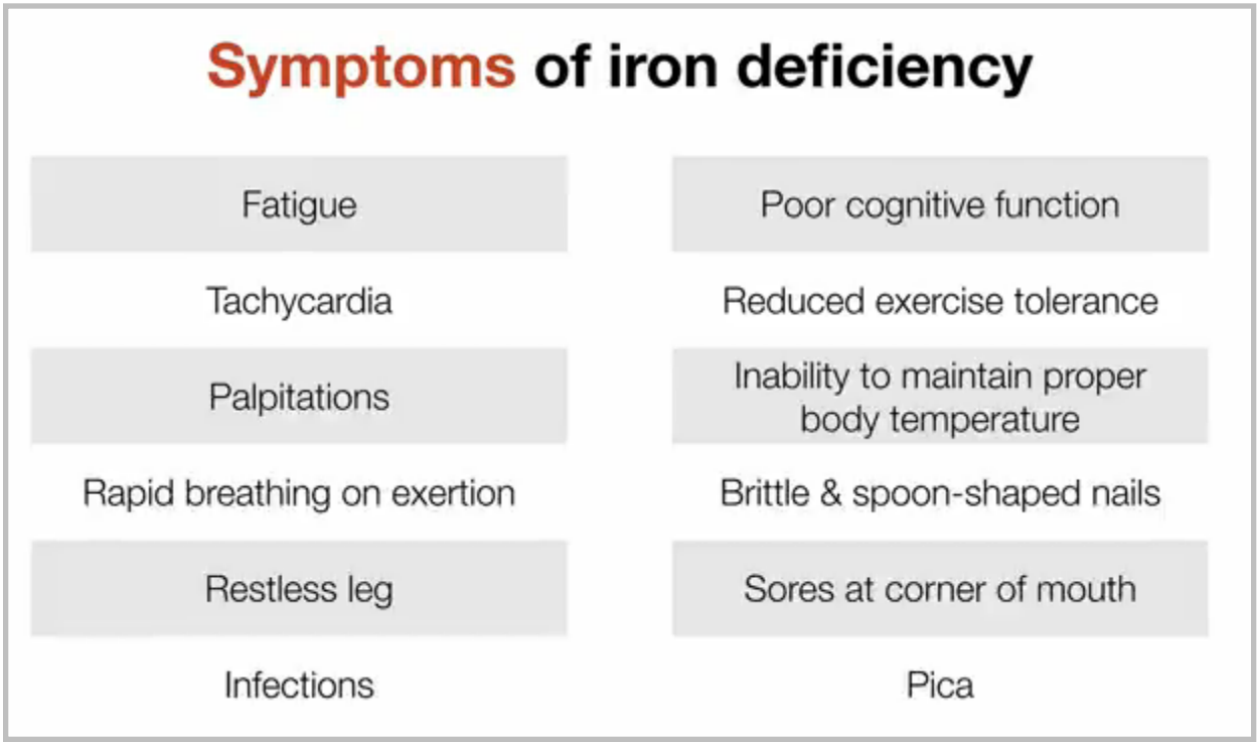
KRESSER INSTITUTE
FOR FUNCTIONAL AND EVOLUTIONARY MEDICINE

Iron Deficiency - Part Two

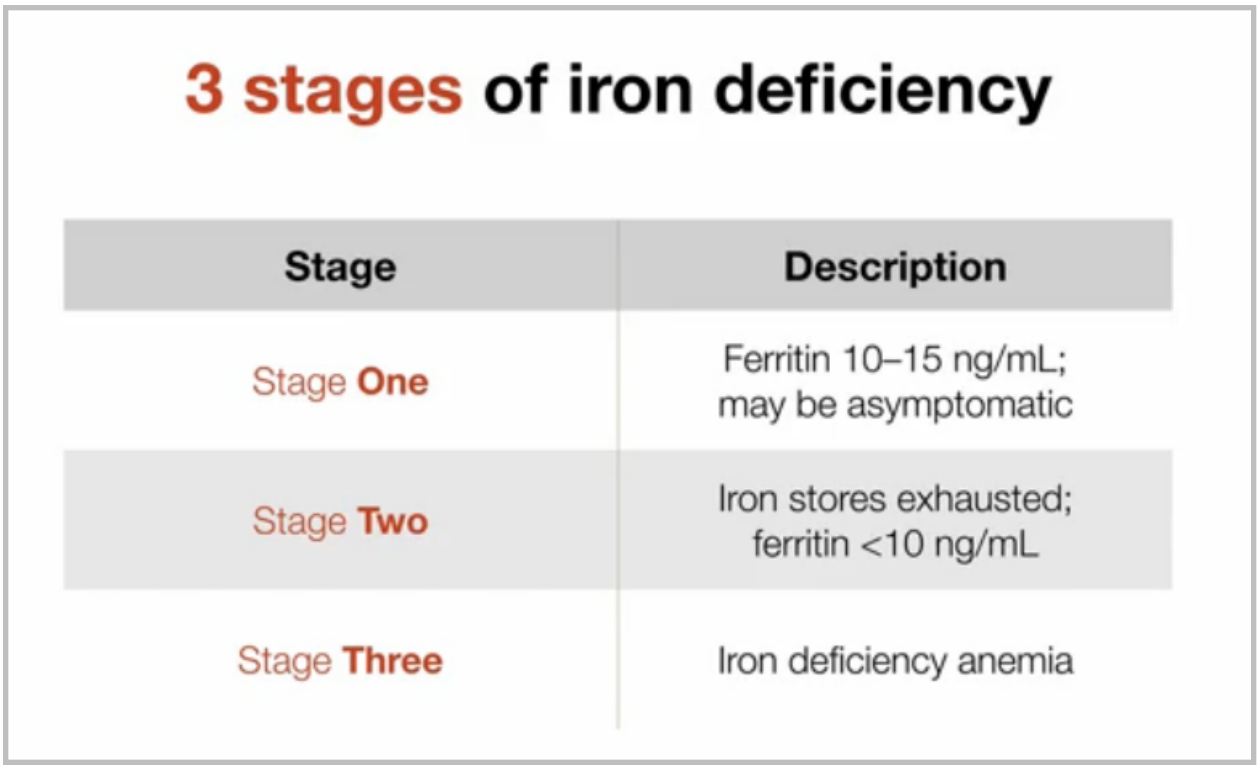


The symptoms of iron deficiency are also numerous. They include fatigue, rapid heart rate, palpitations, rapid breathing on exertion, restless legs, infections, poor mental function, brain fog, and reduced exercise tolerance.

Iron deficiency impairs athletic performance and physical work capacity in several ways, such as decreasing oxygen availability to tissues; decreasing myoglobin levels in muscles, which further limits oxygen availability; decreased oxidative capacity of muscles; and increased lactic acid production in muscles.

Other symptoms include the inability to maintain proper body temperatures, brittle and spoon-shaped nails, sores at the corner of the mouth, taste bud atrophy, sore tongue, and pica, which is a persistent eating of nonfood substances such as dirt or paint. This tends to be more common in kids.

It's important to understand that iron deficiency can occur without accompanying anemia. In fact, this is more common. Iron deficiency typically proceeds in three stages, and anemia is only the final stage. According to the World Health Organization, one in 12 premenopausal women or teenage girls has iron deficiency, but less than a quarter of them have anemia.



I put a table illustrating the three stages of iron deficiency on this slide. It begins when iron stores, which are measured in ferritin, are low, somewhere between 10 to 15 ng/mL, but not exhausted. During this stage, there may not even be any symptoms. The next stage is when iron stores become exhausted and ferritin drops below 10 ng/mL. Symptoms will be present here, and they'll increase in significance with greater deficiency. The final stage is when there is no iron in bone marrow stores, and you'll see red blood cell production and hemoglobin drop here. Anemia becomes obvious, and symptoms can become severe.

Unfortunately, many if not most clinicians in primary care settings don't test iron. They only look at the CBC and things such as hemoglobin, red blood cells, and MCV levels, so they're missing a lot of patients in stage one and stage two of iron deficiency, and this is why iron deficiency so often goes undiagnosed. I can't tell you how often I've seen this in my practice. I run an iron panel and ferritin on every single patient who walks in the door, and I don't think a week goes by where we don't diagnose someone with iron deficiency, or iron overload for that matter, who didn't know that they had it. This can even happen in people in their 50s, 60s, or 70s. They've lived for five, six, or seven decades, and they've never had an iron panel in their entire life, and they never knew that they were iron deficient or had iron overload, so this is a truly significant problem.

Iron deficiency markers

Marker	Value
Serum iron	Low
Serum ferritin	Low
Transferrin saturation	Low
Total iron binding capacity	High
Unsaturated iron binding capacity	High
RDW	High
Soluble transferrin receptor	High

Here are the markers that we use to assess iron status: serum iron, serum ferritin, transferrin saturation, total iron-binding capacity, unsaturated iron-binding capacity, RDW, and soluble transferrin receptor. Ferritin, transferrin saturation, and UIBC, or unsaturated iron-binding capacity, are the most sensitive for detecting iron deficiency, in that order, whereas serum iron, probably one of the most common markers that is run if a clinician tests for iron, is actually the least reliable marker for determining iron status. RDW, or red cell distribution width, is also important, as it's one of the first markers to go out of range in iron deficiency. However, it's not specific to iron. It can also be high in B12 and folate deficiency, and remember that RDW is an inverse marker, which means that when it is high, it indicates low iron stores. The same is true for TIBC, or total iron-binding capacity, unsaturated iron-binding capacity, and soluble transferrin receptor. Now, soluble transferrin receptor is not routinely ordered, but it can be useful for clarifying the diagnosis when the iron panel results are equivocal.

You may be wondering why I haven't included red blood cell indices such as RBC, or red blood cells; hemoglobin; hematocrit; MCV, or mean corpuscular volume; MCH, or mean corpuscular hemoglobin; or MCHC, or mean corpuscular hemoglobin concentration. We'll be covering those

later in the training when we talk about anemia, both iron-deficiency anemia and anemia of chronic disease, and then also B12 and folate-deficiency anemia.

As I mentioned on the last slide, in cases of iron-deficiency anemia, these iron markers here on this slide will go out of range much sooner than you'll see changes in the red blood cell indices on the CBC. Most clinicians see low red blood cells and hemoglobin and assume it's iron deficiency without actually testing for iron. That's backwards according to the stages of iron deficiency, and it's also not a safe assumption because many other things can cause anemia.

Serum iron is, again, one of the most commonly ordered iron indices, but it's also the least accurate. When laboratories test for serum iron, they're testing iron contained in plasma that is generally bound to transferrin. Alcohol and drugs such as oral contraceptives and methotrexate can increase iron levels in serum, while testosterone, large doses of aspirin, metformin, and ACTH can decrease them. Stress and sleep deprivation can also temporarily decrease serum iron levels.

Ferritin is a protein synthesized by the body that is mainly utilized to store iron for future use. It's considered the most sensitive marker for detecting iron deficiency, and it's often the first to go out of whack along with RDW. However, ferritin is also an acute-phase reactant that increases in the inflammatory response much like C-reactive protein, and this can cause confusing results on an iron panel. For example, if a patient is iron deficient, where you would expect lower ferritin, but she also has inflammation, which can increase ferritin, you might see a normal ferritin value even in the face of iron deficiency, and you have to consider this when you're interpreting results, as you'll see when we get to the case study section.

Transferrin saturation percentage is calculated by dividing serum iron by TIBC and then multiplying by 100. The optimal range of transferrin saturation, or iron saturation, as it's also known, is generally between 25 and 35 percent on standard lab tests. When the percentage is calculated to be less than about 17 percent or higher than 45 percent, a condition of either iron deficiency or iron overload is possible. Very low or very high ferritin in combination with low or high transferrin saturation percentage can help confirm a diagnosis of either iron deficiency or iron overload.

Unsaturated iron-binding capacity, or UIBC, refers to the portion of transferrin binding sites that are not bound with iron, which is usually about one-third of the binding sites. Again, this is an inverse marker. When UIBC is at or below the low end of the lab range, it's an indication that there is a limited capacity for transferrin molecules to accept additional iron. When it's at or above the high end of the lab range, it indicates that there is an excess capacity for transferrin molecules to accept iron because there are not enough available. The predictive value of UIBC for iron deficiency is seen as roughly equivalent to transferrin saturation percentage.

Total iron-binding capacity equals the unsaturated iron-binding capacity plus serum iron, so the formula would be TIBC equals UIBC plus serum iron. Most labs include TIBC in the iron panel, but it can be calculated manually using that formula that I just gave you if they don't report it. It's also an inverse marker just like UIBC.

Red cell distribution width, or RDW, is a parameter that measures the variation of red blood cell size or red blood cell volume. Elevated RDW helps to provide a clue for the diagnosis of early nutritional deficiency such as iron, folate, or vitamin B12 deficiency, since it becomes elevated earlier than other red blood cell parameters. As we'll discuss later, it can also help distinguish between megaloblastic anemias, such as folate or vitamin B12 deficiency anemia, where you'll see elevated RDW, and other causes of macrocytosis, where you'll see normal RDW.

Soluble transferrin receptor, which is also known as serum transferrin receptor, or sTfR, refers to the cleaved extracellular portion of the transferrin receptor 1 that is released in the serum. It's used to clarify iron deficiency or overload in patients who may have inflammation, infection, or chronic disease and other conditions in which ferritin does not correlate with iron status, such as cystic fibrosis or insulin-dependent diabetes. The iron transferrin complex mediates iron uptake into cells and binds to transferrin receptors. Transferrin receptors released by cleavage of the extracellular domain result in the formation of a truncated soluble transferrin receptor that circulates freely in the blood. The concentration of sTfR is an indicator of iron status. Iron deficiency causes overexpression of the transferrin receptor and sTfR levels, while iron repletion results in decreased sTfR levels, so it's an inverse marker like UIBC and TIBC. Again, this is not ordered routinely, and I will only order it when clarification is needed. Let's say, for example, we see a patient who has transferrin saturation percentage and UIBC levels that indicate iron deficiency, but her ferritin level is high. In that case, I might order a soluble transferrin receptor and see what its value is to determine whether there really truly is iron deficiency, and perhaps the ferritin is elevated because of an inflammatory condition. This will become more clear, again, during the case studies.