

Iron deficiency

Iron deficiency: much more prevalent than you imagined and posing particular risks for athletes

It is one of life's paradoxes that many of the most familiar features turn out on closer inspection to be the most complex. And so it is with nutrition. Take, for example, iron, one of the most familiar and researched yet, arguably, least 'sexy' nutrients. Most athletes know that iron is a mineral required for the formation of the red blood cells used to transport oxygen to hardworking muscles, and that insufficiency of iron causes anemia, characterized by fatigue, listlessness and a general lack of energy. Because of this, they also know that maintaining iron status and checking red blood cell or hemoglobin (Hb) levels is vital for performance.

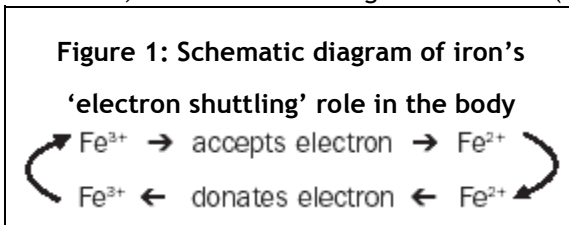
However, most athletes are far less aware of the fact that iron is one of the most difficult minerals to absorb, and that they are especially vulnerable to iron depletion through training-induced losses, especially if their event involves endurance training. To make matters worse, the latest ways of measuring iron indicate that that it is perfectly possible to have a healthy blood Hb count while simultaneously suffering from depleted levels of tissue iron. And, if that weren't enough, new research published this spring has demonstrated this tissue iron depletion impairs the ability of the body to adapt to endurance training.

To better appreciate the complexities of iron nutrition, it helps to understand a little about how iron functions in the body. Most of us are aware of its role in transporting oxygen molecules around the bloodstream to the working muscles; the red color of oxy-hemoglobin in our red blood cells is visible evidence of iron in action. When buried deep in the hemoglobin molecule, an iron atom has the perfect atomic structure to bind strongly enough with an oxygen molecule to be transported around the bloodstream (in the form of oxyhemoglobin) but, crucially, loosely enough to give up the bound oxygen to a muscle needing it.

If your iron status becomes severely depleted (through inadequate intake, poor absorption or iron losses), your blood hemoglobin levels will drop, leading to a reduction in your oxygen carrying capacity. The result is fatigue, tiredness and breathlessness, even after gentle exertion - the classic signs of anemia. Most doctors test for blood hemoglobin levels when they test for iron anemia, although there are other tests, as we'll see later.

However, iron is also crucial for a number of energy-releasing processes because it activates enzymes called catalyses, among others. In this role, iron functions as an 'electron shuttle', passing electrons to and accepting electrons from other molecules, thereby helping to make and break chemical bonds in biochemical reactions that would otherwise not occur.

Although as a plain metal iron is very stable and inert, excellent for making cars etc, it is no good for humans in that form. Biological systems need iron in its 'ionic' form. Strip away two negatively charged electrons from an iron atom and you generate an iron ion, carrying two positive charges (abbreviated as Fe^{2+}); remove a third electron and you get iron ion carrying three positive charges (Fe^{3+}). The energy levels of the Fe^{2+} and Fe^{3+} ions are quite close, which means that these two ions can easily inter-convert by donating and accepting (i.e. shuttling) electrons. If a Fe^{3+} ion accepts an electron from a molecule in a biochemical reaction, it gains a negative charge and becomes Fe^{2+} . If this Fe^{2+} ion then passes that electron on to a different molecule, it returns to its original Fe^{3+} state (see figure 1, below):



So far, so good; but the positive charges carried by these iron ions means that they are easily attracted to negatively charged molecules, or parts of molecules, to which they can often 'lock on' and bind. This is particularly the case with the very strongly positively charged Fe^{3+} ions, which are attracted to and bind especially strongly with molecules containing negatively charged oxygen atoms. A good example of this strong binding is with carbohydrates, which are built from molecules with lots of oxygen-containing fragments. While many carbohydrate foods contain iron, the iron ions are sometimes bound so strongly that the process of digestion is not able to pluck them away. The iron stays joined to these carbohydrates as they pass through the digestive tract, and passes out largely unabsorbed.

If the iron is in the more positively charged Fe^{3+} state, this binding is even stronger than with the Fe^{2+} state because there is more attraction between the negative oxygen's and the more positively charged Fe^{3+} . This accounts for the poor iron bioavailability of many iron-rich foods: the iron is there but can't be easily prized away for absorption. Even in foods whose iron is readily available, uptake can be considerably reduced by the simultaneous consumption of other food or drinks containing 'iron blockers'. The classic example is tea, containing tannic acid, which readily forms complexes with iron, rendering it far less available to the body. Whatever the health benefits of tea, drinking it to wash down your meal is bad for your iron status!

Another barrier to iron absorption arises from the fact that the cell walls of the digestive tract are electrically neutral while iron ions are strongly positively charged, making it

hard to transport them across the gut wall into your body. However, iron that is chemically bonded to protein molecules (eg haem-iron found in meat) carries no overall charge and is much more easily absorbed.

For all these reasons, iron nutrition presents a challenge. It is not just a case of consuming enough iron but of consuming it in a way that makes it fully available to your body. Then there is the problem of iron loss, which is potentially greater than for many other trace minerals. In menstruating women, for example, monthly losses amount to an average 28mg - easily doubled if periods are heavy or if intrauterine contraceptive devices are used. More importantly for athletes, there is a growing body of evidence that heavy training, particularly of the endurance variety, is a major cause of iron loss.

A recent study examined the effects of a six week high-intensity interval training program, followed by two weeks' recovery, on iron status in trained cyclists.⁽¹⁾ Dietary intake was monitored to ensure that iron intake remained consistent throughout the study, but by the end of week three, hemoglobin, haematocrit and red blood cell count (three different markers of iron status) were all depressed. Meanwhile, serum ferritin (a blood protein involved with iron storage) decreased significantly by week five and remained depressed even in the recovery phase. Total iron binding capacity (TIBC - a measure of a blood protein that transports iron from the gut to the cells that use it) was significantly increased after three weeks, suggesting low iron stores. And the researchers suggested that this reduction could be sufficient over time to have an adverse effect on aerobic cycling performance.

Iron loss as a result of endurance exercise has been confirmed in other studies. For example, a large and comprehensive study examined the effects of different types of exercise on the iron status of 747 athletes divided into three groups (power, mixed and endurance sports) compared with untrained controls.⁽²⁾ The researchers found that the endurance athletes had reduced levels of hemoglobin and haematocrit which was mainly attributable to exercise-induced plasma volume expansion: in other words, the same amount of iron carrying compounds were present, but diluted in a larger volume of plasma. However, they also found that physical activity of increasing volume and duration led to decreased ferritin (an iron storage protein) levels, which were particularly pronounced in runners. This was probably a result of hemolysis - the breakdown and destruction of red blood cells caused by the physical pounding action of running, leading to the release and loss of iron.

This effect of endurance training on iron status has been demonstrated even in very young athletes. An eight-month study examined elite swimmers in the 10-12 age bracket and

compared them with non-active controls.⁽³⁾ Although swimming is regarded as a 'non-traumatic' activity, during the competition phase the elite swimmers suffered significant decreases in serum ferritin and iron stores by comparison with the controls.

A true measure of iron deficiency

At the same time, the swimmers showed significantly higher levels of a new and highly sensitive indicator of tissue iron status known as 'serum transferrin receptor concentration' (STFR). When cells require more iron, they signal this need by increasing the number of transferrin receptors on their surface; a small proportion of these receptors actually come off the cell surface and are carried into the blood stream, where they can be measured. A high serum transferrin receptor concentration is, therefore, related to iron deficiency at a truly fundamental level - within the cells or tissues.

Given that iron availability in foods is frequently poor, that iron is difficult to absorb and that training (especially endurance training) can deplete iron stores, it is hardly surprising that iron status in athletes has come under scrutiny. In the past, the age-old hemoglobin test was thought to be sufficient to determine an athlete's iron status, the 'normal' range being 12-16 g/dl (grams per deciliter), with anything under 12g/dl signifying iron anemia. However, more recent research has indicated that you can be quite iron deficient without being diagnosed as anemic. This is because reduced blood hemoglobin is one of the very final stages in iron deficiency, and a lot of iron-dependent systems can suffer before this final stage is detectable.

For example, a Canadian study found that although 39% of Ontario women had depleted iron when assessed by the more sensitive serum ferritin test, less than one tenth of these were identified as anemic by the conventional hemoglobin test!⁽⁴⁾ Moreover, research increasingly shows that a low iron status without a corresponding low blood hemoglobin level impairs physical performance.

Another study found that women athletes who were not conventionally anemic but had a mild iron depletion as demonstrated by the serum ferritin test had significantly lower VO₂max values than those with no iron depletion.⁽⁵⁾ The researchers concluded that this reduction in VO₂max was due to lower stored iron rather than reduced blood hemoglobin. They also demonstrated that when these women were given iron supplements, their serum ferritin values and performances improved without any apparent changes in blood hemoglobin.

Another study examined 40 young elite athletes with normal hemoglobin levels but below average serum ferritin.⁽⁶⁾ The athletes were split into two groups and randomly assigned

to a 12- week treatment with either iron supplements or placebo. Before and after the treatment, aerobic and anaerobic capacity was measured in both groups by means of treadmill tests. At the end of the study period, the iron-supplemented athletes recorded significant increases in VO_2 max and oxygen consumption by comparison with those on placebo, despite the fact that there were no significant changes in hematological measures.

Such findings are not restricted to endurance activities. A very recent six-week study examined the effects of tissue iron depletion on dynamic knee extensions in young women.⁽⁷⁾ The participants, who all had low serum ferritin but normal hemoglobin levels, were treated with either iron or placebo. In the iron-supplemented group, the number of maximal voluntary contractions performed in a subsequent test was significantly higher than in the placebo group. These improvements did not seem to be related to measured changes in iron-status indexes or tissue iron stores. Interestingly, though, serum transferrin receptor concentrations increased significantly in the placebo group, suggesting that they were suffering further iron depletion! It has long been recognized that iron deficiency serious enough to lead to reduced blood hemoglobin also impairs aerobic performance and reduces VO_2 max; the function of hemoglobin is, after all, to transport oxygen to the working muscles. But how do more marginal iron deficiencies that are not accompanied by anemia affect performance? Although this type of iron deficiency is known to be commonplace in Western societies,⁽⁸⁾ there has until recently been a poor understanding of how it impacts on physical performance.

Animal studies have indicated that endurance capacity and the effects of endurance training are diminished when a mild iron deficiency without anemia exists, and that this probably occurs as a result of diminished concentrations of iron dependent muscle enzymes and respiratory proteins involved in the biochemical pathways of aerobic metabolism.^(9,10) However, although many previous human studies have found suggestive relationships between mild iron deficiency without anemia and reduced aerobic performance, many of these findings have failed to reach statistical significance - i.e. the results were not sufficiently clear cut to draw reliable conclusions and were probably clouded by the inclusion of subjects with both normal and deficient tissue-iron status.

The problem has been that until recently there has been no definitive test for a real 'tissue iron deficiency'. While measures like serum ferritin, total iron binding capacity (TIBC) and transferrin saturation do give a much clearer picture of an athlete's iron status than a simple blood hemoglobin test, they still don't tell the whole story - only whether an athlete is within certain 'normal' ranges.

They say that every cloud has a silver lining, and it seems that a really definitive test has emerged from the battle to detect erythropoietin (EPO) abuse in athletes. The use of EPO to artificially enhance the red blood cell count (and therefore the blood's oxygen-carrying capacity) in endurance athletes is believed to have become widespread during the mid-to-late 80s; and in the search to come up with a reliable test for possible EPO abuse, a new marker of iron status was identified - serum transferrin receptor concentration (STFR). As we've already seen, STFR is an excellent indicator of tissue iron status because it actually shows how 'hungry' the cells are for iron.

A marker of iron status

The use of STFR as a marker of iron status is at the centre of some very new US research, which suggests that tissue iron deficiency without anemia can not only impair aerobic performance but also blunt the adaptations that occur following aerobic training. In the first study, 41 untrained iron-depleted but non-anemic women were randomly assigned to receive either a twice daily iron supplement or placebo for six weeks.⁽¹¹⁾ From week three of the study, all the subjects trained on cycle ergo meters five days a week.

As expected, iron supplementation significantly improved several markers of iron status, including serum ferritin, transferrin saturation and serum transferrin receptor (STFR) concentrations, yet this occurred without affecting blood hemoglobin concentrations or haematocrit. And, while the average VO_2 max and maximal respiratory exchange ratio (a measure of how efficiently oxygen is used in aerobic metabolism) improved in both groups after training, the iron group experienced significantly greater improvements in VO_2 max.

When the researchers analyzed the results for relationships between the iron status markers and the measured improvements, it became apparent that it was the STFR concentrations that held the key. In the women whose STFR levels had been greater than 8mg per liter, taking extra iron produced a significant increase in VO_2 max above and beyond that produced by training alone; (remember, higher STFR levels indicate that the cells are signaling they need to take up more iron). Conversely, in women with STFR levels below 8mg per liter there were no significant benefits to iron supplementation.

The same researchers followed up with another study designed to investigate the role of tissue iron status in the impairment of endurance adaptation, using STFR as the main marker of tissue iron deficiency.⁽¹²⁾ Using a very similar testing protocol, 51 iron-depleted but nonanaemic women were selected and randomly assigned to supplementation with either iron or placebo, undergoing five days a week of training on the cycle ergo meter (between 75 and

85% of max heart rate) from week three of the six-week supplementation period. At the end of the study, all of the women completed three consecutive 5k time trials with only a short rest between trials. STFR measurements were taken at the beginning, middle and end of the study. The researchers were particularly interested to see what differences emerged between women with raised levels of STFR and those without, and also how the former were affected by iron supplementation. The results showed that it was the raised STFR group who benefited from iron supplementation, working at a significantly lower percentage of their maximum work capacity during the first and second 5k bouts (indicating improved aerobic efficiency) and showing the largest overall improvement as a result of the training regime, especially by comparison with raised STFR subjects on placebo.

This placebo group reduced their time trial times by an average of only 36 seconds, compared with 3mins 24secs for the raised STFR/iron supplemented group. Moreover, the raised STFR/placebo group had to work at a higher percentage of their VO_2 max than the iron group for their relatively negligible improvement! Given that all the women in this study were assessed as iron depleted but non-anemic, the researchers came to two main conclusions:

1. Iron depletion as measured by serum ferritin was not a reliable indicator of how the women adapted to training. All the women in the placebo group had depleted serum ferritin, but only those with raised STFR suffered an impaired training response. Moreover, in the iron group extra iron only helped those with raised STFR levels. While iron raised serum ferritin levels, it did not produce any significant performance increase in women whose STFR was already below the 8mg per liter baseline. It appears, therefore, that STFR is a far more reliable measure of a truly 'functional' tissue iron deficiency;
2. Iron tissue deficiency not only reduces VO_2 max but also impairs the body's ability to adapt to an aerobic training load (probably due to a decrease in the iron-containing proteins involved in aerobic energy production), with serious implications for athletes!

In the light of the latest research, maintaining an optimum iron status could be far more important for athletes than has previously been realized, especially given that even a mild shortfall appears to not only reduce maximum oxygen uptake capacity and aerobic efficiency but also to reduce the body's response to aerobic training. The fact that iron is more difficult to absorb than most other nutrients and that vigorous aerobic training appears to

readily deplete tissue iron only serves to underline the extent of the potential problem, especially for young female athletes.

Testing for iron status is also far from straightforward. A low blood hemoglobin (Hb) measurement only appears in the very advanced stages of iron deficiency. It's perfectly possible to have a normal blood Hb level while suffering severe effects from a tissue deficiency. Some athletes and coaches seeking a more reliable method of monitoring iron status have been using a combination of tests on iron storage/transport compounds in the body (see table 1, below).

Table 1: Current tests for iron status			
METHOD	VALUES		
	Normal	Depleted	Anemic
Hemoglobin	12-16 g/dl		<12 g/dl
Serum ferritin	40-160 mcg/l	20 mcg/l	<12 mcg/l
Total iron binding capacity (TIBC)	300-360 mcg/dl	360 mcg/dl	410 mcg/dl
Transferring saturation	30-50%	<30%	<10%
Hierocrat	37-47%		<37%
Serum transferrin receptor (STFR)*	<8mgs/l	>8mgs/l	
<p><i>*A new test, which will require further research to determine the ideal values for athletes. Provisional ranges used in scientific studies are shown</i></p>			

However, the latest research suggests that, although better than Hb alone, even these tests are insufficient to assess the real need for iron at the cellular level. For example, a reduced serum ferritin concentration generally indicates depletion of the iron stores; but, as the studies mentioned above showed, a reduced serum ferritin does not necessarily mean that performance will suffer because tissue iron stores may not actually be depleted. Serum ferritin is also what's known as an 'acute phase protein', which means that concentrations are raised during inflammatory conditions. Thus, serum ferritin may be normal (or even raised) in an athlete with such a condition even if he or she is genuinely iron deficient. To determine the real need for iron, a serum transferrin receptor test is the best on offer, although it is relatively new and may not be readily available from your GP.

At this point athletes may be wondering why, given the complexities of iron nutrition, they can't just swallow iron supplements willy-nilly? There are three main reasons:

1. Excess iron is not easily excreted. Self dosage on high-strength iron supplements for long periods of time can induce toxicity;
2. Iron competes for uptake with several minerals in the body, especially copper and zinc; large doses of iron can therefore reduce the uptake of other important minerals, creating imbalances;
3. At high doses, iron is known to function as a 'pro-oxidant', helping to promote the generation of cell-damaging free radicals.

A sensible way forward for athletes is to consume a diet that is naturally rich in iron (see tips below) and to assess their risk for iron deficiency (see below). Those whose diets are not iron rich should consider having their iron status tested, using the STFR test if possible. Those who assess their iron deficiency risk as being significant should seek a test for iron status regardless of diet quality. Routine use of iron supplementation is not recommended until iron status has been properly assessed.

Ways to boost your dietary iron intake

- If you're not vegetarian, try to include some lean cuts of red meat in your diet once or twice each week;
- If you are vegetarian, aim to consume more beans (especially lima beans), lentils, dark green leafy vegetables, eggs and nuts;
- Increase your intake of vitamin C-rich foods (including citrus fruits, berries, new potatoes, broccoli, sprouts, tomatoes, peppers and kiwis). Vitamin C helps convert Fe^{3+} in the body to Fe^{2+} , making it up to four times more absorbable!
- Don't drink tea and coffee with meals as the tannins present strongly bind to any iron in food, making it less available to the body;
- Go easy on your consumption of pure bran as it is very high in phytates, which also bind iron. If you want more fiber in your diet, go for whole grain breads and cereals;
- Use stainless steel cookware, which can add useful amounts of iron to cooked foods.

Are you iron-deficient?

All the factors listed below may increase the risk of iron deficiency, particularly those marked with an asterisk:

- My sport involves significant volumes of running or other forms of endurance exercise*;
- I am female;
- I have regular periods*;
- I have had children;
- There is a history of anemia in my family;
- I am vegetarian;
- I am vegan*;
- I drink tea and coffee with my meals*;
- I use bran products (eg All-Bran);
- I only eat white meat and fish (not red meat);
- I give blood regularly*;
- I cook using aluminum or enamel cookware (not stainless steel or iron);
- I frequently take antibiotics, aspirin or antacids (indigestion remedies).

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