IRON SUPPLEMENTATION AND ITS EFFECT ON FERRITIN LEVELS IN FEMALE COLLEGIATE TRACK AND FIELD ATHLETES

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The Supervisory Committee certifies that this ***disquisition*** complies with North Dakota State University's regulations and meets the accepted standards for the degree of

MASTER OF SCIENCE

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ABSTRACT

Adequate stores of iron are necessary for optimal athletic performance and severe iron depletion resulting in iron-deficiency anemia may depress performance. This is important for athletes, particularly females, to address because they can be prone to iron deficiency anemia. This review examines research data that has shown oral iron supplementation in doses of at least 45 mg ferrous sulfate or 106 mg ferrous fumarate improves iron status and may improve measures of athletic performance. It is recommended that female athletes most at risk of iron deficiency be screened at the beginning of and during training seasons using ferritin measures. Appropriate dietary and/or supplementation recommendations should be made to those with compromised iron status.

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CHAPTER I. INTRODUCTION

Iron is an essential component to the human body, and especially, to the athlete who places such high demands on the body every day. As part of myoglobin, iron plays a significant role in the transfer of oxygen in the muscle cells, and as part of hemoglobin, participates in the exchange of oxygen and carbon dioxide in the blood (di Santolo, Stel, Banfi, Gonano, & Cauci, 2008). Without adequate levels of iron, an athlete cannot efficiently produce ATP (adenosine triphosphate), which is the body's primary energy source (Hagler et al., 1981). Unfortunately, iron deficiency is all too common. In fact, 25 to 36% of adolescent and adult females competing in a variety of sports report low iron levels, with those numbers increasing to nearly 70% during the competitive season (Auersperger, Skof, & Lainscak, 2013). Iron deficiency is particularly harmful for athletes because impairment in blood gas transport in the body may decrease athletic performance and may be a reason for fatigue, weakness and dizziness (di Santolo et al., 2008).

Iron depletion seems to occur more frequently among athletes than in the general population and may affect performance capacity (Koehler et al., 2012). For at risk groups, prevalence rates for iron depletion as high as 58% have been reported, with the main causes of such depletion pointing to reduced dietary iron and increased iron requirements (Peeling et al., 2009). Dietary iron availability may be diminished due to inadequate intake or impaired intestinal absorption. When low iron intake is coupled with a diet high in compounds, such as tannins from tea or coffee and phytates from whole grains and/or occur in combination with a diet low in vitamin C or meat, iron status might be impaired. Beard and Tobin reported that athletes often ingest less than the recommended intake for iron (Beard & Tobin, 2000). Additionally, individuals performing regular exercise might have higher needs for iron because

of a higher demand for iron as muscle mass increases and blood volume expands with the additional physical training (Gropper, Blessing, Dunham, & Barksdale, 2006).

Non-dietary factors may also compromise iron status. For the athlete, iron demands may be elevated because of increased losses via menstruation (for women), gastrointestinal bleeding that occurs during prolonged and intense exercise, exercise-induced hemolysis due to repetitive foot strike, exercise-induced inflammatory processes or even genetics (Rodenburg & Gustafson, 2007).

Numerous studies have shown that iron-deficiency anemia has negative effects on athletic performance and work capacity (Haas et al., 2006; Haas & Brownlie, 2001). For example, iron-deficiency anemia is associated with reductions in oxygen carrying capacity, which impairs maximum aerobic capacity (Haas & Brownlie, 2001). However, previous research has shown that athletic performance improved mechanical efficiency following iron supplementation in individuals who were iron deficient at baseline (Brutsaert et al., 2003).

When iron levels are low enough to classify the individual as iron deficient or anemic, they are often prescribed oral iron therapy. While there are two categories of iron supplements, the ferrous form and ferric form, the ferrous form is used more often because it is better absorbed by the body. The three commonly administered types of ferrous iron supplements are ferrous fumarate, ferrous sulfate, and ferrous gluconate (Johnson-Wimbley & Graham, 2011). However, these three differ in the amount of elemental iron they provide. That is, the form of iron in the supplement that is available for absorption by the body. Ferrous fumarate contains the most elemental iron at 33%, with ferrous gluconate (20%) and ferrous sulfate (12%) providing less (Johnson-Wimbley & Graham, 2011). The recommended daily dose of treatment by the Centers for Disease Control and Prevention ranges from 150 mg/day to 180 mg/day of elemental iron, to

be taken two to three times per day with food (Centers for Disease Control and Prevention, 1998). According to the National Institutes of Health, the red blood count begins to increase within the first week of iron therapy (National Institutes of Health, 2010). Therefore, oral supplements appear to be an appropriate line of therapy as they are safe, relatively inexpensive, and effective in restoring iron balance in those who are deficient. Side effects from taking oral iron therapy may include: constipation, diarrhea, nausea, vomiting, heartburn, stomach upset, black or darkened stools, temporary staining of teeth, and headache (National Institutes of Health, 2010).

Statement of the Problem

Active women are more vulnerable to iron deficiency. Maintaining optimal iron stores via increased dietary iron intake and/or supplementation is recommended for this population. There is currently no standard for the evaluation of iron status of female college athletes; however, the Academy of Nutrition and Dietetics and the American College of Sports Medicine suggests that female athletes' iron status should be assessed periodically (DellaValle, 2013). Iron status as well as dietary and supplement compliance of anemic and iron deficient athletes should be closely monitored throughout the training season to ensure sufficient dietary intakes and prevent further decrements in iron status while training. In addition to that, once an athlete is placed on a supplement program, it is unknown as to which form of iron supplement (ferrous gluconate, sulfate or fumarate), is best absorbed by the body with the least amount of side effects seen. The question arises then, how do we effectively create a system in which female athletes are regularly screened for iron deficiency anemia, along with setting a standard protocol for supplementation in appropriate amounts once iron deficiency anemia is diagnosed?

Purpose of the Study

The primary aim of this study is to first identify the prevalence of female track and field athletes experiencing low ferritin levels. Based on those levels, another aim is to determine which of those athletes are currently taking a supplement or would benefit from a strict iron supplementation regime. From there, it is important to identify which iron supplements the athletes are using, stemming from the two available at the University. These two iron supplements are ferrous fumarate and ferrous sulfate. Lastly, it is hoped that the change, if any, over time is seen in the improvement of iron status in these athletes.

Research Questions

1. What is the prevalence of female track and field athletes with low ferritin levels?
2. Of those athletes with low enough iron levels requiring supplementation, how many are currently taking supplements?
3. Of the two supplements offered at the University (ferrous fumarate and ferrous sulfate), which one is the athlete currently taking?
4. Does supplementation improve iron status? If so, which of the two is more effective?

Limitations

The potential limitations of this research include:

1. Participants were white, female long-distance runners competing in track and field at a Division I university, so results may not be generalizable to other athletes competing at a different university.
2. Initial levels of iron status varied widely among the individuals, and as such, the effect of supplementation could vary widely amongst this group of athletes.

3. Other factors playing a role in iron status, such as diet, menstrual cycle, and training loads were not taken into consideration, all of which could impact iron levels in the blood.
4. Level of compliance may vary greatly amongst these individuals, in that some individuals may fail to take their supplements regularly or apart from foods that impact absorption, and this was not accounted for.
5. The majority of participants were completing a bachelor's or graduate degree. The sample may not have been representative of individuals without post-secondary education.

Definition of Terms

Anemia – insufficient mass of red blood cells (RBCs) circulating in the blood (World Health Organization, 2001).

Erythropoiesis – the process in which erythroid precursor cells differentiate into red blood cells. It is stimulated by a decrease in oxygen circulation, which is then detected by the kidneys, prompting the release of the hormone erythropoietin (Elliott, 2008).

Ferritin - an intracellular store of iron that carries bound iron from the brush border to the basolateral membrane of the absorbing cell (Mahan, Escott-Stump, & Raymond, 2012).

Ferroportin - a transmembrane protein that transports iron from the inside of the cell to the outside of it (Mahan et al., 2012).

Hematocrit (HCT) – the volume (percentage %) of red blood cells in blood (Mahan et al., 2012).

Heme iron - dietary iron present in hemoglobin, myoglobin and some enzymes. Heme iron is more readily absorbed across the brush border of intestinal mucosal cells after it is digested from animal sources (Mahan et al., 2012).

Hemoglobin (HGB) - a protein present in red blood cells that is synthesized from immature cells in bone marrow. Hemoglobin works in two ways: the iron-containing heme combines with oxygen in the lungs; and the heme releases the oxygen in tissues, where it picks up carbon dioxide and then releases it in the lungs after its return from the tissues (Mahan et al., 2012).

Hemolysis - the destruction of red blood cells (RBC) through impaction incurred through weight-bearing exercise (Miller, Pate, & Burgess, 1988).

Hepcidin - the main iron regulatory hormone. Production in the liver is responsive to liver iron levels, inflammation, hypoxia, and anemia. Its major action is to act on the mucosa cell and inhibit iron absorption. Therefore, chronic inflammation can lead to decreased iron absorption from increased production of hepcidin (Mahan et al., 2012).

Iron Deficiency – a state in which there is insufficient iron to maintain the normal physiological function of tissues such as the blood, brain and muscles. Iron deficiency can exist in the absence of anemia if it has not lasted long enough or if it has not been severe enough to cause the hemoglobin concentration to fall below the threshold for the specific sex and age group (Mahan et al., 2012).

Mean Corpuscular Volume (MCV) – measure of the average blood cell volume (Mahan et al., 2012).

Myoglobin - also a heme containing protein, serves as an oxygen reservoir within muscle (Mahan et al., 2012).

Non-heme iron - dietary iron existing in plant foods, but also in some animal foods as non-heme enzymes and ferritin. It is less readily absorbed when consumed in combination with fiber, tannins and other interfering substances (Mahan et al., 2012).

Total Iron Binding Capacity (TIBC) - The percentage of iron bound to transferrin. Normal transferrin saturation is 30% to 35% in healthy, meat-consuming individuals (Mahan et al., 2012).

Transferrin - a storage protein that transports iron and other materials within the body (Mahan et al., 2012).

CHAPTER II. REVIEW OF LITERATURE

Iron is one of the most abundant metals on earth and is essential to most life forms and to normal human physiology (National Institutes of Health, 2010). Iron is an integral part of many proteins and enzymes that help to maintain good health. When iron intake does not meet the daily need for iron, however, iron deficiency develops. Iron deficiency is a severe consequence of iron depletion and is considered to be the most common nutrient deficiency worldwide (World Health Organization, 2001). In fact, it is thought to affect the health of more than one billion people, with a global prevalence estimated at 24.8% (Shaw & Friedman, 2011). While the etiology of iron deficiency is multifaceted, it generally results when the iron demands by the body are not met by iron absorption. Individuals with iron deficiency usually have inadequate intake, impaired absorption or transport, physiologic losses associated with chronologic or reproductive age, or chronic blood loss secondary to disease (Clark, 2008). This loss of iron can result in diminished work or exercise capacity, impaired thermoregulation, immune dysfunction, gastrointestinal disturbances, and neurocognitive impairment (Clark, 2008).

Normally, iron loss and gain is in balance with the amount lost daily being equal to the amount absorbed daily. The human body has the ability to increase intestinal iron absorption dependent on the body's iron needs. However, when more iron is being lost than what is absorbed, stores become depleted and the individual develops iron deficiency (Rockwell & Hinton, 2005). Iron deficiency occurs in three stages: depleted iron stores (low serum ferritin levels), early functional iron deficiency without anemia (erythropoiesis); and iron-deficiency anemia. In the first stage, storage iron is significantly reduced or sometimes absent. A low ferritin level often characterizes this first stage but hemoglobin itself is still in normal ranges. Therefore, low iron levels in the first stage can escape detection by hemoglobin or hematocrit

screening and instead, ferritin measures are used to check for depleted iron stores. Ferritin is a measure of hepatic (liver) iron stores. The cut-off for what is considered "low" varies but it is generally assumed that values less than 15 µg/L are inadequate. In a summary of surveys, ferritin concentrations in female athletes were found to be <12 µg/L (35%), <25 mg/L (82%), and <30 mg/L (60%), as compared to those in the nonathletic female population (Beard & Dawson, 1996).

In the second stage, there is a shortage of iron available to the red blood cell (RBC) precursors in the bone marrow for hemoglobin synthesis. Hemoglobin levels may be reduced but the resulting mild anemia may not be detectable using normal cutoff values for hemoglobin (Cook, 2005). For that reason, iron deficient erythropoiesis may be difficult to detect using traditional laboratory parameters. Anemia is the final stage of iron depletion and is characterized by low hemoglobin and hematocrit levels, low ferritin levels and a decreased mean corpuscular volume. In this stage, iron stores are insufficient to maintain red blood cell synthesis (Cook, 2005).

Table 2.1. *Stages of Anemia*

Stage	Serum Ferritin	Transferrin Saturation	Hemoglobin
Iron depletion	<35 µg/L	>16%	>11.5 g/dL
Erythropoiesis	<20 µg//L	<16%	>11.5 g/dL
Anemia	<20 µg//L	<16%	<11.5 g/dL

Significance

It has long been known that iron deficiency, no matter the stage, is associated with weakness and tiredness. Now it is recognized that even without anemia, mild to moderate iron deficiency has far reaching consequences and can affect "cognitive performance, immunity, and energy sources used by muscles and thus the physical capacity and work performance of a

population" (World Health Organization, 2001). Moreover, iron deficiency impairs gastrointestinal functions and alters patterns of hormone production and metabolism. Specifically, reduced levels of iron stores affect neurotransmitters and thyroid hormones, which play critical roles in neurological, muscular, and temperature-regulatory mechanisms. This is why iron deficient individuals typically have difficulty maintaining body temperature when exposed to the cold. In addition, DNA replication and repair occurs as a result of the enzymes dependent on iron to function (World Health Organization, 2001).

Etiology

Endurance athletes, especially female distance runners, have been identified as being at risk for developing iron deficiency (Nachtigall, Nielsen, Fischer, Engelhardt, & Gabbe, 1996). One epidemiological study of endurance runners showed that 82% of the female athletes participating in the study were iron deficient (Clement & Sawchuk, 1984). What puts an athlete at an increased risk of developing iron deficiency?

For the athlete, iron demands may be elevated because of increased losses via menstruation (for women), repetitive strenuous training, gastrointestinal bleeding that occurs during prolonged and intense exercise, exercise-induced hemolysis due to repetitive foot strike, and/or exercise-induced inflammatory processes (Rodenburg & Gustafson, 2007).

Gastrointestinal Bleeding

What happens to the body during exercise to affect iron status in the female athlete? Other than issues related to inadequate dietary intake, losses through gastrointestinal bleeding are the most prevalent. The cause of gastrointestinal bleeding may be due to gut ischemia, stress gastritis, and/or the repetitive traumatic jarring effect on the organs (Feller, 2003). Another possible cause is the frequent use of and reliance on aspirin and anti-inflammatory drugs athletes

often use to alleviate daily aches and pains. These drugs may cause damage to the mucosal cells lining the gut, cause gastritis, and inhibit platelet aggregation, which prolongs bleeding (Feller, 2003). However, the significance of the gastrointestinal bleeding depends on the quantity of blood loss and the frequency at which it occurs. Lastly, gastrointestinal bleeding may also be related to the degree of running stress, with increasing losses being linked to increased effort (Feller, 2003).

For the female athlete, iron losses stemming from menstruation can result in a loss of 30 milliliters of blood per menstrual cycle (Chatard et al., 1999). This loss is equivalent to 0.5-0.6 milligrams of iron per day during the menstrual cycle (Chatard et al., 1999). Lastly, the menstrual flow is inversely associated with ferritin levels, such that an increased flow results in decreased ferritin levels (Chatard et al., 1999).

Repetitive Strenuous Training

Intense training accelerates hemolysis, or destruction of red blood cells (RBCs). The destruction of RBCs is what is responsible for an acute decrease in hemoglobin levels since hemoglobin is lost in the urine when significant hemolysis occurs (Chatard et al., 1999). Moreover, with frequent training involving little rest, low hemoglobin levels can become chronic. The severity of low hemoglobin in turn affects saturation in transferrin, the carrier that transports iron (Chatard et al., 1999). Saturated transferrin then stops the release of iron from intestinal mucosal cells. As such, when transferrin saturation is high, intestinal absorption of dietary iron is decreased (Chatard et al., 1999).

Hemolysis

Distance running has been associated with not only significant destruction of RBCs but also, delayed and reduced RBC turnover (Weight, Byrne, & Jacobs, 1991). Once RBCs have

been damaged, hemoglobin and iron are released into the surrounding plasma, which in turn promotes oxidative tissue damage (Telford et al., 2003). In a study conducted by Telford and colleagues, it was found that after 60-minutes of continuous running at 75% peak VO_2 (the maximum amount of oxygen in milliliters an individual can use in one minute per kilogram of body weight), free hemoglobin levels increased four times the original amount, primarily as a result of foot strike (Telford et al., 2003). In the study, 10 elite male triathletes completed two separate one hour sessions of running and cycling at 75% peak oxygen uptake, which were performed in random order one week apart. Plasma free hemoglobin concentrations were measured as an indicator of hemolysis. While plasma free hemoglobin increased both after running and cycling, the increase was four times higher after running. Results indicated that foot strike is a major contributor to hemolysis during running (Kenny et al., 2011; Telford et al., 2003). Additionally, RBCs are extremely vulnerable to oxidative damage because of continuous exposure to variations in oxygen uptake, which is a characteristic phenomenon in athletes (Smith, 1995). Because superoxide generation appears to be in direct proportion to oxygen flux, oxidative stress may increase as related to the VO_2 max associated with exercise (Clark et al., 1988). For athletes, increases in VO_2 are important because maximum VO_2 sets a limit to the exercise intensity or pace one can sustain for a prolonged period of time (Mier, Alexander, & Mageean, 2012). Additionally, VO_2 max has been found to correlate well with an individual's degree of physical conditioning, and has been accepted as an indicator for total body fitness (Mier et al., 2012).

Inflammation—Hepcidin

Hepcidin is a circulating protein produced by the liver that binds to ferroportin to initiate its internalization and degradation, and thereby affects iron regulation (De Domenico, Ward,

Musci, & Kaplan, 2007). Ferroportin is a transmembrane protein that transports iron from inside of the cell to the outside of the cell (Donovan, Roy, & Andrews, 2006). Through the use of animal models, the role of hepcidin in iron metabolism has been well established, with overexpression of hepcidin resulting in severe anemia (Nicolas et al., 2001). Hepcidin expression has also shown to be increased in periods of inflammation, which occurs in response to exercise (Nemeth et al., 2004). In a study done by Roecker and colleagues (2005), 14 female marathon runners provided urine samples before, immediately after, one day after and three days after a marathon race. Urinary hepcidin was measured and expressed relative to urinary creatinine, which is an indicator of muscle breakdown. Results showed that hepcidin increased after the marathon in 10 of the 14 women with maximal increases seen one day post-race. Therefore, long distance female runners could be at higher risk for iron deficiency because of chronic increases in hepcidin, which affect iron absorption and release from cells (Roecker, Meier-Buttermilch, Brechtel, Nemeth, & Ganz, 2005).

Screening/Diagnosis

Early identification and diagnosis of athletes who may be iron-deficient can help prevent chronic iron deficiency and subsequent decreases in performance. Results of a recent survey sent to 55 Division I university athletic departments found that 43% of the universities regularly screened their athletes for iron deficiency (Cowell, Rosenbloom, Skinner, & Summers, 2003).

In order to determine whether an athlete is deficient or not, a blood sample must be drawn. Ideally, a complete blood count (CBC) wherein ferritin, serum iron, hemoglobin, transferrin, and percent transferrin, would be collected (Fallon, 2004). In the event that a CBC cannot be collected, it is recommended that ferritin levels be checked because the level of ferritin in the blood is directly proportional to the total iron stores: for every one microgram of ferritin in

the body, there are eight milligrams of iron storage (Walters, Miller, & Worwood, 1973). Lastly, when collecting iron data from athletes, it is important to standardize these tests such that they are done at the same time of day, prior to workouts, and without recent ingestion of iron (Pagana & Pagana, 2014).

Interventions

A varied array of interventions has been designed to prevent and correct iron deficiency anemia. These include dietary improvement, fortification of foods with iron and iron supplementation. The Food and Drug Administration (FDA) recommends that women 18 to 50 years of age get 18 mg of iron per day (National Institutes of Health, 2010). Because of an athletes' high iron turnover, it is recommended that all endurance or intensely trained athletes use the guideline as a minimum (National Institutes of Health, 2010). The best way to help athletes protect their iron stores is by helping them choose a diet that supplies adequate iron from a variety of sources.

There are two forms of dietary iron: heme and non-heme. Heme iron is derived from hemoglobin, the protein in red blood cells that delivers oxygen to cells and is found in animal foods. Table 2.2 displays examples of heme iron containing foods.

Table 2.2**.** *Selected Food Sources of Heme Iron*

Food	Mg/ serving	% DV*
Chicken liver, pan-fried, 3 ounces	11.0	61
Oysters, canned, 3 ounces	5.7	32
Beef liver, pan-fried, 3 ounces	5.2	29
Beef, chuck, blade roast, lean only, braised, 3 ounces	3.1	17
Turkey, dark meat, roasted, 3 ounces	2.0	11
Beef, ground, 85% lean, patty, broiled, 3 ounces	2.2	12
Beef, top sirloin, steak, lean only, broiled, 3 ounces	1.6	9
Tuna, light, canned in water, 3 ounces	1.3	7
Turkey, light meat, roasted, 3 ounces	1.1	6
Chicken, dark meat, meat only, roasted, 3 ounces	1.1	6
Chicken, light meat, meat only, roasted, 3 ounces	0.9	5
Tuna, fresh, yellow fin, cooked, dry heat, 3 ounces	0.8	4
Crab, Alaskan king, cooked, moist heat, 3 ounces	0.7	4
Pork, loin chop, broiled, 3 ounces	0.7	4
Shrimp, mixed species, cooked, moist heat, 4 large	0.3	2
Halibut, cooked, dry heat, 3 ounces	0.2	1

*%DV = Daily Value. This is the percent of iron needed to meet Dietary Recommended Intake.

As seen in Table 2.3, non-heme iron is found in plant food sources such as some vegetables, grains and iron-fortified foods (National Institutes of Health, 2010). Individuals rely heavily on a non-heme iron heavy diet, despite its lower absorptive value. This is because athletes tend to follow a very high carbohydrate diet, are on a limited budget to purchase animal foods, or have limited cooking skills (National Institutes of Health, 2010).

Table 2.3. *Selected Food Sources of Non-Heme Iron*

Food	Mg/ serving	%DV*
Ready-to-eat cereal, 100% iron fortified, ¾ cup	18.0	100
Oatmeal, instant, fortified, prepared with water, 1 packet	11.0	61
Soybeans, mature, boiled, 1 cup	8.8	48
Lentils, boiled, 1 cup	6.6	37
Beans, kidney, mature, boiled, 1 cup	5.2	29
Beans, lima, large, mature, boiled, 1 cup	4.5	25
Ready-to-eat cereal, 25% iron fortified, ¾ cup	4.5	25
Black-eyed peas, (cowpeas), mature, boiled, 1 cup	4.3	24
Beans, navy, mature, boiled, 1 cup	4.3	24
Beans, black, mature, boiled, 1 cup	3.6	20
Beans, pinto, mature, boiled, 1 cup	3.6	21
Tofu, raw, firm, ½ cup	3.4	19
Spinach, fresh, boiled, drained, ½ cup	3.2	18
Spinach, canned, drained solids ½ cup	2.5	14
Spinach, frozen, chopped or leaf, boiled ½ cup	1.9	11
Raisins, seedless, packed, ½ cup	1.6	9
Grits, white, enriched, quick, prepared with water, 1 cup	1.5	8
Molasses, 1 tablespoon	0.9	5

*%DV = Daily Value. This is the percent of iron needed to meet Dietary Recommended Intake.

Daily Values (DVs) are reference numbers developed by the Food and Drug Administration (FDA) to help consumers determine amounts of specific nutrients. The FDA requires food labels to include the percent DV (%DV) for iron. The percent DV reports what percent of the DV is in one serving. The DV for iron is 18 milligrams (mg), and as such, a food that provides 5% of the DV or less is a low source, a food providing 10–19% of the DV is a good source, and a food that provides 20% or more of the DV is a high iron-containing food.

Factors Affecting Iron Absorption

Iron absorption by the body is determined by the amount already stored relative to a constant level. Therefore, the lower the stored levels of iron (ferritin), the more room there is for iron absorption (Clark, 2014). A lower iron intake creates a higher risk for low iron stores, which

in turn can develop into iron deficiency anemia, poor oxygen carrying, diminished energy and poor athletic performance (Clark, 2014)

In addition to consuming more iron, both vegetarian and meat-eating athletes can take steps to enhance the iron their bodies absorb from non-heme sources. One of the easiest ways to accomplish this is combining non-heme sources with foods high in vitamin C (Rockwell & Hinton, 2005). For example, when eating iron-fortified cereal, an athlete can pair it with grapefruit, or top spinach salad with strawberries. Vitamin C helps release a higher percentage of iron from non-heme sources, thereby boosting the body's ability to absorb more iron from these foods than it would otherwise (Rockwell & Hinton, 2005). Vitamin C also helps overcome the adverse effects of the phytonutrients that inhibit non-heme iron absorption, including oxalic acid, phytic acid, tannins and polyphenols (Rockwell & Hinton, 2005). Furthermore, preparing non-heme iron foods in cast iron cookware can also increase the iron content of these foods (Rockwell & Hinton, 2005). In particular, foods high in citric acid (tomato sauce) and lactic acid (cream sauces), considerably increased the absorption of iron from the pan into the food (Kröger-Ohlsen, Trúgvason, Skibsted, & Michaelsen, 2002).

There are also some foods that inhibit iron absorption and should be limited in the diet for those currently diagnosed with iron deficiency. Coffee and tea can inhibit iron absorption by as much as 60% when consumed with a meal (Zijp, Korver, & Tijburg, 2000). Compounds known as polyphenols are responsible for the inhibitory action and are present in large amounts in beverages such as coffee, tea, and wine (Zijp et al., 2000). Additionally, "calcium, richly supplied through dairy products, has been known to inhibit iron absorption by up to 50%" (Zijp et al., 2000). For that matter, individuals with iron deficiency should avoid consuming dairy with non-heme iron-rich foods or supplements to improve iron absorption. Soy has also been found to

inhibit iron absorption due to the presence of an acid called phytate, which binds iron and prevents its absorption (National Institutes of Health, 2010). Soy is a common ingredient in many processed food items, and is often added to protein shakes, protein bars, and meat alternative products (National Institutes of Health, 2010).

Supplementation

Once there has been a diagnosis of iron deficiency, an athlete is often advised to begin supplementation. Supplementation is used to restore lost iron stores, prevent additional iron loss, and to maintain adequate iron levels (Chatard et al., 1999). Iron supplementation has been shown to improve aerobic capacity and endurance performance in athletes who are deficient (Fallon, 2004).

Iron supplementation is most commonly supplied through pill or liquid form (Chatard et al., 1999). Oral forms include ferrous fumarate, ferrous gluconate and ferrous sulfate. Three hundred milligrams (mg) of ferrous fumarate contains 100mg of elemental iron (33%), 300 mg of ferrous gluconate contains 35 mg of elemental iron (11.6%), while 300 mg of ferrous sulfate contains 60 mg of elemental iron (20%), as illustrated in figure 2.1 (Skidmore-Roth, 2014). Ferrous iron is usually recommended over ferric iron because it has a greater bioavailability (Nielsen & Nachtigall, 1998).

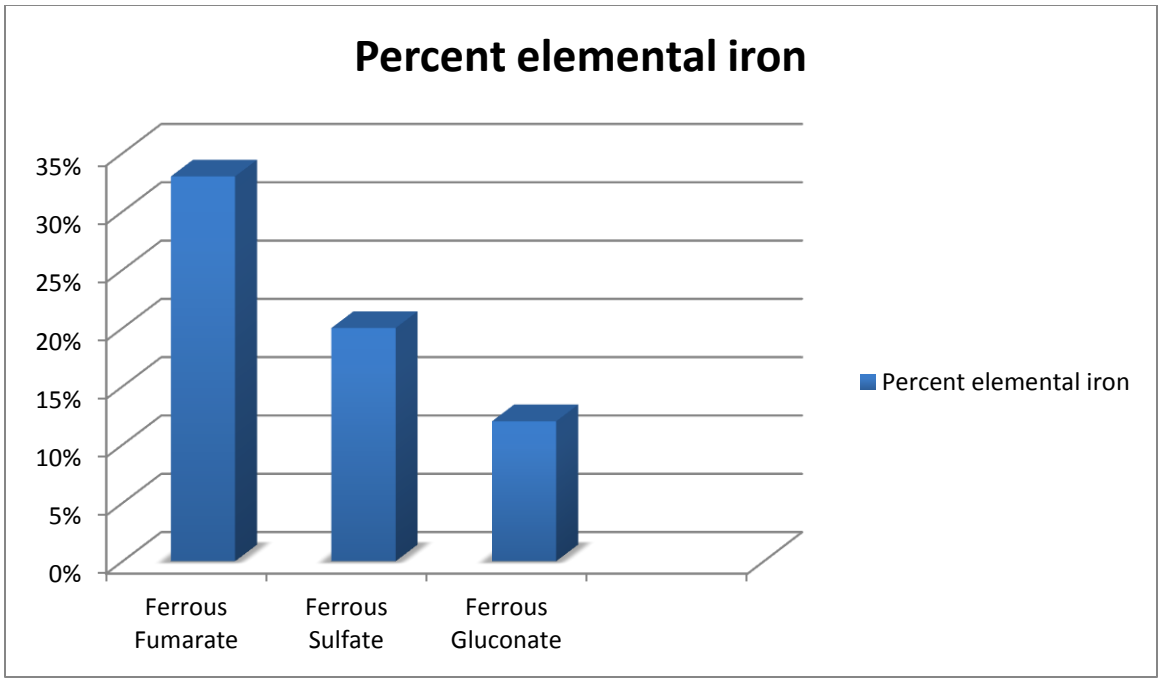

Figure 2.1. Percent Elemental Iron in Iron Supplements (National Institutes of Health, 2010)

The most prevalent supplemental dose for the NCAA universities providing their athletes with supplements is > 300 mg (>60 mg elemental) of ferrous sulfate/day (Cowell et al., 2003). Furthermore, Eichner recommends 325 mg ferrous sulfate/day for individuals with ferritin values < 20 µ/L (Eichner, 2001). Therefore, the recommendation for individuals needing iron supplementation (ferritin < 35 µg/L) is ferrous sulfate with total doses between 300-325 mg/day for supplementation. However, physicians evaluate each person individually and prescribe according to individual needs (National Institutes of Health, 2010).

Blood samples are used to determine the effect supplementation has on iron levels in the body. For instance, hemoglobin should increase approximately 1 g/L per week as hemoglobin levels typically increase proportionally to increases in iron supplementation (Ryan, 2004). With that being said, when analyzing an athlete's iron levels, there may be significant variation in the levels due to blood dilution that stems from training and hydration (Ryan, 2004). Usually, full iron repletion takes three months of oral supplementation but the length of supplementation is

dependent on the individual (Cowell et al., 2003). Consequently, follow-up testing is encouraged every six months (Nielsen & Nachtigall, 1998).

As far as comparing the different forms of iron that is often administered to athletes, there are three different factors that affect its absorption. Firstly, the form administered is important in determining how well it is absorbed. Ferric products tend to have lower absorption because all iron has to be reduced to ferrous form in order to enter the mucosal cells (Santiago, 2012). Ferrous iron passes through gastrointestinal mucosal cells directly into the blood and is immediately bound to transferrin, which transports iron to the bone marrow where it is incorporated into hemoglobin (Santiago, 2012). In addition to that, slow-release iron tablets may bypass the site of optimal absorption because maximal absorption takes place in the lower portions of the stomach (Santiago, 2012). Secondly, dosage can affect absorbability. Therefore, dosage calculation should always be in terms of elemental iron content (amount of iron in a supplement that is available for absorption) and bioavailability (fraction of the elemental iron that reaches the systemic circulation) (Santiago, 2012). Lastly, the status of a patient's iron stores can affect how much is absorbed. Absorption will be increased in iron deficient individuals (Santiago, 2012).

What form of ferrous iron is the best to recommend for an iron deficient athlete? Ferrous sulfate is water-soluble, and it is also the most inexpensive iron supplement. Ferrous fumarate has dissolves poorly in water but dissolves in the presence of gastric acid. Ferrous fumarate also provides the most elemental iron per tablet (Hurrell, 1997). Therefore, it is assumed that iron supplementation, no matter the type, will have a positive effect on iron stores.

Previous Studies Involving Iron Supplementation

Despite the systematic use of iron supplements in the athletic population, the causal link between supplementation and increased physical work capacity remains unclear. Nevertheless, there are several studies indicating an improvement of physical performance in iron depleted, non-anemic athletes following iron supplementation. For example, in a recent study, 40 young elite athletes with low ferritin (<20 μg) and normal hemoglobin (>13.5 g/dL males, >11.7 g/dL females) levels, were assigned to a 12-week treatment with either twice a day ferrous iron, or with a placebo. Before and after treatment, iron levels were determined. Results indicated that, after the 12-week treatment program, ferritin levels increased to normal in the iron-treated group (increase of 20+ μg/L), as opposed to a slight decrease in the placebo group. Additionally, for the iron-treated group, significant ($p<0.05$) increases in VO_2 max and O_2 consumption were seen, which was not present in the placebo group (Friedmann, Weller, Mairbaurl, & Bärtsch, 2001). In a separate study, female collegiate rowers, categorized as iron-depleted (ferritin <20 μg/L, hemoglobin >12 g/dL), rowed about 4% slower than athletes with normal ferritin values (>20 μg/L) in a 2-km race on a row ergometer (DellaValle, 2013).

Research has also indicated that diet alone may not be sufficient enough to establish healthy iron levels for those who have iron deficiency among the general population. In a study done with 25 female varsity collegiate swimmers (n=67), 17 of which had depleted iron stores (ferritin <12 μg/L) and five of which were anemic (hemoglobin <12 g/dL), it was shown that increased iron from the diet was not effective in raising iron blood levels. All of the swimmers were placed on a five-week placebo treatment program and results indicated that after the placebo treatment, plasma ferritin decreased in 24% of the subjects, despite consuming 16.3

mg/day of iron stemming from heme sources where phytates were controlled (Brigham, Beard, Krimmel, & Kenney, 1993).

McClung et al. (2009) reported that iron supplementation (300 mg elemental ferrous sulfate taken once daily) prevented the decline in iron stores following eight weeks of basic combat training and as assessed by a two-mile run time trial in female soldiers (n=75) (McClung et al., 2009). Similarly, Hinton and Sinclair (2007) found that iron supplementation positively affected ventilatory threshold (V_T) and energy efficiency during a steady-state test in iron-deficient, chronically trained (≥60 min/day; ≥3 days/week; ≥6 month) subjects (17 women, three men) versus placebo. The effects of iron supplementation on ventilatory threshold were greatest in participants with the lowest baseline ferritin (Hinton & Sinclair, 2007). Similarly, iron supplementation of iron-deficient, collegiate rowers during six weeks of training resulted in increased ferritin levels and improved race times in a four-km time trial (DellaVelle & Haas, 2014). Thus, it appears that even mild repletion of iron stores in iron-depleted athletes positively affects aerobic function (Hinton & Sinclair, 2007).

Summary

Iron plays a critical role in aerobic capacity and performance because of its role as an oxygen transporter to working muscles. Depleted iron stores result in less oxygen delivered to muscles, which can lead to decreases in maximal oxygen consumption and ultimately, less than optimal performance outcomes. Athletes have a higher rate of iron deficiency than their non-athletic counterparts because of loss of iron through menstruation (for women), the gastrointestinal tract, hemolysis through repetitive foot strike, and increased inflammation in the body, which can reduce absorption. Depleted iron stores occur in stages, and at any one stage, performance can suffer. Thus, athletes need to pay special attention to routine screening for low

iron stores in the body, as well as taking proper measures to ensure that iron levels stay within appropriate and healthy ranges.

CHAPTER III. IRON SUPPLEMENTATION AND THE FEMALE ATHLETE: DOES IRON SUPPLEMENTATION HAVE AN EFFECT ON IRON STATUS

Abstract

Adequate stores of iron are necessary for optimal athletic performance and severe iron depletion resulting in iron-deficiency anemia may depress performance. This is important for athletes, particularly females, to address because they can be prone to iron deficiency anemia. This review examines research data that has shown oral iron supplementation in doses of at least 45 mg ferrous sulfate or 106 mg ferrous fumarate improves iron status and may improve measures of athletic performance. It is recommended that female athletes most at risk of iron deficiency be screened at the beginning of and during training seasons using ferritin measures. Appropriate dietary and/or supplementation recommendations should be made to those with compromised iron status.

Introduction

Iron is an integral part of many proteins and enzymes that maintain good health. When iron intake does not meet the daily need for iron, iron deficiency develops. Individuals with iron deficiency usually have inadequate intake; impaired absorption or transport; physiologic losses associated with chronologic or reproductive age; or chronic blood loss secondary to disease (Clark, 2008). When more iron is being lost than what is absorbed, stores become depleted and the individual develops iron deficiency (Rockwell & Hinton, 2005). Iron deficiency occurs in three stages: depleted iron stores (functional iron remains normal); early functional iron deficiency without anemia (erythropoiesis); and iron-deficiency anemia. A low ferritin level often characterizes this first stage, but hemoglobin (Hgb) itself is still within normal ranges. In the second stage, there is a shortage of iron available to the red blood cell (RBC) precursors in

the bone marrow for hemoglobin synthesis. Anemia is the final stage of iron depletion and is characterized by low Hgb and hematocrit (HCT) levels, low ferritin levels and a decreased mean corpuscular volume (Cook, 2005).

It is widely recognized that iron deficiency, no matter the stage, is associated with weakness and tiredness. Now it is recognized that even without anemia, mild to moderate iron deficiency has far reaching consequences and can affect cognitive performance, immunity, and energy sources used by muscles and thus the physical capacity and work performance of a population (World Health Organization, 2001).

Endurance athletes, especially female distance runners, have been identified as being at risk for developing iron deficiency (Nachtigall, Nielsen, Fischer, Engelhardt, & Gabbe, 1996). For the athlete, iron demands may be elevated because of increased losses via menstruation (for women), repetitive strenuous training, gastrointestinal bleeding that occurs during prolonged and intense exercise, exercise-induced hemolysis due to repetitive foot strike, and/or exercise-induced inflammatory processes (Rodenburg & Gustafson, 2007).

Individuals can lose iron is several ways. Firstly, individuals can have blood loss through gastrointestinal bleeding. The cause of gastrointestinal bleeding may be due to gut ischemia, stress gastritis, and/or the repetitive traumatic jarring effect on the organs (Feller, 2003). Another possible cause is the frequent use of and reliance on aspirin and anti-inflammatory drugs that athletes often use to mediate daily aches and pains. These drugs may cause damage to the mucosal cells lining the gut, cause gastritis, and inhibit platelet aggregation, which prolongs bleeding (Feller, 2003). For the female athlete, iron losses stemming from menstruation can result in a loss of 30 milliliters of blood per menstrual cycle (Chatard et al., 1999). This loss is equivalent to 0.5-0.6 mg of iron per day during the menstrual cycle (Chatard et al., 1999).

Intense training accelerates hemolysis, or destruction of red blood cells (RBCs). Red blood cell hemolysis occurs as a result of foot strikes which releases hemoglobin (Chatard et al., 1999). Once RBCs have been damaged, hemoglobin and iron are released into the surrounding plasma, which in turn promotes oxidative tissue damage (Telford et al., 2003). Red blood cells are extremely vulnerable to this oxidative damage because of continuous exposure to high-oxygen flux, which is a characteristic phenomenon in athletes (Smith, 1995). This also leads to delayed and reduced RBC turnover (Weight, Byrne, & Jacobs, 1991). Moreover, with frequent training involving little rest, low hemoglobin levels can become chronic (Chatard et al., 1999).

Early diagnosis of athletes who may be iron-deficient can reduce decreases in performance. In order to determine whether an athlete is deficient or not, ferritin levels in the blood are often checked via a venous blood draw. This is because the level of ferritin in the blood is directly proportional to the total iron stores: for every one microgram of ferritin in the body, there are eight milligrams of iron storage (ferritin) (Walters, Miller, & Worwood, 1973). Ferritin is an intracellular protein that stores iron in the body and releases it in a controlled fashion. The amount of ferritin stored is reflective of the amount of iron stored. For athletes in training, the 'normal' recommended ferritin levels are different from individuals who are sedentary. For the average person, normal ferritin levels are 12-300 µg//L for men and 12-150 µg//L for women. (Santiago, 2012).

The first place an athlete should start in order to increase iron levels would be to consume heme iron, which is found in animal foods. Even then, most athletes should supplement in addition to consuming a heme-iron rich diet because diet alone has not been proven to increase stores.

Once there has been a diagnosis of iron deficiency, an athlete is often advised to begin iron supplementation. Iron supplements are commonly supplied through pill or liquid form (Chatard et al., 1999). These oral forms include ferrous fumarate, ferrous gluconate and ferrous sulfate. Three hundred milligrams (mg) of ferrous fumarate contains 100 mg of elemental iron (33%), 300 mg of ferrous gluconate contains 35 mg of elemental iron (11.6%), while 300 mg of ferrous sulfate contains 60 mg of elemental iron (20%). Elemental iron is the total amount of iron in the supplement available for absorption (Skidmore-Roth, 2014). See Table 3.1.

Table 3.1. *Iron Supplements Available to Athletes and Estimated Absorption (Skidmore-Roth, 2014)*

Iron Supplement	Total consumed (mg)	Elemental iron (mg)	Amount absorbed (%)
Ferrous Fumarate	300	100	33 %
Ferrous Gluconate	300	35	12 %
Ferrous Sulfate	300	60	20 %

Ferrous iron is usually recommended over ferric iron because it is more bioavailable (Nielsen & Nachtigall, 1998). The most common dose given by NCAA Division I universities is > 300 mg (>60 mg elemental) of ferrous sulfate/day (Cowell et al., 2003). This is the amount of elemental iron in one 300 mg tablet of ferrous sulfate. For therapeutic treatment, an athlete should take this amount twice daily for three months (National Institutes of Health, 2010).

Absorption of supplemental iron is influenced by three factors. First, the form of iron that is taken is important in determining how well it is absorbed by the body. Ferric supplements tend to have lower absorption rates because all iron is reduced to ferrous form in order to enter the body for absorption (Santiago, 2012). Second, the amount of the dosage can affect absorbability. Therefore, dosage calculation should always be in terms of the elemental iron content (amount of iron in a supplement that is available for absorption) and the bioavailability (fraction of the elemental iron that reaches the systemic circulation) (Santiago, 2012). Last, the status of an

individual's iron stores can affect how much is absorbed. The absorption rate increases as iron deficiency increases. (Santiago, 2012).

What form of ferrous iron is the best to recommend for an iron deficient athlete? Ferrous sulfate is the least expensive and most common form of iron; however, it is also more likely to cause gastrointestinal distress (i.e. nausea, upset stomach, and constipation). Ferrous fumarate, while less common and more expensive, provides the most elemental iron per tablet and is still gentle on the stomach (Santiago, 2012).

Despite the systematic use of iron supplements in the athletic population, the association between supplementation and increased physical work capacity remains unclear. Nevertheless, there are several studies indicating an improvement in physical performance of iron depleted athletes following an iron supplement regimen (Friedmann, Weller, Mairbaurl, & Bärtsch, 2001). Research has also indicated that diet alone may not be sufficient to establish healthy iron levels in competitive athletes (Brigham, Beard, Krimmel, & Kenney, 1993). McClung et al. (2009) reported that iron supplementation prevented the decline in iron stores following eight weeks of basic combat training as assessed by a two-mile time trial in female soldiers (McClung et al., 2009). Similarly, Hinton and Sinclair (2007) found that iron supplementation positively affected ventilatory threshold (V_T) during a steady-state run test in iron-deficient, chronically trained (≥60 min/day; ≥3 days/week; ≥6 month) subjects (17 women, 3 men). The effects of iron supplementation on ventilatory threshold were greatest in participants with the lowest baseline ferritin. Similarly, supplementation of iron-deficient, collegiate rowers during six weeks of training resulted in increased ferritin and energy expenditure in a four-km time trial versus placebo (DellaVelle & Haas, 2014). Thus, it appears that even mild repletion of iron stores in iron-depleted athletes positively affects aerobic function (Hinton & Sinclair, 2007).

Iron plays a critical role in aerobic capacity and exercise performance because of its role as an oxygen transporter to working muscles. Athletes have a higher rate of iron deficiency than their non-athletes because iron is lost through the gastrointestinal tract, hemolysis through repetitive foot strike, and increased inflammation in the body, which can reduce absorption. Female athletes have additional losses through menstruation. Thus, athletes need to pay special attention to routine screening for low iron stores in the body, as well as taking proper measures to ensure that iron levels stay within appropriate and healthy ranges.

The primary objective of this study was to determine the effectiveness of iron supplementation on iron status in female Division I collegiate track and field and cross country athletes competing at an NCAA Division I University. Particular focus will be given to ferritin measures and how ferritin is affected by supplementation through two different types of ferrous elemental iron (ferrous sulfate or ferrous fumarate).

Methods

Informed consent was not required since this was a retrospective study and IRB exemption was received. The team physician released the data per agreement from the athletes earlier. A venous blood draw was used to determine ferritin levels during the track and field and cross-country seasons at two different times: Fall, 2013 and Winter, 2014. After not exercising the previous 24 hours, all the athletes had blood collected in the morning by a trained phlebotomist.

Participants

Included in this study were 48 female Division I collegiate athletes competing in track and field and cross-country. All of the women were distance runners who trained between 40-70 miles per week, and were 18-22 years of age. All of the women had high school running

experience, and as such, had been training consistently for the previous six or more years. Only two of the 48 athletes included in this study did not take iron supplements during the time of blood testing.

For this study, athletes were categorized into one of three groups based on their baseline iron measure taken in Fall, 2013. Recommendations from Peeling and colleagues were used to separate the athletes into three groups (Peeling et al., 2008). Group one had ferritin levels > 50 µg//L and were not given iron supplements. This was true unless their ferritin levels reached 50 µg//L while using supplements, in which case they remained on the same iron supplement regimen. Group two had ferritin levels 35-50 µg//L and were given iron supplements in the form of either a ferrous sulfate tablet to be taken once a day or a ferrous fumarate tablet to be taken once a day. In other words, athletes in this group were either taking 45 mg elemental iron from ferrous sulfate or 106 mg elemental iron from ferrous fumarate. Group three had ferritin levels <35 µg//L and were also given either ferrous sulfate to be taken twice a day or ferrous fumarate to be taken twice a day (essentially—twice the amount group two were taking). For that matter, athletes in group three were taking either 90 mg elemental iron from ferrous sulfate or 212 mg elemental iron from ferrous fumarate. Athletes were supplied with either ferrous sulfate (45 mg elemental iron—to be taken once or twice a day), or ferrous fumarate (106 mg elemental iron—to be taken once or twice a day). As an alternative to these supplements, athletes could use an "over the counter" supplement, which they purchased on their own, and the types and amounts were unknown.

Athletes were also grouped based on the iron supplement they were prescribed by the athletic department at this university. Four groups were constructed: ferrous fumarate (FM),

ferrous sulfate (FS), none (no prescription given), and OTC (over the counter-the amounts and types are unknown).

Statistics

Data analysis included descriptive statistics using Statistical software SAS 9.3. Frequencies were calculated using the descriptive statistics feature in SAS. Independent Student's t-tests were used to test group differences (i.e. groups based on form of elemental iron taken) at baseline and again, in Winter, 2014. Models were constructed with ferritin indices as the dependent variables and form of ferrous iron as the independent variable. Statistical significance was set at $p<0.05$. Results are presented as means ± standard deviations.

Results

Mean ferritin level for all participants at baseline were 41.9 µg//L (± 22.1). Range at baseline was 8.0-108.0 µg//L. Mean ferritin level at time two were 50.0 µg//L (± 25.5). Range at time two were 14.0-128.0 µg//L. Even though values at time two were higher than baseline, a two-sample t-test comparison showed that there was no significant differences between baseline (Fall 2013) and time two (Winter 2014) mean ferritin level ($p= 0.10$).

Table 3.2 shows the percentage of athletes who were using the various iron supplements. Over two-thirds of the athletes (n=33, 68.8%) consumed ferrous sulfate with most of the others consuming ferrous fumerate (8, 16.7%). Two athletes (4.1%) did not report using any iron supplements while the remaining athletes (5, 10.4%) consumed over the counter iron supplements.

Table 3.2. *Baseline and Time Two Mean and Range Ferritin Levels*

Supplement	N=48 (%)	Mean Baseline (µg/L) ± SD	Range Baseline (µg /L)	Mean Time Two (µg /L) ± SD	Range Time Two (µg /L)	p-value
Ferrous Fumarate	8 (16.7)	40.1 ± 15.7	23.0-64.0	53.1 ± 31.9	14.0-98.0	0.32
Ferrous Sulfate	33 (68.8)	39.7 ± 22.4	8.0 – 108.0	45.0 ± 18.9	17.0 – 116.0	0.30
None	2 (4.1)	81.0 ± 16.97	69.0 – 93.0	90.5 ± 36.1	65.0 – 116.0	0.77
Over the Counter	5 (10.4)	42.6 ± 38.9	33.0 – 128.0	62.2 ± 20.8	28.0 – 76.0	0.35

For those athletes taking ferrous fumarate, ferritin levels increased by 13 µg /L in three months; however, a two sample t-test revealed no significant difference between baseline and time two (p=0.32). Responses to ferrous sulfate showed an increase of 5.3 µg /L from 39.7 µg /L at baseline to 45.0 µg /L at time two. A two-sample t-test comparison showed that there was no significant different between baseline and time two for those taking ferrous sulfate (p=0.30). Only two athletes (4.1%) tested were not taking supplements baseline. Athletes (5, 10.1%) taking "over the counter" iron supplements also experienced an increase in ferritin levels of 19.6 µg /L from baseline to time two measures, but the types and dosage they were taking were unknown. A two-sample t-test comparison showed that there was no significant differences baseline and time two (p = 0.35). In subsequent analysis, athletes who were not taking supplements were not included since there were only two athletes not taking supplements.

A one-way analysis of variance (ANOVA) was calculated to determine baseline differences between the three types of supplements. Ferritin levels of athletes at baseline showed no differences between those taking ferrous fumerate, ferrous sulfate or over the counter supplements (F=0.04, p=0.96). A second one-way analysis of variance (ANOVA) was calculated

to determine mean ferritin measures at time two, three months after taking the assigned supplements. The analysis was not significant (F=1.32, p=0.28) again indicating that there was no difference between iron supplements in their ability to raise serum ferritin levels.

Another ANOVA analysis comparing each supplement to the other supplements is presented in Table 3.3. Results show that there is no significant difference between any of the supplements, and that, regardless of type or dosage given, taking a supplement in any form is beneficial to the athlete looking to raise iron stores, or, at the very least, preventing a decline in iron status, given that all values remained positive.

Table 3.3. *Levels of Significance for Various Supplement Groups*

Supplement	FM	FS	OTC
Ferrous Fumarate (FM)		0.5619	0.5051
Ferrous Sulfate (FS)	0.5619		0.1985
OTC	0.5051	0.1985	

Discussion

The results of this investigation showed that an athlete's iron status is impacted by iron supplementation, regardless of type and dosage being taken. Using results from blood samples taken from 48 female athletes at a Division I university during the fall 2013 (baseline) and winter 2014 (time two) seasons, methods were structured to assess whether or not iron supplementation had an effect on ferritin levels. Previous studies have indicated that mean ferritin values do increase following supplementation, but specific ferrous forms were not identified to be more beneficial over another (Friedmann, Weller, Mairbaurl, & Bärtsch, 2001; McClung et al., 2009; Hinton & Sinclair, 2007). Unlike other studies, however, this study specifically assessed two various forms of iron supplementation (ferrous fumarate and ferrous sulfate), and compared those two alongside athletes who were taking an "over the counter" supplement, and those who

did not take any supplement at all. This study is also unique in that it focused specifically on female long distance runners training at greater than or equal to 40 miles per week.

Overall, the research found that mean ferritin values for all athletes increased from baseline to time two measurement regardless of which supplement they were taking. However, there was no significant difference between baseline and time two, as ferritin values increased an average of 10 µg /L. Additionally, the majority of athletes were taking ferrous sulfate (68.8%), yet did not see a significant increase in mean ferritin values between baseline and time two measurement. The 14.7% of athletes taking ferrous fumarate, or the 10.4% that were taking an over the counter supplement also did not experience a significant increase in mean ferritin values from baseline to time-two measurements. Particularly noteworthy is that two students (4.1%) were not taking supplements, yet still experienced a rise in mean ferritin values, albeit non-significant. For those not taking any supplement, ferritin measures stayed within healthy ranges at both the baseline and time two measurement, which may indicate a genetic predisposition to normally high ferritin level values despite rigorous training. Athletes in this group may also have been injured or not running at the time of data collection, which would also preserve their iron stores. Another possible explanation is that the athletes were dehydrated at the time of blood collection resulting in a higher concentration of ferritin compared to a well-hydrated individual.

Knowing ferritin levels is critical for the athletic population as iron is crucial in delivering oxygen to working muscle, thus allowing the athlete to perform maximally. As such, it is worth noting that iron supplementation is crucial for the endurance athlete, not so much in the way that it improves iron status, but that it could at least prevent severe deficits that would negatively impact training loads and subsequent performances. Research by DellaVelle (2013)

supports the notion that iron supplementation, while not necessarily improving iron status, at least may help to reduce iron deficits.

The main limitations of this study were the small size of the study population and, as a result, relatively low power to detect differences between the groups. Additionally, this study was done specifically with female long distance athletes so results may not be generalizable to other groups of athletes. There was no dietary evaluation of the athletes, and therefore it is not known whether some of the athletes were nutritionally deficient. Menstrual cycles, specific training volume, stress level, and injury history/status were also not taken into account, which may skew results either positively or negatively. Lastly, the types and amounts of the "over the counter" supplement some of the athletes (n=5) were taking were not known.

Future research in this area should consider supplement use over a longer period in order to provide more information on patterns and trends. A larger population including a wider range of ages and sporting events would also address some of the limitations of this study.

Conclusions

While results indicated non-significance for between group differences amongst the various supplements athletes were taking, either at the baseline or time two measurement, it is clear that iron supplementation in any form does have a positive effect on iron status, either at improving levels slightly or preventing severe deficits. This is critical because it has been shown that reduced levels of ferritin in the blood can decrease athletic performance (Hinton & Sinclair, 2007).

Results of this study point to the continued need for further testing to be done with iron supplementation and athletic performance. The findings of this study could be used to enable the sports dietitian and physician to either identify common misconceptions or barriers held by

athletes regarding nutritional supplements and their compliance with taking them regularly or implementing educational programs, to not only educate but encourage athletes (especially females) to be consistent with their iron intake. Acknowledging those barriers and limitations may lead the sports physician and dietitian to be more credible and useful to the athlete in providing medical care and guidance that supports the desire to improve performance.

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CHAPTER IV. SUMMARY AND CONCLUSIONS

This study of a small sample (n = 48) of female long distance runners showed that overall iron status improved, while not significantly, from baseline (fall 2013) to time two measurement (winter 2014). This suggests that although iron supplementation did not necessarily improve tissue iron status in the present study, it did prevent further depletion (as evidenced by few declines in ferritin values seen across all supplement groups).

The principle finding of this study was that there was no significant difference among supplement groups for the various forms of iron being taken by the athletes (ferrous fumarate, ferrous sulfate, and "over the counter"). These results are consistent with those of animal and human studies suggesting that iron status mediates the capacity for long-term aerobic exercise (DellaVelle, 2013).

This study does not provide direct evidence as to which supplement is most beneficial in raising ferritin levels in the blood. However, this could be a consequence of sample size because power analysis showed relatively low power (<0.50) to detect a relation between improvements in tissue iron status and supplement use. Alternatively, the effect of the supplement and consequent rise or fall in ferritin level may be related to other factors that were not measured in this study.

It is well documented that athletic women are at risk for developing iron deficiency. The large number of women with diminished iron stores may have several possible explanations. Chronic exercise may increase iron loss and/or utilization (Beard & Tobin, 2000), blood losses through the gastrointestinal may accelerate iron depletion (diSantolo et al., 2008), repetitive foot strike can enhance losses, and increases in hepcidin affect iron absorption as well (Elliot, 2008;

Ausperger et al., 2013). These issues have not been addressed in female athletes, and additional studies with all of these factors controlled for would be required.

In summary, the results of this study add to the evidence that iron status is an important issue facing female endurance athletes during a training season. The prevalence of iron depletion is higher in this population than in the general population of young women because of many factors. Female endurance athletes should be screened regularly to identify iron depletion, which is likely to impair performance, and once identified, should receive counseling regarding supplementation and food choices to enhance iron stores. While training loads and supplement dosage vary widely among highly trained female athletes, iron supplementation does indeed impact iron status.

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APPENDIX

NDSU NORTH DAKOTA STATE UNIVERSITY

August 19, 2014

Dr. Ardith Brunt
Dept of Health, Nutrition & Exercise Sciences
351 EML

Re: Your submission to the IRB: "Iron Supplementation and its Effect on Iron Biomarkers in Female Collegiate Track and Field Athletes"

Research Team: Hanna Grinaker

Thank you for your inquiry regarding your project. At this time, the IRB office has determined that the above-referenced protocol does not require Institutional Review Board approval or certification of exempt status because it does not fit the regulatory definition of 'research involving human subjects'.

Dept. of Health & Human Services regulations governing human subjects research (45CFR46, Protection of Human Subjects), defines 'research' as "…a systematic investigation, research development, testing and evaluation, designed to contribute to generalizable knowledge." These regulations also define a 'human subject' as "…a living individual about whom an investigator conducting research obtains (1) data through intervention or interaction with the individual, or (2) identifiable private information."

It was determined that your project does not require IRB approval (or certification of exempt status) because the NDSU researchers are not interacting or intervening with human subjects, nor are they obtaining private, identifiable information. This determination is based on protocol materials received on 8/19/14.

We appreciate your intention to abide by NDSU IRB policies and procedures, and thank you for your patience as the IRB Office has reviewed your study. Best wishes for a successful project!

Sincerely,

Kristy Shirley
Digitally signed by Kristy Shirley
DN: cn=Kristy Shirley, o=NDSU, ou=SPA, email=kristy.shirley@ndsu.edu, c=US

Kristy Shirley, CIP; Research Compliance Administrator

For more information regarding IRB Office submissions and guidelines, please consult www.ndsu.edu/irb. This Institution has an approved FederalWide Assurance with the Department of Health and Human Services: FWA00002439.