Exploration of a Novel Treatment Method for Hemochromatosis

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Abstract:

Hemochromatosis is the most common genetic disease in white people; it is characterized by progressive iron accumulation, which can lead to organ dysfunction and death. There are three treatment options: phlebotomy, pharmaceuticals, and dietary management. For patients who cannot use the first two, diet is essential to managing the disease. However, more research is needed to understand how diet can be fully utilized as a treatment method. There is hope that natural iron chelators, such as oxalates, can be used to reduce dietary iron absorption. Oxalates are common in vegetables such as spinach; however, previous research suggests that the application of heat to plants containing oxalates can reduce their iron chelation potential. This study proposes to evaluate the effectiveness of consumption of oxalates in spinach for decreasing dietary iron absorption, taking into consideration the effect of heat on spinach preparation. Participants will consume spinach prepared at home via blanching for pre-determined times while other factors that affect iron absorption are controlled. Iron and oxalate levels will be evaluated before and after spinach consumption, and then compared to determine if oxalates in spinach increase or decrease dietary iron absorption. The results will be significant to future hemochromatosis dietary management.

Hemochromatosis is a genetic condition characterized by unusually efficient dietary iron absorption.[[1]](#footnote-1) Essentially, more iron than the body requires is absorbed from the diet. This excess iron progressively accumulates throughout the body, especially in organs and joints.[[2]](#footnote-2) The resulting condition, massive iron overload, leads to various health concerns, including organ failure and death.[[3]](#footnote-3)

Hemochromatosis is caused by certain gene mutations. The most common of those, H63D, is not always symptomatic. [[4]](#footnote-4) The most commonly expressed mutation is the HFE C282Y mutation on chromosome six, which results in the substitution of tyrosine for cysteine in the corresponding HFE protein.[[5]](#footnote-5) Although the exact process through which HFE protein works is unknown, some recent research suggests it is similar to hepcidin, a key iron-regulatory hormone.[[6]](#footnote-6) Hepcidin monitors ferroportin, which transports iron in a variety of cells.[[7]](#footnote-7) When sufficient iron is absorbed, hepcidin binds to ferroportin, which reduces additional iron absorption.[[8]](#footnote-8)

Hemochromatosis is the most common genetic disorder in people of white descent.[[9]](#footnote-9) The disease originated as an evolutionary adaptation to the Stone Age shift from a meat-dependent diet to a grain-dependent diet.[[10]](#footnote-10) While meat is typically high in iron, grains are not naturally. However, modern technologies have allowed for fortification of grains with artificial iron.[[11]](#footnote-11) The result is that individuals with hemochromatosis, a once adaptive trait, are now at a disadvantage because they absorb too much iron. This evolutionary history is confirmed by the strong geographic distribution of the disease and its particular mutations. The C282Y mutation is most common in people of Northern European descent.[[12]](#footnote-12) However, C282Y is also common in Australia and the Mediterranean region.[[13]](#footnote-13) H63D is most common in people of Southern European descent.[[14]](#footnote-14)

Hemochromatosis cannot be cured, but there are a variety of treatment methods. The primary goal of treatment is normalization of iron levels in the body and prevention of organ dysfunction.[[15]](#footnote-15) If organs have already been damaged when treatment begins, the goal is to minimize additional damage.[[16]](#footnote-16) Currently, there is only one effective method for normalizing iron stores: phlebotomy.[[17]](#footnote-17) Phlebotomy is the periodic removal of blood using a large needle.[[18]](#footnote-18) This stimulates the production of new red blood cells, which requires the body to use excess stored iron.[[19]](#footnote-19) The result is a temporary overall reduction in bodily iron stores. However, patients undergoing phlebotomy must regularly undergo the procedure, otherwise iron levels will once again rise. Although phlebotomy improves the “quantity and quality of life” for hemochromatosis patients, it comes with a variety of risks. These risks include vein access issues and negative reactions to blood loss, including fainting.[[20]](#footnote-20) Additionally, phlebotomy requires a significant time commitment, and can be poorly tolerated due to fear of needles or blood.[[21]](#footnote-21)

Phlebotomy’s inherent flaws led to the development of another treatment option: a pill. Iron chelation drugs, like hepcidin, prevent excess iron absorption.[[22]](#footnote-22) Although these drugs show promise in reducing the amount of iron absorbed, they come with a variety of risks, and quite a bit of research is still necessary to determine long-term side effects.[[23]](#footnote-23)

For patients who cannot or will not tolerate phlebotomy and drug treatment, there is only one other option: dietary management. Dietary management is the simplest and least expensive of hemochromatosis treatment methods, but also the least researched. Dietary management falls into three categories: avoiding iron, avoiding substances that increase iron absorption, and consuming substances that reduce iron absorption.[[24]](#footnote-24) Of these, the simplest is avoiding substances that are high in iron, which include: red meat, liver, seafood, enriched/fortified grains, and spinach.[[25]](#footnote-25) Substances that increase iron absorption, such as ascorbic acid and alcohol, are also relatively well known because of their role in treatment of patients who need to increase iron absorption.[[26]](#footnote-26) There are several compounds thought to decrease dietary iron absorption, including: tannins, polyphenols, calcium, and oxalates.[[27]](#footnote-27) However, their precise effects are neither confirmed nor understood. What I hope to accomplish in this study is to clarify the effect of oxalates, a particular compound suspected to inhibit iron absorption, on bodily iron levels.

Oxalate is an iron chelator, similar to hepcidin and hemochromatosis treatment drugs. However, oxalate is unique because of its relationship to oxalic acid; when heat is applied, oxalate transforms into oxalic acid.[[28]](#footnote-28) It is unknown if oxalic acid has the same iron chelation potential that oxalates do. In general, it is recommended that substances containing either compound be consumed in moderation due to their toxicity.[[29]](#footnote-29) However, the reasons that the compounds are toxic to many could pose a significant benefit to a select few: hemochromatosis patients. Oxalate binds minerals and metals, including iron, before the body can absorb them; therefore, the compound should be a good iron chelator. While iron chelators are dangerous to someone with low to normal blood iron levels, they can greatly reduce symptoms in hemochromatosis patients. Many common vegetables, such as rhubarb, spinach, and beets, have naturally high levels of oxalates.[[30]](#footnote-30)

This study will evaluate the effectiveness of oxalates and oxalic acid in spinach as iron chelators. Spinach was selected because it is high in iron and oxalates; additionally, it is relatively inexpensive and easy to prepare.[[31]](#footnote-31) Participants will consume one of several variations of prepared spinach, before and after which iron and oxalate levels will be measured. What follows is a basic summary of the methodology for this proposed study.

Although previous studies of oxalates are somewhat limited, a variety of studies have been performed on similar substances. Typically, a serving of food high in the compound being studied is administered, after which blood and/or urine is examined. This study will follow a similar format.

Although the goal of this research is to help hemochromatosis patients, the general effects of oxalates and oxalic acid on iron can be determined using a population of non-hemochromatosis individuals. Therefore, participants without major dietary restrictions will be welcomed regardless of hemochromatosis diagnosis status. Participants will be required to confirm that they have access to transportation to the lab-testing site, and that they have access to the necessary materials for spinach preparation. Additionally, patients will be asked to stop all alcohol consumption and any iron supplements for a period of one week prior to the first labs, and for the entirety of the study.

Spinach preparation will occur in the participant’s home according to a detailed set of instructions. These instructions will be based on Yadav and Sehgal’s 1995 study.[[32]](#footnote-32) Although *Yadav and Sehgal 1995* tracked a wide variety of factors, this study will be limited to just one: blanching time. Blanching involves boiling something for a set amount of time, followed by rapidly cooling it to prevent further cooking. Participants will be assigned a blanching time (0, 5, 10 min). The amount and variety of spinach will be controlled for. Participants will be asked to consume one-hundred grams of spinach, or one serving, once a day between the hours of four and seven in the afternoon, for seven days.[[33]](#footnote-33)

Iron and oxalate levels will be measured via blood and urine analysis, respectively. Blood will be collected in iron-free vessels before and after the weeklong oxalate-loading period.[[34]](#footnote-34) Urine will be collected over a twenty-four hour period before the trial begins, and on the last day of the trial. The two tests that will be run in lab are serum iron and oxalate urine.[[35]](#footnote-35)

This study will have significant implications regardless of the precise results. If iron levels decrease after a week of oxalate loading, it suggests that the blanching method used was effective at freeing iron chelators to bind iron from the spinach. In contrast, if iron levels increase over the course of the study for any particular blanching time, it suggests that the oxalates have been transformed or incapacitated by the heating mechanism.

The broader medical implication of this research applies specifically to individuals at risk of iron overload, i.e. hemochromatosis patients. If spinach proves to contain an iron chelator, it should be recommended to patients as a new, supplemental method of managing hemochromatosis. If spinach increases iron levels, patients should be instructed to avoid it, as they would other high iron foods. Based off the previous study by Dagostin 2017, it seems likely that increased blanching time will result in lower oxalate concentration, which will in turn result in higher iron levels. If this is true, and this study reflects only an increase in iron levels for cooked spinach, then patients should specifically be warned of the dangers of eating cooked spinach and other foods high in oxalates.

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Budget

**EXPENSES**

**Materials**

Stipend for Participants **$3000**

Participants will be provided with a $100 stipend for their participation in the study. This will cover transportation costs to and from the lab on the first and final days of the study, as well as any labor required in the spinach production. There are three experimental treatment groups, and each will have 10 participants assigned to it randomly. Therefore, there will be 30 total participants.

Lab Tests **$8280**

Lab tests will be ordered online for each patient, and then performed at a nearby LabCorp location (12555 W Jefferson Blvd). Serum Iron Tests are $23 each, and Oxalate Urine Tests are $115 each. Each participant will undergo each test twice.

Spinach **$195.46**

Spinach will be provided to the participants at the beginning of the one-week trial period to control for type of spinach. One hundred gram servings will be pre-divided into individual Ziploc bags to control for amount of spinach. Each participant requires seven hundred grams of spinach, so twenty-one-thousand grams of spinach are needed in total. This is the equivalent of seventy-five ten-ounce bags of spinach from Walmart. These are available for $2.38 with 9.5% sales tax.

Ziploc Gallon Bags **$31.47**

Ziploc bags will be used to divide one hundred gram spinach servings for participant use. Each participant will need seven bags, so two hundred and ten bags are needed in total. Bags are available for $4.79 per thirty eight bags at Target, with 9.5% sales tax.

**TOTAL $11,506.93**

1. Wapnick 705, Adams 3. [↑](#footnote-ref-1)
2. Surber 1, Adams 2. [↑](#footnote-ref-2)
3. Wapnick 705, Surber 1. [↑](#footnote-ref-3)
4. Aranda 768. [↑](#footnote-ref-4)
5. Surber 1, Aranda 768. [↑](#footnote-ref-5)
6. Adams 3, McCune 526. [↑](#footnote-ref-6)
7. McCune 526. [↑](#footnote-ref-7)
8. Ibid. 526. [↑](#footnote-ref-8)
9. Surber 1. [↑](#footnote-ref-9)
10. Naugler 691. [↑](#footnote-ref-10)
11. Olsson 782. [↑](#footnote-ref-11)
12. Naugler 691. [↑](#footnote-ref-12)
13. Surber 1. [↑](#footnote-ref-13)
14. Aranda 768. [↑](#footnote-ref-14)
15. Adams 2. [↑](#footnote-ref-15)
16. Ibid. 8. [↑](#footnote-ref-16)
17. Ibid. 3. [↑](#footnote-ref-17)
18. Ibid. 9. [↑](#footnote-ref-18)
19. Ibid. 3. [↑](#footnote-ref-19)
20. Ibid. 13. [↑](#footnote-ref-20)
21. Adams 13, McCune 527. [↑](#footnote-ref-21)
22. Adams 16. [↑](#footnote-ref-22)
23. McCune 527. [↑](#footnote-ref-23)
24. Adams 18. [↑](#footnote-ref-24)
25. Iron-Rich Foods, Adams 19. [↑](#footnote-ref-25)
26. Adams 20-22, Herbert 1995. [↑](#footnote-ref-26)
27. Adams 22, Hallberg 1987, Aranda 771. [↑](#footnote-ref-27)
28. Noonan 68. [↑](#footnote-ref-28)
29. Ibid. 66. [↑](#footnote-ref-29)
30. Ibid. 64. [↑](#footnote-ref-30)
31. Yadav and Seghal 126. [↑](#footnote-ref-31)
32. Ibid. 126. [↑](#footnote-ref-32)
33. Aranda 768. [↑](#footnote-ref-33)
34. Aranda 768, Wapnick 705, Serum Iron Test. [↑](#footnote-ref-34)
35. Oxalate Urine Test, Serum Iron Test. [↑](#footnote-ref-35)