without an initial iron deficiency (anemia of chronic disease)

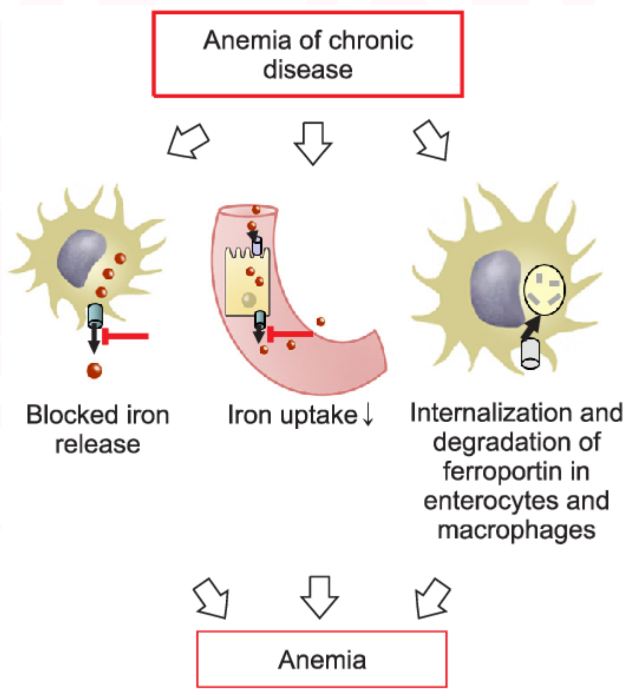


Image from: [D'angelo, Blood research 2013; 48(1): 10-15](#).
© 2013 Korean Society of Hematology

Dr. Peeling noted that, most commonly, measures of serum ferritin and hemoglobin are used to determine what stage someone is at (although there may be issues with these markers).

Typically this means cut-offs of:

- **Stage One**
  - Serum ferritin level is below 35 micrograms per liter, and your hemoglobin was normal
  - Athlete could be considered “iron depleted”
  - Most likely they are asymptomatic at this point
- **Stage Two**
  - Serum ferritin levels < 20 micrograms per liter. But hemoglobin is still normal (~120-130 grams per liter, or 12-13 grams per deciliter).
  - So you've got deficient iron stores, but they're not yet impacting your ability to produce red blood cells or your hemoglobin.
- **Stage Three (Anemia)**
  - Serum ferritin < 12 - 15 micrograms per liter.
  - Hemoglobin is now starting to be impacted - Compromised function.

There is some conjecture around how good those measures are because hemoglobin is impacted by plasma volume, and in athletes that can change quite a bit. If this is not accounted for, it can lead to pseudo-anaemia or “sports anemia”. And if there's inflammation around, then you may get an elevated ferritin level as a result of that inflammatory process.

Dr. Peeling and colleagues proposed the following **definitions** for the stages of iron deficiency **for athletic populations** (Peeling et al., 2007):

- **Stage 1—iron deficiency (ID):** iron stores in the bone marrow, liver and spleen are depleted (ferritin<35 µg/L, Hb>115 g/L, transferrin saturation>16%).
- **Stage 2—iron-deficient non-anaemia (IDNA):** erythropoiesis diminishes as the iron supply to the erythroid marrow is reduced (ferritin<20 µg/L, Hb>115 g/L, transferrin saturation<16%).
- **Stage 3—iron-deficient anemia (IDA):** Hb production falls, resulting in anemia (ferritin < 12 µg/L, Hb<115 g/L, transferrin saturation<16%).

Sim et al., 2019: *“it appears that depleted iron stores (stage 1) may have a minimal impact on physical performance; however, early correction of iron depletion is likely to prevent the issue from further progressing into stages 2 and 3”*

Athlete Risk of Iron Deficiency

Athletes in general may be at increased risk of iron losses for a few reasons. This includes:

- **Sweating** - We lose iron in our sweat. And if we're exercising more, then we need to replace that iron.
- **Dehydration** - Dehydration can cause small lesions in the bowel, and therefore we can have micro blood loss, which can over time lead to iron deficiency.
- **Red blood cells senescence (hemolysis)** - If we have older red blood cells in the system, just the impact of exercise itself can cause those red blood cells to to break down and therefore we lose the iron to the system of those red blood cells.
- **Hormone elevations from exercise** - So we know that when we exercise, we get an increase in a hormone called **hepcidin** (more later)

So the general person will lose between one and two milligrams of iron per day, but an athlete will lose between three and four milligrams per day.

Dr. Peeling highlighted four groups of athletes at **higher risk** of iron deficiency:

1. **Pre-menopausal female athletes**
    a. Increased iron loses via menstruation
2. **Endurance athletes**
    a. High training volumes & commonly athletes fail to refuel adequately
    b. Exercise-induced hemolysis: Distance running has been associated with significant destruction of red blood cells (RBC), which is mainly due to the footstrike when running.
3. **Athletes in weight-class or physique-related sports**
    a. Due to restricted energy intake
4. Athletes consuming vegan/vegetarian diets
    a. Those on such diets, on average, tend to have lower iron status

Risk of having low iron status can be increased by low energy intake, vegetarian diets and endurance exercise (Castell et al., 2019).

Hepcidin

- **Hepcidin** is a liver-derived, iron-regulating peptide hormone
- "It controls the delivery of iron to blood plasma from intestinal cells absorbing iron, from erythrocyte-recycling macrophages, and from iron-storing hepatocytes." (Ganz et al., 2016)
- It binds **ferroportin** transporters at the small intestinal cells and blocks them from being able to export iron into the bloodstream. So it directly blocks iron absorption.
- When hepcidin is high, it limits iron export into the plasma.
- Hepcidin can be upregulated in a few situations, most notably during periods of **inflammation**, which is what occurs with exercise.
    - There's a transient period post-exercise where there's a reduction in iron absorption as a result of elevations in hepcidin.

Researchers have also found some ways to *suppress* hepcidin levels.

- When you go to **altitude** the body produces a different hormone, **erythroferrone**.
- And erythroferrone seems to attenuate the elevation in hepcidin
- When we go to altitude, the stimulus is causing us to produce more red blood cells to be able to deal with the altered environment and altitude.
- So the body's response is to suppress hepcidin so that we can absorb more iron so that we can start to make the new red blood cells that are required to survive at that altitude.

Work from Stephen Hennigar at Florida State University showed that (Hennigar et al., 2021):

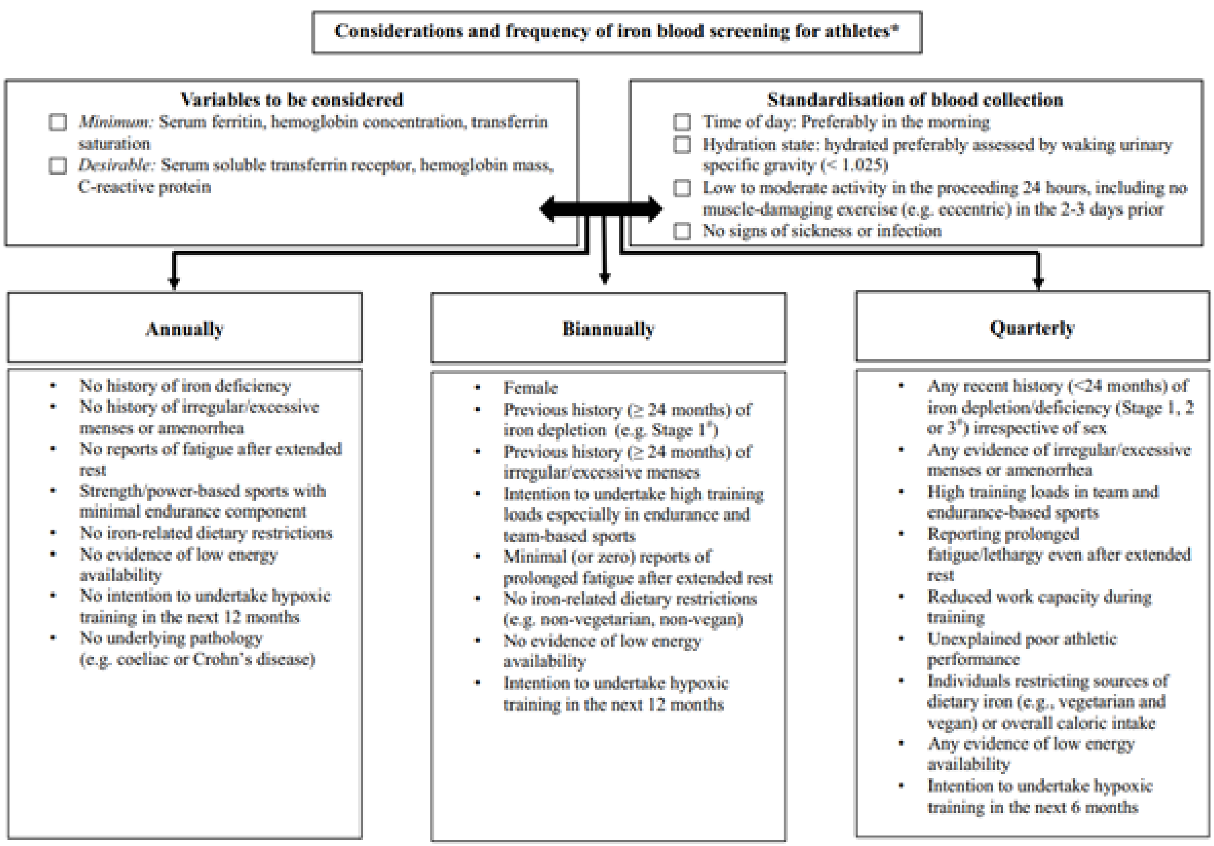
- Strenuous physical activity decreases dietary iron absorption compared with rest.
- Energy deficit exacerbates both the hepcidin response to physical activity and declines in dietary iron absorption compared with energy balance.

Testing & Screening in Athletes

Factors to consider when testing:

1. Training and/or heat adaptations can lead to too much fluid in the blood, which would give an inaccurate plasma iron concentration (Voss et al. 2014)
2. Athletes should standardize the time of day, the hydration state and their prior activity levels leading to the blood assessment (Castell et al. 2019)
3. Muscle damaging exercise should be avoided for the 2–3 days prior to the assessment due to the inflammatory response (Peake et al. 2005)

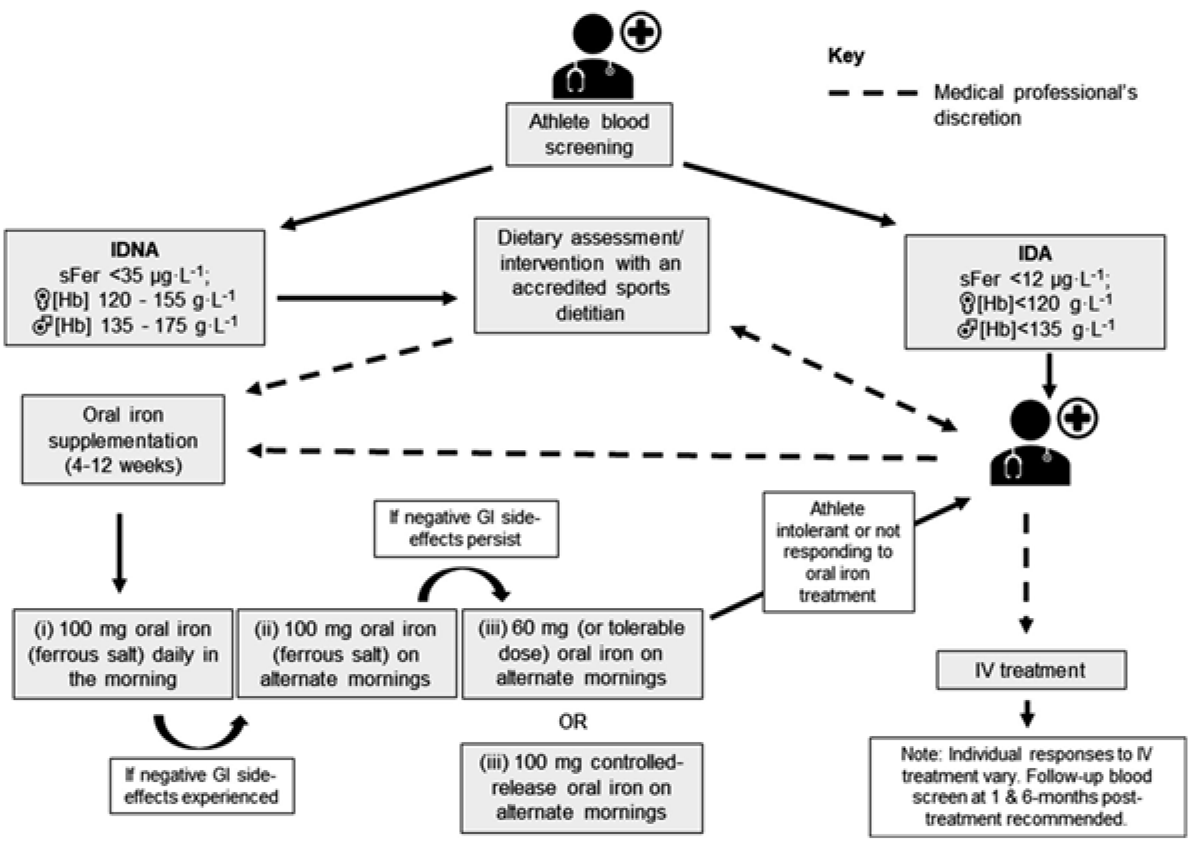
Framework of considerations for the frequency of iron blood screening in athlete populations:



From: Sim et al., European Journal of Applied Physiology volume 119, pages1463–1478 (2019)

Treatment Strategies for Iron Deficient Athletes

- After looking at diet (and potential causes of blood loss), oral iron supplementation is typically the first iron replacement therapy intervention to be used.
- However, many athletes encounter associated gastrointestinal side-effects which can lead to them stopping the treatment plan before it is finished.
- **Alternate day oral iron supplementation** may be an effective strategy to address negative gastrointestinal side-effects from iron supplementation in athletes.
- Work from Peeling's group (McCormick et al., 2020) has shown that iron consumed in the morning, and in close proximity (30 minutes) to the end of an exercise bout may *"make strategic use of a potential short-term 'open window' for increased iron absorption, prior to the increase in hepcidin levels."*
- Therefore, Dr. Peeling and his colleagues have proposed "a contemporary strategy of oral iron therapy entailing morning supplementation, ideally within the 30 min following morning exercise, and in athletes experiencing gut sensitivity, consumed on alternate days or at lower doses." (McCormick et al., 2020)



From: McCormick et al., Sports Medicine volume 50, pages2111–2123 (2020)

McCormick et al., 2020 Study

- Wanted to see whether iron absorption would improve in the morning versus the afternoon, with exercise or without exercise.
- They fed participants an iron isotope and traced how much of that iron ended up in a red blood cell 14 days later.
    - The more in the red blood cell, means the more that they absorb.
- Participants exercised in the morning, and were fed the isotope within 30 minutes of finishing exercise.
- In the morning exercise group, it improves the amount of iron they absorb if they consume the iron within 30 minutes of finishing exercise.
- But that didn't happen in the afternoon group. So if you exercise in the afternoon, you didn't absorb any more of that iron, likely a result of that diurnal increase in hepcidin levels.

Alternate day oral iron supplementation

- Diego Moretti and colleagues in Switzerland.
    - A lot of work looking at iron deficiency in African children.
- "Oral iron supplementation schedules usually entail the daily provision of a total of 100–200 mg elemental Fe in single or in divided doses.
- Iron absorption from supplements is generally low, 5–25% when administered in fasting state, and 0.5–13% when consumed with meals.
- Recent studies suggest that oral iron doses ≥60 mg elicit an acute iron-induced rise in hepcidin, which reduces iron absorption of a subsequent dose at 24 h, but not at 48 h (Moretti et al., 2015).
- **Alternate day dosing** provides higher fractional iron absorption than daily dosing and may, by providing an overall lower Fe dose, lower gastrointestinal side effects.
- Recent guidelines suggest that **daily morning doses** of 50–100 mg iron on alternate days may be a viable treatment option for oral iron supplementation in iron-deficient patients with or without mild anemia."