Episode Transcript

Danny Lennon: Dr. Austin Baraki, welcome back to the podcast.

Austin Baraki: Hey, thanks for having me back.

Danny Lennon: It's my pleasure. And I think as we'd mentioned, once we have something of note in the medical and clinical diagnosis realm, you're on speed dial for the podcast. This will be something that we've chatted about privately recently, at least some of the topics.

And so I think this is going to prove quite useful to a lot of our listeners getting into some of the nuance of all things related to iron. But maybe as a start point, if we get clear on some typical definitions of certain terms that are related to iron. And even before that, just thinking about what the importance of iron is in the body. What are some of the primary functions of why we should care about it at all? What would might be the general introduction you give when you start talking about this topic? Or you're teaching this topic, what is the easiest gateway into it?

Austin Baraki: Yeah so iron is a really important component of our physiology in a bunch of different ways. The overwhelming component, I would say the majority of iron is used as part of oxygen binding and oxygen transport. There

is a molecule that we have that again plays many roles called heme. And heme is something that is found in hemo proteins. These are proteins that contain a heme group.

And a heme group itself is comprised of iron and another molecule called a porphyrin ring. And this complex is actually quite effective at binding oxygen and facilitating a variety of other kind of biochemical reactions. And so our blood is comprised of a bunch of different things, but our red blood cells contain something called hemoglobin, which contains heme, which contains iron, and that binds oxygen.

And that's basically what helps oxygen get around our body. And most of the iron in our body is contained in red blood cell hemoglobin. There's probably 2,500 milligrams or so of iron comprised in that particular compartment. And obviously, oxygen binding to that, getting delivered to our tissues where the tissues will take it up and use it for oxidative metabolism.

Hemoglobin has a cousin called myoglobin, which also performs similar functions in muscle instead of in our red blood cells. So hemoglobin and myoglobin together contain a fair amount of the iron that's in our body. A much, much smaller fraction can be found in heme groups that are in other sorts of biochemical pathways.

The cytochrome system... if people remember their biochemistry class, the cytochromes in the electron transport chain. There's uh, cytochromes in the liver system. There's a whole bunch of other enzymes that rely on iron, either in the form of heme or as non-heme iron, where iron is just being used as a co-factor for the chemical reaction.

That includes things like DNA synthesis of a whole bunch of neurotransmitters and other signaling molecules like dopamine and tryptophan and tyrosine and things like that, are all synthesized in multi-step complex, biosynthetic pathways; that at some point along the way, iron plays some role in it.

And so I would say that if I'm to distill this down the principle role relates to oxygen transport and delivery. And so that is where if say you have deficiency, you can basically develop symptoms that are related to

inadequate, oxygen delivery to your tissues. But there are also a whole other variety of biochemical and biosynthetic functions where iron plays a role.

And those can lead to a variety of other symptoms. And they are less specific to oxygen delivery and oxygen utilization. And they can also be related to symptoms that can occur even in the absence of frank anemia. So I would say that's the overview, mostly oxygen delivery, a ton of other biosynthetic stuff. And that explains the whole wide variety of potential symptoms that people can experience when they have iron deficiency.

Danny Lennon: Fantastic. And we'll certainly dig into the details of that a bit later on. For the moment, think one of the really interesting things when you start looking at iron is the regulation of that and why homeostasis of iron levels is so important.

And it's this kind of weird situation where we have something that is unbelievably crucial, but can also be quite toxic in certain ways as well. So we have this weird kind of paradox, hence this need for this tight regulation and that this regulation can take place at I think a couple of different levels, whether we look at plasma or cells.

Could you maybe speak to this: about this crucial importance of iron homeostasis and then the, these different levels that regulation can take place.

Austin Baraki: As I said, a lot of the iron is in our blood, some's in our muscles, a ton of others contained in enzymes and things like that. Any surplus iron is stored in the liver and the bone marrow and the spleen.

It's stored in complex with a molecule called ferritin. And this will come up later on when we get to lab measurements and things like that. And because excess iron or free iron can exert a ton of oxidative stress, it can generate free radicals, which can damage and injure our organs and tissues.

Only about 0.1% of iron is actually circulating in our blood and it is carried by another molecule called transferrin. So we have ferritin and we have transferrin. And so these are again, things that will come up when we talk about labs. And so you can see how we do a quite an effective job at only having the amount around that we need and the rest is in our tissues doing

its function or its stored complex kind of hidden away because we don't want a ton of free iron floating around because of the potential downsides and risks of that, which can become much more apparent in states of iron excess, which we'll talk about.

We can start this story basically at birth. We're born with a supply of iron that's determined by our birth weight, by the duration of gestation, basically how many months you were in the womb and then after delivery; whether or not they did something called a delayed clamping of the umbilical cord. Typically they will try to delay that clamping by a few minutes and that can allow a little bit of extra blood to get into the now newborn to the neonate and mitigate some of the risk of iron deficiency and anemia. . But so that's the supply of iron that we're born with. By the time we get to around six months or so, there's more of a transition to where the level of iron that we have in our body at that stage of life is determined by the balance between how much iron is being used for growth versus our nutritional intake.

And so there's a bunch of nutritional factors that come into play in that kind of neonatal infant stage which I do not claim to be an expert in, but that can be a significant player in the risk of iron deficiency in infancy in childhood, which we'll talk about some of the consequences of that later.

And so across the lifespan, say by the time we get to adulthood, on average, only about a milligram or two of iron is absorbed from the diet per day. It's relatively small. And this is for a variety of reasons. So if we trace the path of dietary iron intake from the moment you eat it, this can be helpful.

And this is actually how I conceptualize it, how I think about this process when it comes to evaluating patients for iron deficiency and trying to figure out where in the path of iron in the body versus iron out of the body, is leading to this problem of iron deficiency. And by tracing that, I can try to figure out where the problem is.

So we typically will eat foods containing iron, which is ideally in the Ferris form, which is the 2+ kind of chemical state. And that gets down into our esophagus, down our stomach, into the proximal, aspect of the small bowel, the duodenum, where there are specialized transporters.

There's a transporter called DMT-1: divalent metal transporter. And that's important because it absorbs a variety of divalent metals, meaning metals that are in the 2+ state. . And the reason just as an aside that becomes important is say you're taking iron together with a bunch of other 2+ metals... say you take it with a multivitamin that contains a bunch of manganese and, other things like that. There can be some competition for absorption if you do that together. And so we prefer the iron is most readily absorbed in that 2+ state, the faris state instead of the ferric state, which is 3+.

And so that is where the acidic medium of the stomach, our stomach acid, helps to maintain that. And you may have heard people say, take iron with vitamin C or whatever the case is, vitamin C being ascorbic acid. And things like that may improve absorption by mitigating that oxidation process that can happen once the alkaline secretions of your pancreas hit it.

So we want that ferrous form to get down into our duodenum. And once it gets absorbed into the intestinal cells called enterocytes, those cells will then export the iron on the other side into your bloodstream, onto transferrin, which is that protein that carries it around our blood. It does that through a transporter called ferroportin.

And so that is the principle site of regulation that you are getting at. The way this regulation process happens, there is a protein that our liver can synthesize, and it's called hepcidin, and it's going to perform a really important role here. It's a liver derived, effectively a, hormone. And what hepcidin does is it binds that ferroportin transporter on the backside of your small intestinal cells and blocks them from being able to export iron into your bloodstream. So basically, directly blocks that absorptive step.

And so basically what ends up happening is when hepcidin is high and active and doing its thing blocking this ferroportin transporter. It limits iron export into your plasma, be it from the in enterocytes of your small bowel or macrophages that are swimming around in your blood or liver cells where iron can also be stored if you recall, and complex with ferritin.

So when hepcidin is high, it blocks basically export of iron into the blood so that we don't end up with too much of it there. That's when the process is working correctly and things are properly regulated and so problems can arise. For example, hereditary hemochromotosis is a genetic condition where

you have a mutation leading to inappropriate suppression of hepcidin, meaning you're not expressing that hepcidin protein.

So if that's not being suppressed, then ferroportin is just sucking up all the iron in the world and putting it into your bloodstream so you have inappropriate over, over absorption of dietary iron. And you can end up with these iron overload, iron excess states which is less common and less relevant to our conversation today, which we're going to end up talking a bit more about iron deficiency.

But that's basically how a condition like hemochromatosis, which is systemic iron overload, can happen when you lose that ability to regulate, where you lose that ability to say, we've got plenty of iron, we can shut down GI absorption at this point. So that's basically the way this process overall works.

Outside of that genetic condition, hereditary hemochromatosis, hepcidin expression, and its activity goes up or down depending on the needs of the human. So when you're iron deficient, for example, or when you're using a ton of iron during periods of growth, say, as a child during adolescence, during pregnancy, hepcidin is going to be suppressed because you need more iron and so by suppressing it, ferroportin, the door stays wide open and you suck up all the iron coming in from your diet. On the other hand, there are situations where hepcidin can be increased, upregulated, even in the absence of that genetic condition. And the most relevant one for our conversation is going to be during periods of inflammation.

And inflammation can happen for a variety of reasons. It can be due to various chronic diseases like a patient who has chronic kidney disease, chronic heart disease, cancer cirrhosis, lung disease from smoking, things like that. Or it can be, that's long-term inflammation, chronic inflammation, or it can be acute inflammation like during an infection.

And this is thought to be at least the story that, that we all tell ourselves in medicine. If it's true or not, who knows. But the idea is that during there are that, that there are certain kinds of bacteria that really thrive and seek out and use iron. And so perhaps there was this evolutionary mechanism where during infections, hepcidin was upregulated and we try to sequester and hide

away as much iron as possible so the bacteria can't utilize it while we clear the infection and then things go back to normal.

And so what happens when hepcidin is high in those situations, those states of inflammation, most importantly for the kind of patients that I see those with chronic inflammation from these, long-term diseases is you end up not necessarily with absolute iron deficiency, but you end up functionally iron deficient because all of the absorption is being blocked and it's being sequestered in your liver and spleen and bone marrow where it's stored and not being allowed to get exported into the bloodstream (and tissues around the body).

So I know that was long and complicated, but the overall the short story version of that is take it in our diet, absorb it in our small bowel and that small bowel absorption is regulated by this protein called hepcidin, which goes down facilitating absorption when we really need iron and it goes up during periods of inflammation and infection to block absorption when we want to try to shut that down either temporarily or long term.

Danny Lennon: I want to put a pin in a few of those ideas that you mentioned that will be relevant later on, just for people listening. One of those that you mentioned is that when we think of the iron in the body, actually a very small amount of that is actually what's going to be in plasma. And then even when we think within the plasma pool, I think you only said one to two milligrams maybe is from diet per se. And so therefore, presumably most of the iron that we see in this plasma pool is derived from just reprocessing heme from the body already?

Austin Baraki: Scavenging. Yeah, exactly. It gets aggressively recycled and scavenged the body treats it as something that is quite precious. And so for example, with red blood cell turnover, we have mechanisms by which, you know, around that 120 day timeframe or so, 90 to 120 day timeframe. When your red blood cells start dying off, the iron gets scavenged and re reutilized. There's not really a physiologic mechanism for humans to excrete excess iron or to get rid of it, which can be problematic. So for example, if if you have a male or a postmenopausal woman, postmenopausal being relevant here because they're no longer having regular menstrual blood losses, because that can be a way by which they effectively lose iron is from bleeding.

But if you have a male or a postmenopausal woman or somebody who is no longer experiencing menstrual periods and they're taking a bunch of irons, say they're taking tons and tons of supplements, there's not a way for that to be excreted if there is excess, which can lead to the same kind of complications that somebody might have from hereditary hemochromatosis, even if they don't have that genetic condition because they have they're accumulating iron overload, be it from supplements or say they have another medical condition that requires them to get a bunch of blood transfusions. So they're getting 250 or so milligrams of iron with every blood transfusion or something like that. And that can accumulate over time to where you can see consequences of iron overload since absorption is regulated.

But there is not a way that we can, regulate in terms of excretion and getting rid of iron outside of routine physiologic losses from menstrual bleeding in women, or very trivial amounts that we get from skin turnover and things like that, which is effectively negligible.

Danny Lennon: So if we start talking a about iron status now and certainly will, this will probably bring us into a conversation around determining what level someone's at deficiency and otherwise.

But if we think of just generally the determining someone's iron status from everything you've said so far, we can note. Many of these different things that could be measured, and there's probably some advantages and disadvantages to each. So in a clinical setting of all these different things people have just heard about, what are typically we looking to measure?

What do those things tell us and how does that allow us to make some distinctions about what someone's iron status is?

Austin Baraki: Sure. Because I am who I am and having spoken on some of the topics I have on your podcast before I will answer your question, but first I should raise the question of: "should we measure (with) this test?" Why are we checking this test in the first place?"

And so to be fair, iron deficiency is the most common nutritional deficiency in the world by far. It is up high on the list of leading contributors to disability and other sorts of issues. About a quarter of the world has anemia and about half of that is due anemia due to iron deficiency because this will be an

important take home point for people: not all anemia is due to iron deficiency. So there are, billions probably of cases of this around the world. So it's very important that we are aware of this and thinking about it when we're talking to people. The symptoms of iron deficiency, as I mentioned, can be really varied.

You can have iron deficiency with no symptoms at all. It can be completely asymptomatic. You can have symptoms of iron deficiency without having anemia, and that may be due to, some of these other pathways that iron plays a role in outside of just oxygen carrying capacity. And then you can have symptomatic anemia where you have a low amount of hemoglobin carrying oxygen around your body and your bloodstream.

And those symptoms, they're pretty variable between people. They also vary depending on the acuity or the chronicity. Meaning how quickly did this develop or how slowly did this develop? So if somebody has a massive episode of blood loss and they lose four units of blood, I would expect them to develop symptoms pretty quick.

But if this iron loss happened in a slow trickle over the course of, months to years, our tissues can adapt and get better and better at extracting oxygen out of our bloodstream such that we may not develop symptoms. I've seen people with profoundly low blood hemoglobin levels who said, you, you look at them, they might look white as a sheet and you're like: "how do you feel?" And they're like: "doc, I feel great. I don't understand". But you do understand if, you can presume, you can surmise that this happened over a very long period of time. Symptoms can include anything, any symptom of anemia, which again, can be due to iron deficiency or other causes of anemia where people can have fatigue shortness of breath, particularly shortness of breath with exertion, they can get pale skin. They might feel rapid heart rate because their heart is trying to keep up and get more blood out to the tissues due to an inability to meet their demand for oxygen. Those are basically what we'd call non-specific symptoms of anemia, meaning any cause of anemia can cause those symptoms.

If some of the more specific ones that people might think of, they might have heard of is something called pica, where you have this compulsive consumption of non-nutritive items, be it clay or ice or soil or weird things like that, that people feel this weird compulsion to eat. And why they feel that

way, why this happens, I don't know that we have a great explanation for the direction of the relationship between iron deficiency and pica is not even super clear. Other interesting things is I dunno if you've heard of beeturia. If you eat beets and it makes your urine turn dark that can happen in a substantial, fraction of healthy quote unquote normal people.

But there is a relationship with iron deficiency where if that happens, that may be a sign of that. And restless leg syndrome is actually something where you're trying to sleep at night and you feel like you just have these restless legs and you feel com this compulsion to move your legs around, to try to relieve that sensation.

That's something that is known to be tied to iron deficiency. There are tons of other potential symptoms, things that are less specific. Somebody might have a headache or some dizziness or changes in the skin or their hair or their nails. They might have some cognitive issues, things like that, which is particularly relevant in children in an adolescence and things like that.

So there's a variety of symptoms. Some be it related to anemia, some be it related to other things. with varying degrees of specificity for iron deficiency. And so these are the kind of things that if a patient is telling me about them, I will be more inclined to check some of these biomarkers that will, that we'll get to next.

If somebody has no symptoms whatsoever, they feel completely fine. They're doing fine. Again, as you can probably guess from some of my prior conversations with you, (it’s) not something that is recommended to be screened by default in healthy adults who are not pregnant. That would be the main caveat there.

So if we are going to measure some biomarkers, the typical initial testing that's going to get done is a complete blood count, often abbreviated a CBC, which gives us a couple different measures. It measures our white blood cell count, our hemoglobin level platelet. And then it gives us a whole bunch of other parameters that are descriptive of our red blood cells. It can tell us about the size of our red blood cells the how varied they are in their size, how much hemoglobin is in them, things like that. So a complete blood count can help us determine, does somebody have anemia? Is their hemoglobin low, say below 12 or so grams per deciliter in women? Or do they have or do they

not have anemia? And then we can also look at some of those other descriptors of their red blood cells. Are their red blood cells really tiny? Are they really variable in width? Because the bone marrow is cranking out red blood cells whenever they're ready, coming off the production line, whether they're fully mature or not, we have this increased variability in the size of our red blood cells.

So these are measures that you'll see if you look at a CBC that you've had done called the MCV, mean corpuscular volume, or the red cell distribution with RCD, there's a bunch of different metrics on the complete blood count that can point us in more towards a diagnosis of potential iron deficiency anemia or further away if they look not consistent with that.

So there are other findings that are, that can be more subtle that I don't necessarily need to get into. So complete blood count would be the first test. And then another one would be a what we generally call an iron panel. And an iron panel contains a few different things.

First is it measures a ferritin level. And remember, ferritin is what I described earlier as the storage form for iron where iron is bound complex to it in liver, bone marrow, spleen, things like that. And obviously there's some in circulation. It measures our actual iron. and it measures something called the total iron binding capacity, which is a descriptor of basically our transferrin situation, the protein that carries it around in the bloodstream.

And from that, if you take the iron level and you divide it by the total iron binding capacity, you get something called the transferrin saturation. And so that basically comprises an iron panel. And so the numbers that I look at the most, I don't really tend to look at iron levels for most diagnoses, I tend to look most at the ferritin.

And a ferritin that is below 15 or so is definitively like iron deficient. The problem though is that, as I've discussed on, on, on some of the prior episodes we've done where we set diagnostic cutoffs for some of these labs, has implications for whether we make a diagnosis or whether we miss a diagnosis.

And so there are certainly situations where a ferritin can be higher than 15, where I will still be worried about iron deficiency. If I have somebody who is

telling me all the textbook symptoms of iron deficiency and I'm concerned about that and I get a ferritin of 20 or 30 or something like that, I might say, yeah, I still buy that this is probably iron deficiency.

The other thing is that inflammation, in the same way that inflammation can impact hepcidin expression inflammation can drive ferritin up potentially very high. There are some inflammatory disorders that I sometimes see in, in, in practice that are so inflammatory that they can deriv people's ferritins in the multiple thousands.

I've seen ferritins of, 5,000, 10,000 plus. Those are usually very ill. But the principle is really important because if you have any kind of chronic inflammatory condition, ferritin becomes much more difficult to interpret. Say you get a, somebody who has symptoms of iron deficiency and they have an inflammatory condition and you get a ferritin and it's a hundred, that is very tricky to interpret because is it high because they have inflammation but not super high because they're still iron deficient or whatever the case is.

So our solution in that situation we look at a couple other things. A transferrin saturation of less than 20% is something that will raise concern for either absolute iron deficiency or that kind of functional iron deficiency that can happen when somebody has inflammation. Meaning that the iron is being sequestered, hidden away from whatever the inflammatory stimulus is.

And that means there's not really enough for your bone marrow to do what it needs to to make blood. So you can still get anemia. We just call that an anemia of chronic inflammation. And so to, as a tiebreaker in this kind of a situation, if I have somebody whose iron panel looks like they have inflammation, they have a high ferritin and they have a really low transferrin saturation then there's a separate measurement that you can get called a soluble transferrin receptor.

And a soluble transferrin receptor is another measurement. But this one is not impacted nearly as much by inflammation such that if a trans soluble transferrin receptor is high, it's a sign that the body is thirsty for iron. So a high soluble transferrin receptor in the setting of inflammation is something that would still suggest iron deficiency.

And so I might be inclined to give that person iron. In that kind of a situation unless they have an infection, in which case I'll just wait until the infection is cleared and deal with it after the fact. So the basic, some, there's plenty of other, evaluation that can be involved if somebody does have iron deficiency. Because if you find iron deficiency, the most important thing is to figure out why. Why are they iron deficient? Isn't it, is it an intake problem or is it a blood loss problem? And blood loss as a potential cause of iron deficiency is the much more morbid possibility in the short term, meaning it can cause much more problems.

It can be life-threatening. It could represent a colon cancer someplace or an ulcer or something like that. So I definitely want to figure out why they have iron deficiency. So that's where additional subsequent testing will come into play. But the initial testing would typically involve, at minimum a complete blood count, looking at the hemoglobin level and some of those red blood cell parameters, and then an iron panel looking at things like, Ferritin transference, saturation, and if they look inflamed then I might order a soluble transferrin receptor. That's the summary.

Danny Lennon: I think from some of the stuff that people may initially come across when they start looking in this area, it's common to see the, for the development of iron deficiency anemia, you have these three stages that we can look at that are represented by different cutoffs, which we can maybe get to, but you've mentioned much of those that we may test for.

And I think from what you've said, it's it goes to show just how important it's to look at things in combination at a big picture scale as opposed to one specific marker. So you give the example of a serum ferritin where that could run you into issues or I think for example, hemoglobin's been used for quite a period of time to look at iron deficieny anemia, but that seems to have its own issues with both sensitivity and specificity for a range of reasons based on the individual. Can you maybe just speak to some of those?

Austin Baraki: Yeah, for sure. This is probably one of the topics I find myself talking about the most, including on this podcast in the past where, you know, there are the vast majority of clinical medicine as far as it uses diagnostics, like blood tests, you cannot use just a number in isolation. Anytime somebody sends me a lab and they want to get my opinion on it, do they say, what are your thoughts on these numbers? I'm like, before I even

look at the numbers, tell me the backstory. Tell me what led to this being ordered. Tell me what's going on with the person that prompted somebody to check this.

And unfortunately, in our scene here, a lot of times the story that I get is, oh, I just thought I'd get checked. In which case, it's okay, I'm going to probably be able to give you a not especially satisfying answer as far as an interpretation of these numbers go. If I can't understand the context that led to it being ordered, right?

Because the idea is that the more of those, for example, those symptoms, if I have somebody who tells me they're tired, short of breath, restless legs, constantly eating ice, all this stuff, Then this concept called pre-test probability, my probability that they have iron deficiency is relatively high before I even order the test.

And so that frames my subsequent interpretation of the test and whether I'm likely to say, all right, yes, this nails the diagnosis, this explains everything. Or instead, is it, this doesn't fit. I don't know if I should trust this lab test or this lab test only partially explains what's going on and I want to make sure I'm not missing something else that could be going on at the same time.

Because people can have lots of different conditions at the same time. It doesn't all have to be one nice, neat, tidy picture, right? As much as people might want to find the one root cause a common saying in medicine as people can have as many diseases as they please. And so that's something that we have to keep in mind when we're doing these kind of evaluations because you don't want to miss potentially bad morbid things that might lead to disability and premature death and things like that.

So you're right that the hemoglobin only has modest utility here. It can be helpful to tell us whether or not somebody has anemia. If somebody has anemia, I still have not necessarily gotten closer to a diagnosis of iron deficiency at least much closer because again, there are a wide variety of reasons why somebody may have anemia.

They could have blood loss but not yet developed frank iron deficiency. They could have something called hemolysis where their red blood cells are just bursting, which can happen for a variety of reasons. Their blood can be

getting sequestered someplace in the body and not really showing up on the blood test.

They can have other deficiencies, not iron, that lead to anemia, be it vitamin B12 deficiency, folate issues, zinc, copper. They can have genetic conditions, something called thalassemia, where instead of the heme, part of the hemoglobin being the problem, they have the globe as part of the problem. And that can lead to deficiency.

So I don't say all these things to for the listeners to be like, I need to know all these things, but rather to illustrate how complicated this is. And the other reason I mentioned this, and I hope that this is a good take home is that iron deficiency must be both diagnosed and it must be explained.

And so what I mean by that is I've seen, I've heard stories and seen patients where maybe they felt a little bit short of breath with activity or something like that and they looked it up and they said, oh, this could be anemia due to iron deficiency. Just try taking some iron and see what happens.

And it's like the list of things that you could be missing. if you do that and you have shortness of breath is endless. And similarly, even if they did get a blood test and find that they have anemia, you could be and they just say, oh, I'll just, I just thought I'd take some iron. because I heard that's what fixes anemia.

Similarly, the list of things that you could be missing is also endless, whether it is, you may well have iron deficiency, but that iron deficiency could be coming from colon cancer. And taking iron does not fix that . You would want to find an explanation for that, right? Or if you had a bleeding ulcer, those are not always horrifically painful. They can be present and then they can perforate and you can die from that. It's if you have iron deficiency, it must be explained. You might have undiagnosed celiac disease. That would be important to diagnose not only for the dietary modification, but also long term, if it goes untreated, you could develop lymphoma in your gut from untreated celiac disease.. Worth identifying and knowing. So this is why I'm such a stickler, for lab, laboratory medicine, diagnostics and things like that, is there should be there should be a clinical assessment, meaning like the history. Most importantly, potentially an exam done to guide your framing of

the case that will then justify whether or not to order certain tests, and then also frame your interpretation of those tests.

And in this context, if you find iron deficiency, you must explain it. You must, must explain it. Iron overload is something that we find way less often compared to iron deficiency and has a much smaller list of potential causes. It's typically a lot easier to explain iron overload compared to iron deficiency which often requires a bit more of a, more of an evaluation to figure out.

Is this a problem with not enough intake or are they taking it in, but there's some reason it's not getting absorbed like they have an inflammatory disorder and hepcidin's doing its thing? Or do they have a malabsorptive disease, like celiac disease or do they have bariatric surgery and their proximal din has been cut out so they can't absorb it?

Or do they have, inflammatory bowel disease or something else going on? Or are they actually losing blood some someplace? Most often, somewhere along the gastrointestinal tract, be it from an ulcer, bleeding vessel, a tumor, something like that, which is all something that, again, needs to be sorted out or in again, menopausal women. Are they losing it through heavy menstrual losses which is quite common.

Danny Lennon: An accurate diagnosis is fantastic, and what we look for, but is half of the issue. It's then explaining that so then you can go, what to do about it? Why? And I certainly want to circle back to that, because I think that's one of the most fascinating things to discuss here. So I definitely want to get into that.

One final thing that I did want to ask about, because when we think of this development of anemia due to iron deficiency, it seems that if we look at those stages, it's typically laid out something like we initially see some iron depletion, maybe iron stores are lowered. Then from there we start to get to a point where the supply of iron to bone marrow starts to get restricted. And then finally with anemia, we're getting to a point where, The iron supply to the bone marrow is so low that we have this problem with producing hemoglobin. And one of the things I saw mentioned was that you can look at staining bone marrow a way to test here and seen as like a gold standard for checking for this iron efficiency if you can stain the bone marrow. But given it's an invasive nature, in, in what situations would that be used clinically? Is

it used often or in what particular cases might you use something like a bone marrow staining?

Austin Baraki: Yeah, so that is in fact the gold standard for this. However, in practice it is almost never done for iron deficiency because we have great ways through which we can diagnose that. And if we do diagnose it, then we would start treating it. And then we would look for the more usual sources. It's rarely necessary to do a bone marrow, which is a pretty painful, as you said, invasive procedure to, to diagnose this when we have so many non-invasive diagnostics.

A situation where a marrow would be done is a situation where we're not so much worried about... say we get a complete blood count and we see pretty substantial derangement in multiple different blood cell lines, for example. Because then we're worried about does this person have, for example, some form of leukemia or something like that, right?

Because we can see anemia in concert with other blood cell line derangement, be it really low white blood cells or really high white blood cells really low platelets or really high platelets. And so when I get a complete blood count and I see not just an isolated anemia, but rather I see multiple different cell lines being affected.

Then that starts to make me at least a little bit, it's not, it's automatically diagnostic that there's a bone marrow problem going on, but it makes me a little bit more suspicious that there could be something going on in the bone marrow and bone marrow can it's really a fascinating organ and it can be impacted for a variety of reasons.

There are chronic infections that can get into the bone marrow. There's even acute infections that can get into the bone marrow suppress the bone marrow, I should say. Lots of viral infections can suppress the bone marrow. There are autoimmune conditions that can get into and mess with the bone marrow.

There are medications that can suppress the bone marrow. And so with all of these different things, we can see some of the impacts of that suppression manifest on the complete blood count. But as it relates to just plain old iron

deficiency, I have yet to need to do a bone marrow ever in order to diagnose it.

Even though it is the gold standard, but we can get pretty darn close with non-invasive means, and and figuring out where and it's usually relatively straightforward for us in practice to try to get to the bottom of where is the source of this iron efficiency? Why is this happening most often in my world again, in a relatively resource rich, developed world kind of country is going to be due to blood loss in a lot of the situations. Whereas in the rest of the world, again, given that it's one of the leading nutritional deficiencies worldwide, in other places, it's more often going to be an intake problem rather than a bleeding problem. So yeah, you don't need a marrow to figure that out.

Danny Lennon: Let's touch on some of those things you've just raised and go into a bit of detail and just solidify some of the answers that you've already given. One is on this issue of when there's infection or inflammation present, and you mentioned how this can essentially throw off any measured iron status results unless we account for that.

And so really as two kind of questions that, number one, how do we account for that when trying to look at iron status? And then in such situations, how would you go about distinguishing between iron deficiency anemia or that other case you mentioned earlier of there being an anemia due to a chronic disease?

Austin Baraki: I'll tackle the first part with respect to an infection. In an infection, the easy answer is just don't check the iron panel. That's just not the time to do that. Do it after the infection's been cleared. That would be preferable. Less common would be a situation where somebody has a super chronic infection that's going to take like months and months to try to clear, which is a very, which is a much smaller minority of of infections, right?

Most infections are relatively shorter term, particularly if they get appropriate treatment. So in general, if I have a patient with an acute infection for whom I don't expect that this is going to be a super long-term thing. I just don't check it. This is just a check it on the back end after you get through this.

That's fine. Unfortunately, there's a lot of chronic medical conditions that I cannot expect are going to resolve, that are associated with or cause chronic inflammation. Super common would be the chronic, all the chronic organ failure syndromes, be it chronic kidney disease, chronic liver disease and cirrhosis, chronic lung disease, like due to smoking, chronic bronchitis, emphysema, things like that.

And chronic heart failure are probably like the big four that I see and deal with all the time. All of those are inflammatory in nature or they contribute to systemic inflammation. And they can be quite complex to manage the kidney one in particular is really important because the kidney produces a hormone called EPO that you may be familiar with from the sports world and doping and things like that.

That's where EPO comes from. It's made from the kidney and that's what stimulates the bone marrow to make blood. And so anemia is incredibly common in patients with advanced chronic kidney disease because they make less and less EPO and they have this chronic inflammation that is sequestering away all their iron.

So their bone marrow is not only not stimulated to produce blood, but it is starved for iron. And so these patients, particularly like when they get on dialysis, they get lots of intravenous iron to make sure they have enough iron available, and then they get hit with doses of EPO multiple times a month in order to drive their bone marrow to do its thing and try to improve their anemia.

That's quite a common. So to get back to the question the infection situation, not checking it in the, in these chronic inflammatory conditions, I'm fine checking it. I'm just knowing my brain is expecting when I order this test that, okay, the ferritin is probably not going to be super helpful if I order it, and the ferritin is very low.

If I happen to have a patient with these conditions and their ferritin is, 10 or something like that, I'm like, this is exceptionally bad iron deficiency because I expect it to be really high, and it came in as low as it would for anybody else with iron deficiency who does not have an inflammatory disorder that's like profoundly low, in which case it's an easy answer.

You just give them iron. But more often is patients who have these conditions, be it these chronic organ failure syndromes or an autoimmune disease like say rheumatoid arthritis or lupus or something like that. They have cancer, they have a chronic infection like H I V or tuberculosis or something like that.

Those are all long-term things that can contribute to systemic inflammation. It would be expected that the ferritin is not quite as interpretable. There are no great evidence-based cutoffs in these situations. I think the WHO says that if it's less than 70, it's still consistent with iron deficiency, but that still leaves like a gray area, even a little bit above that.

Is it possible that they're effectively deficient above it? And so that's where, as I said, I'll still look at the transference saturation, looking for that to be low, probably less than 20% or so. And then I might order that soluble transferrin receptor. And if that's high, then that would lead me even further towards iron deficiency as a potential explanation for what's going on.

Danny Lennon: With that then, the other thing that you had mentioned was that once we have a diagnosis of iron deficiency anemia, going about working out why that is the case is crucial. And actually one of the things that this conversation came off the back of is some of our private conversations in relation to essentially an issue where I was asking about, in a case where someone doesn't respond to iron supplementation, for example and their iron levels are low and they're going really high dose for long period of time: what's up with that? I think this relates to earlier, like you said, either that dietary supplement, otherwise, if those things aren't really moving the needle, then it's probably not down to intake per se. There's something else going on. So I know you've mentioned already a number of these different potential reasons for that. Could you recap that initial thought process of how someone in clinical practice goes about that decision making process of how do we start working out what's going on here?

Austin Baraki: Yeah, for sure. And this is my favorite part of this whole deal and why I like doing what I do for all the different kind of problems that I see is k cracking this kind of diagnostic puzzle is fun. And especially when you can get an answer and make people feel better. So the a the simplified kind of framework that I have in my mind is iron in versus iron out . And so that is how I think about this problem. And I trace how is iron coming in? So I'll take

a dietary history. So if I have somebody who's long standing absolute strict vegan or something like that, then I may think of that as a potential contributor.

I'm not going to hear that story and say, okay, case closed, because could I still be missing that this person who's a strict vegan has colon cancer? Yes, I could. It's possible. So that may be viewed as a contributor with respect to "iron in". Let's say that okay, their iron and their diet intake seem they're eating a reasonable diet.

The next question is, okay, the iron gets down to their stomach. What's happening? Is it getting absorbed or not? There are things that can impair absorption of iron between the stomach and the small bowel. And so things that I'm thinking about in this situation might be, is their situation where they have low or suppressed stomach acid, like they're taking a bunch of, acid suppressing medications.

Do they have a problem anatomically or physiologically with their stomach? Have they had bariatric surgery or metabolic surgery and had part of their stomach taken out? And there's small intestine taken out. Are there is there concern for potential, chronic infections like h pylori infection, things like that could be going on in the stomach or autoimmune conditions like the diagnosis that's traditionally known as pernicious anemia, which is autoimmune gastritis for any reason or a problem with absorption when it gets to the small bowel where they have the typical would be celiac disease, which affects that aspect of the duodenum.

I'm looking at what's in their diet. If their diet's reasonable and they're consuming it, how likely is it that they're absorbing it? Is there something physiologically that could be going on with their stomach and small bowel that is impairing absorption, infections, inflammation from an autoimmune condition something like that.

Or on the other hand, now if none of those things are potentially at play, then I'm starting to think about blood loss and where can blood loss happen from? The most common that we should be thinking about is anywhere in the gastrointestinal tract, and that starts from the esophagus all the way to the rectum.

And I'm asking for questions like are you throwing up any blood? Are you having blood in your stools? Believe it or not, these are things that I see pretty regularly. And then if I'm not getting a strong history for that, then I may lean a little bit further away from that and look in l look in other places.

But it's quite common for me to refer patients who have iron deficiency for endoscopic evaluation, meaning a gastroenterologist, they'll put a camera down their throat, down their esophagus, look at their stomach and the duodenum, where they can potentially take biopsies to look for evidence of celiac disease, for example.

And then they'll also often undergo a colonoscopy to look for evidence of colon cancer, colon polyps abnormal blood vessels that are, right at the surface of their intestinal wall that could be leaking a little bit of blood. Not that I would see this very often in the US but in other countries you can have various kinds of parasitic infections, worm infestation hook worms, things like that, that are unfortunately common in other areas of the world that can contribute to, to iron deficiency and to chronic bleeding.

And then all the way down to the rectum, where you can see things called diverticula, little outpouching of your intestinal wall that can bleed and hemorrhoids. So start to finish. Gastrointestinal tract can be a source of blood loss. The next would be the genital urinary tract. Again, most often in women is going to be due to menstrual bleeding, or not menstrual bleeding, but maybe they have a, a bleeding polyp in their uterus or some something else that's going on.

They're contributing to abnormally heavy blood losses. Outside of that there are less likely and less common sources of bleeding. So it would be very unusual for somebody to lose a profound amount of iron and blood from their lungs, like to cough up so much blood that, that made them anemic. It's technically possible, but by no means is it common or from the urinary tract where they're actually urinating blood.

People can urinate blood for a whole variety of reason. That are beyond our scope here, but again, it is difficult to pee out that much blood, or at least patients will come in relatively early if they start seeing that most of the time. And then another one that may be more relevant for some of the folks

listening here is that iron deficiency is quite common in high level endurance athletes.

And that's due to a variety of reasons, both on the intake side of things and on the blood loss side of things. And like with runners, the, you may have heard of like the repeated impact hemolysis where their red blood cells, as I mentioned, can burst with repeated pounding the pavement , if you will.

So there's a bunch of different reasons why that can happen, but it's, that's quite common in endurance athletes and restoring their iron status can actually improve endurance performance in those kind of situations. So take home kind of summary again, is iron in versus iron out? I'm thinking about what's in the diet. Is it likely to be getting absorbed? Whether due to any of those anatomic or, physiologic issues with the stomach and small bowel, or could hepcidin be blocking it in the setting of some inflammatory condition. And then if none of those things are likely, then I'm looking for blood loss. I'm actually looking for doing both of this.

It's not if then but I'm looking for all of this. I'm thinking about all this at the same time. So blood loss from the gastrointestinal tract menstrual blood losses, and then looking for these other less common rarer causes is the overview.

Danny Lennon: Presumably, of course then in any situation where we're looking at treatment, it would completely depend on which of those has been termed to be the issue. In relation to hepcidin, one of the things I think I'd asked you about before is this potential relationship between hep side and estrogen as one example, and I'm sure there's many others. Is there anything there that would indicate that there could be explanations here of if someone is seeing massively elevated levels of estrogen or other hormones that ties into this story through hepcidin or is that very unlikely to be something at play.

Austin Baraki: So it is true that estrogens and androgens can impact hepatic synthesis of various proteins. So it, hepcidin being a liver derived protein and hormone, a lot of these, their synthesis can be impacted by these by hormones like estrogen. Some go up, some go down.

It's entirely like a case by case individual thing. I cannot quote to you what the specific impact of estrogen is on hepcidin. And probably the reason why is that there is not a role in clinical practice to measure either of those. We do not measure estrogen levels in this situation or in many other situations, nor is there a current role for measuring hepcidin levels.

That's more of a research thing. It does have hepcidin measurements in the research do appear to have some predictive value for who is more or less For example, to respond to oral iron supplementation, which should make sense, right? Because hepcidin impacts your ability to absorb, enter oral iron, meaning iron you take by mouth and has to go through that ferroportin transporter in the small bowel.

But in clinical practice, it's not really gotten to that point yet. There's probably more work that needs to be done to figure that out or to make it cost effective or I don't know the details, but we don't measure hepcidin levels in practice, nor do we measure estrogen levels. So I can't really speak to that as far as a role in practice here.

Danny Lennon: Sure. So if we have a situation where any of those more severe or urgent issues has been ruled out, and then we can start to say, okay, now we need to start getting someone's iron status back up and maybe look at the intake side because we're at least pretty sure there's none of these major issues contributing to a lot of blood loss.

There's obviously things like dietary advice you mentioned, or supplemental advice, which would be quite common beyond that. In situations where someone's iron status may be particularly low, or they're reporting that supplementation or diet hasn't really improved things for them, what are the kind of typical go-to's that you might look at?

Austin Baraki: Yeah, so if we're at a point where we think we can correct the deficiency by replacing iron, meaning that we, there's not a source of ongoing losses that needs to be addressed first, because that would always be the issue. The goal is going to be to restore iron levels, restore normal hemoglobin concentration if the person was anemic.

There are some ways actually to estimate or approximate what somebody's like iron deficit is in terms of how much are we going to have to replace.

There's a, there's an estimation equation called the Ganzoni equation that can be used. It just has a couple basic parameters like your, I think it's your weight and then your target hemoglobin level and things like that.

And it helps to approximate how much iron is this person down, how much are we going to have to get into them? And so that can be a helpful tool in some situations to, to guide some of our decision making.

I know that you're going to have another guest to talk more about the details of the dietary iron piece. It is worth pointing out that different food sources do have varying bioavailability of the iron in them, meaning that they can be more or less efficiently absorbed. And that can be due to the food source itself, and that can also be due to other, food nutrient kind of interactions.

So that's worth noting if you're going to, in a position to, to be giving dietary advice to patients to try to mitigate this. And also remember that our absorption it, let's say we, we have a situation where the person does not have significant inflammation going on that would suppress their ability to absorb.

On average, our day-to-day absorption is going to be about one to two milligrams or so. That probably increases a bit when hepcidin is very much suppressed. Meaning that when you have iron deficiency and your body's real thirsty for iron, that's going to go down and your ability to absorb might go up a bit, but it's not going to go up massively.

And the reason I say this is because, restoring iron status through diet or through supplementation is a slow process. And so this was an important conversation that we had with the client that we talked about privately and I did a consultation with was this had been going on for a long time and we weren't making progress.

And the possibilities are, there's enough of an iron deficit that it needed an even longer amount of time in order to catch up. That would be one possibility. The next possibility is the iron that you're be, that you're taking is not being absorbed particularly well. That would also make this take a very long time.

Or there is a source of ongoing blood losses and we are simply not keeping up with the losses, right? There's more going out than there is coming in. And so that's basically how I thought about it and how I conveyed the issue. So that's how I think about it. In practice there are oral iron supplements.

Most of these are some form of ferrous salt. What that means is fair, the phis form of iron, that 2+ form that is bound to something else. And the most common one that we use in practice is ferrous sulfate. There are tons of other agents available that, that can be prescribed and used, although most of them don't really have significant differences in effectiveness.

And so I don't typically deviate to many of the other ones. We don't have clear evidence of superiority for one over another. The one thing that is worth pointing out with the different formulations is that like controlled release or like extended release, slow release, enteric coded, you'll hear these terms around various medicines.

And sometimes that's done with medicines to either prolong the effectiveness or to mitigate side effect risks to make it more gradual absorption or whatever the case is, that is a bad idea when it comes to iron. Do not recommend anybody take those formulations. The reason why is because if you recall where iron gets absorbed principally in the proximal duodenum.

So if you have an enteric coated, protected iron formulation that is in a capsule that is slow release, it's going to get all the way to the end of the intestine before it's fully broken down and you're past the point where you have most of those DMT transporters and the ferroportin, transporters that will actually absorb the iron.

So there is no role for enteric coated extended release kind of iron formulations. And so all these different irons, they are typically dosed based on their elemental iron content. And so like a 325 milligram tablet of iron sulfate or ferrous sulfate may contain about 65 milligrams or so of elemental iron.

And so one to two tablets of those is about as much as I'll give anybody at a time. They can have some intolerance issues things like nausea, some irritation to the gastrointestinal ta tract. About 10% of patients who take it

can experience constipation and things like that. So there are some considerations when it comes to people's ability to tolerate it.

And then the other thing that is, that has come out, I would say more recent, more significantly in the past, I don't know, five, 10 years of research or so, Is that when you give somebody an element, a dose of elemental iron of about 60 milligrams or greater, so that would be just one of those tablets that actually immediately raises concentrations of hepcidin for about 24 hours or so.

And so think about what the consequence of that would be. I give you a dose of iron a fraction of it gets absorbed, and then that drives up hepcidin, which will then suppress subsequent absorption. Now, ferrous sulfate used to be dosed, like when I went through training, it would typically be dosed three times a day. And you can see why that makes less sense in that kind of a situation, right? You take your morning dose that gets absorbed, cranks up, hepcidin, you take your afternoon dose that a tiny fraction of that gets absorbed. And then you take your third dose and effectively none of that gets absorbed.

And maybe by then you're one of the unlucky 10% who's starting to get constipated while you're not absorbing the iron. And so they've done trials where they've compared either multi-time a day administration versus once a day versus every other day. And they've found, fairly comparable absorption across these different things.

And so for people who be it, for reasons of convenience tolerance, some of these gastrointestinal side effects, whatever the case is, a lot of them by default, we often just recommend they take it every other day or like a Monday, Wednesday, Friday kind of thing. Now if you take it more often, you do absorb more absolute iron.

It's just that you're absorbing a smaller and smaller fraction of it with subsequent doses. The higher those doses go the higher the likelihood of experiencing some of those kind of the side effects can be. So the bottom line here is that it's oral iron can be quite effective.

However, it is relatively slow. And therefore as a result, I tend to use it more in relatively mild iron deficiency or uncomplicated iron deficiency, meaning

they don't have severe anemia, they don't have severe symptoms, because that's a situation where if I put you on iron and I'm like, yeah, this is probably going to take, I don't know, six months to get enough of this in you, or something like that's just you're living with severe symptoms for not a justifiable reason for that long.

And so that's a situation where I may pivot and try to give somebody IV iron. Unfortunately, we'll get to this in a moment, but IV iron is not necessarily easily available in a lot of places. Not a lot of doctors are super comfortable with the use of IV iron, even though in my opinion they should be.

And in places again where nutritional deficiency is the primary driver in a lot of the kind of developing world iron deficiency and the infrastructure for that infusion clinics, things like that is just not available. So that makes it a really tough problem to solve. So for oral iron replacement, again, for milder symptoms, milder anemia, if they have anemia I don't really pick and choose too much between the different formulations. Don't use enteric coated capsules or sustained release formulations. Try to avoid taking it actually with other food, with, with tea, with antacids, things like that because some of these other food, nutrient interactions can impair absorption. Including multivitamins. As I said, especially if your multivitamin has other kind of 2+ metals in it that will compete for that same transporter.

And you will often see and hear people recommend patients take vitamin C together with it, which I don't necessarily have a huge problem with. There's not really great high quality data that co-administering it has a significant impact on people's outcomes. So I don't actually tend to do it routinely for most people because most people would just prefer to take fewer pills than more. And I'm not super convinced that this is going to have a dramatic impact. If I'm really worried that I want to get as much in them as possible, then I'll probably just say, Hey, let me give you a thousand milligrams of IV iron and call it good, which I can do in an hour or something like that. Or sometimes even 15, 30 minutes depending on the IV formulation.

So yeah that's the short story on oral iron replacement. And again, the situation that we had with the client, there was concerns in my mind. Whether the, whether there could have been ongoing iron losses that we were not keeping up with. Because I think that, I was recommending some, endo endoscopic evaluation, be it colonoscopy, whatever the case is because

it, that would be one very concerning potential situation is they have anemia, they have iron deficiency. The doctor or the person themselves just says, Hey, I just thought I'd take some iron to catch up with this. And it's you're bleeding faster than you're supplementing from a potentially, dangerous or life-threatening source. So we gotta get to the bottom of that.

Danny Lennon: Fantastic. Just as on a side note, when you mentioned around the IV iron, what are some of the concerns or hesitancies of some doctors?

Austin Baraki: Yeah so IV iron has been around for quite a long time. However, in the quote unquote old days, which I'll admit was before my time in practice, there was this formulation called high molecular weight iron dextrans. And those had a risk of anaphylaxis, which yeah, I can understand making people a little squeamish about giving those to patients willy-nilly. Now we have low molecular weight, iron d strands that are much safer.

And then we also have other formulations of IV iron, and these are basically irons that are encapsulated in some form of a carbohydrate shell that delays, slows the release of iron. So one formulation is ferric carboxy maltose. There's ferri-moxytol, there's a few other forms of IV iron that I've used several of them generally quite safely.

And and we tend to see very little of those kind of concerns. There's always a risk of an infusion reaction when you give anybody any IV medication. But the kind of IV infusion reactions that I've seen have not been anaphylaxis fortunately. Additionally, there are still some mitigating measures that are put into place.

Oftentimes with some of these formulations, they'll give a little tiny, what they call a test dose. A tiny little bit. Wait a few minutes and see if anything happens. And then if not, then you're good to go. And then you give the rest of the dose. And so we can give people, again, like I said, up to, 500, 750, a thousand milligrams of IV iron, and that can be done in anywhere from 15 minutes to an hour.

And you have just fixed the person insofar as you have restored their iron status within that short period of time, rather than taking months and months through oral iron supplementation if they have more substantial

deficiency. And additionally, the other role for IV iron is in these situations where I do not expect the person is going to be not just a severe deficiency,th but an addition, a situation where I don't think they're going to be able to absorb it, especially well.

So that might be that patient with chronic kidney disease who has chronic inflammation, who's hepcidin is ramped up. I can give them all the oral iron in the world. They're not going to absorb it, and so I'm just going to give them IV iron instead. Or somebody who has, substantial surgical alteration to their anatomy. Maybe they underwent Rouen-Y gastric bypass surgery. They don't have part of their stomach, they don't have part of their duodenal, whatever the case is not going to happen, and it's going to be potentially more irritating to, to, to their stomach now that, that's also been surgically altered. So just give 'em a dose of IV iron if they're deficient.

There are various other situations where I would do that, but that's my approach to it in practice is situations where there's severe symptoms, severe anemia oral intolerance, inability to keep up with blood. Or if there's a reason to believe that oral absorption's going to be impaired, those would all be reasons why I would go to the IV iron formulations and the newer ones are quite a bit safer.

Mild infusion reactions technically if it like leaks out of the vein that it's being infused into, it can cause some skin discoloration and things like that in the area, but otherwise, pretty safe. And then the only other consideration is does this patient have an infection or not? And if they have an infection, then I'm not giving them IV iron until they're done with that that they're through it and successfully treated.

Danny Lennon: To get to iron excess and iron overload; first of all with iron overload in general, why is this such a concern? What are the problems with having this excess storage of iron?

Austin Baraki: Yeah, I think that's worth getting into for a few reasons. So I mentioned that iron chemistry is super complex, but when we have excess iron, particularly excess, free iron, it can facilitate some of these free radical producing reactions in the body.

And free radicals are highly reactive, relatively not super stable compounds that can cause damage to our tissues, to our dna n things like that. So that's the very, very simplified mechanism of how iron excess can harm us. And it's, I think it's important that you are asking this given that you have, are in, I believe Ireland and you have this general, highly European audience.

Because when I think of hereditary hemochromatosis, I think about Caucasians of European descent. I think I had a professor in medical school who was teaching us this and he was I think he might have even been Irish, and he was like, yeah, I have it. And so I have to, go about managing this.

Danny Lennon: I'm pretty sure Ireland has like the highest prevalence in the world as an individual country.

Austin Baraki: When I think of it, I think about Irish people. Yeah, exactly.. So again, the way it works is there are, it's an umbrella condition. There are lots of different mutations that can cause hereditary, hemochromatosis being the g being a genetic reason why people can have iron overload.

Again, it's not the only reason people can have iron overload because outside of hereditary hemochromatosis, which is this mutation that leads to inappropriate suppression, Or lack of expression of hepcidin, which then leads to over absorption of dietary iron, meaning that regulation, that feedback process is lost.

So you absorb all the iron whether you need it or not. And again, remember, we don't have a physiologic way to excrete iron. That is when, if it's too much in our system. And so the people in whom this tends to manifest is going to be in men who do not bleed preferably. And then in postmenopausal women, once they have stopped having menstrual blood losses or say they're on, some form of contraception, that shuts down their menstrual periods, that would be another situation where you be at higher risk, but there is a bit of a male predominance with hemochromatosis in particular. But aside from this genetic condition, other, like the general concept of iron overload is the opposite of iron deficiency. Whereas iron deficiency, I thought about more iron out than in. Now it's just the other way more iron in than out.

Be it from dietary excess. I don't know that I've seen a case of somebody who had true iron overload from dietary excess or from taking tons and

supplements, but I suppose it's plausible. And then other situations would be people who have a medical condition that requires them to get a lot of blood transfusions.

So people, this is most often people with certain kinds of hematological disorders, be it sickle cell anemia or some form of bone marrow disorder that leads them to be unable to produce blood. And so they need to get blood replaced often. And this. Every unit of blood comes with a bunch of iron that is going to stay in their system because again, we don't have ways to excrete it.

And then he genetic kind of hemochromatosis issues would be the third one be of big category that I think of in terms of ways that we can get iron overloaded. So once we have this excess iron, it's causing all these, free radical reactions, tissue damage, DNA injury, things like that.

And so the main complications or consequences that I think of one is visible. So Hemochromatosis has a nickname, it's called Bronze Diabetes. And so that's because you get iron deposition in the skin and soft tissues, and so you get nicely tanned, which that's “fantastic”; as you can imagine, it might be something that's unusual to see a very nicely-tanned Irish person, right? And so you also develop diabetes. The iron can get deposited in the tissues of the heart. So these patients can get heart failure in the liver. They can get cirrhosis. It can get deposited in the pituitary gland. And the pituitary secretes a variety of hormones that are really important for various physiological functions.

They can get hypogonadism clinically, significant low testosterone and it can get deposited in the joints so they can get significant osteoarthritis. And so those are the main manifestations that I think of and it leads to complication again, most often in men over 40. And that's because, again, in the same way that it takes a long time for these iron changes to happen in most situations, it takes a while to accumulate enough iron, not just to accumulate it, to deposit it, to cause all this harm, such that you get an organ that fails in some way to cause symptoms because this is often a pretty delayed diagnosis. And in postmenopausal women who no longer have that kind of effectively protective mechanism. If you have a premenopausal women who's having menstrual blood loss every month, that's actually protecting them from the

consequences of something like hemochromatosis or iron overload, because they're losing some iron every month.

And so you can see why. Then for patients who have this condition, unfortunately at the moment we don't yet have the ability to gene edit or crispr people to be better from hemochromatosis. But but therapeutic phlebotomy is the treatment for this. What that means is you donate blood effectively.

And so they will get, they will have their iron panel, that blood test that I mentioned where you measure ferritin and transferrin and iron and things like that will be monitored much more frequently than it would be monitored in anybody else. And they will donate. to achieve normal, target ferritin levels, so their ferritin is not 400, but instead maybe it's I don't know, 100 or something like that.

That would be much more preferable for somebody with hemochromatosis. And by doing that, you can prevent all of the complications if you can get into that normal range and keep it there long term.

Danny Lennon: How would someone go about an early diagnosis, given that in most cases we're seeing that later on, once more serious complications ever arise in that they get this diagnosis? Finally, is there a way to get an early diagnosis for people who may have hemochromatosis?

Austin Baraki: Yeah, so overwhelmingly the most important factor is going to be if there's a family history, I would 100% be, do you know, evaluating people who have a family history of this condition? I'm not aware of any sort of general either generalized or targeted screening guidelines for this. I think that if somebody had undergone any form of testing and say their blood count was actually on the high side, meaning like the opposite of anemia, that would be one thing that might catch my attention. Or if they got an iron panel for whatever reason and instead of being glow, their ferritin was on the high side, be it over 200 or 300 or something like that.

But most importantly, I look for a transferrin saturation of over 45% and that will catch my attention. Now again, there are a lot of reasons why this can happen. Just because you have a transferrin saturation of over 45% or you

have a ferritin on the high side, that does not mean you have hemochromatosis.

There are a whole list of possibilities. But if the person is of the right demographic and I rule out all those other possibilities, like I don't find evidence of liver disease and inflammatory condition, they don't drink too much alcohol, that can also drive those levels up, things like that, then I may, I may pursue a little bit of further testing but I see this condition very infrequently and like I see iron deficiency probably near daily. I can count probably on one hand at the number of cases of hemochromatosis or patients who've had it, that I have seen in the past whatever decade or something like that. And again I think that's probably because I live and work, I don't know, a couple miles from the Mexican border, not in Ireland.

And and so I'm sure there's probably more expertise over on your side of the pond as far as methods for an early diagnosis. Because like we talked about when we do testing, we need this idea of a pre-test probability in mind. And my pre-test probability for patients for hemochromatosis and where I live is near zero, right? And as you can see why, like even if I saw a blood test where the transference sat was, 48 or 50% I'm still thinking, nah, it's probably not that they probably, drink too much or something like that. Some other reason that can cause that.

Danny Lennon: Is there anything that I've mentioned that we haven't closed a loop on or that you wanted to mention?,

Austin Baraki: I think some good take homes are that iron is super important, does a whole lot of things. Iron deficiency is very common, most common nutritional deficiency worldwide. But I think it's really critical for people to remember those other two important take home points that not all anemia is iron deficiency.

And if you find evidence of iron deficiency, you must explain it. Do not just say, "oh, I'll just take some iron and make this better". Because you could be missing something that is potentially dangerous or life-threatening on a shorter time scale than you think . So I think that this is a situation where, as I have mentioned on other podcasts, I'm generally not a fan of folks doing a whole bunch of their own lab testing when they're not necessarily trained to

do this more comprehensive contextual, evaluation, including pre-test probabilities and training and how to interpret these things.

But if you do that for whatever reason, and you get results that suggest anemia or suggest iron deficiency, do not just take iron and think it's going to be good. You may get lucky, but I would not roll those dice. I would talk to a clinician to figure out why is this iron deficiency going on? Because there are a bunch of potentially lethal causes.

And they may not be causing symptoms at that time or ever, and it may catch up with you. Anemia and iron deficiency deserve a definitive causal diagnosis. And then, whether it can be mitigated through diet alone, through oral supplementation or whether you need to escalate to IV iron replacement.

That's also a decision that can be guided by by a clinician who has experience with these things.

Danny Lennon: Fantastic. So before we finish for people that are looking maybe to get in contact with you or find more of your work or your whereabouts on the internet, where would you send them?

Austin Baraki: Yeah. So I as some folks may know from the prior episodes, I work with a company called Barbell Medicine, where we do a lot of coaching and consultation and create a lot of content related to health and performance and things like that. So the Barbell Medicine website there's some contact emails there if people want to try to reach us for any reason.

I'll probably leave it at that. I'm present on Twitter, although not highly interactive. And and I will admit not super responsive to the DM inbox on Instagram because it tends to stay, it tends to stay pretty full. So that's probably the best way to find my stuff or to reach me is Google the name or Barb Medicine or whatever the case is.

Danny Lennon: So to be clear, you are not interested in the types of conversations about health that would appear on social media? That doesn't stimulate you?

Austin Baraki: I'm generally not thrilled with the level of conversation on social media around these complex health topics, no.

Danny Lennon: No, the level is quite low. We will leave it there. Dr. Austin Baraki, thank you so much for taking the time to come and talk to me today about this, and thank you for all the information you've given. I think people are really going to enjoy this. Thank you for that and for giving up your time in general. It's much appreciated.

Austin Baraki: Yeah. Always great to talk to you and and to hang out and go over these things. Happy to do it again.