KRESSER INSTITUTE
FOR FUNCTIONAL AND EVOLUTIONARY MEDICINE

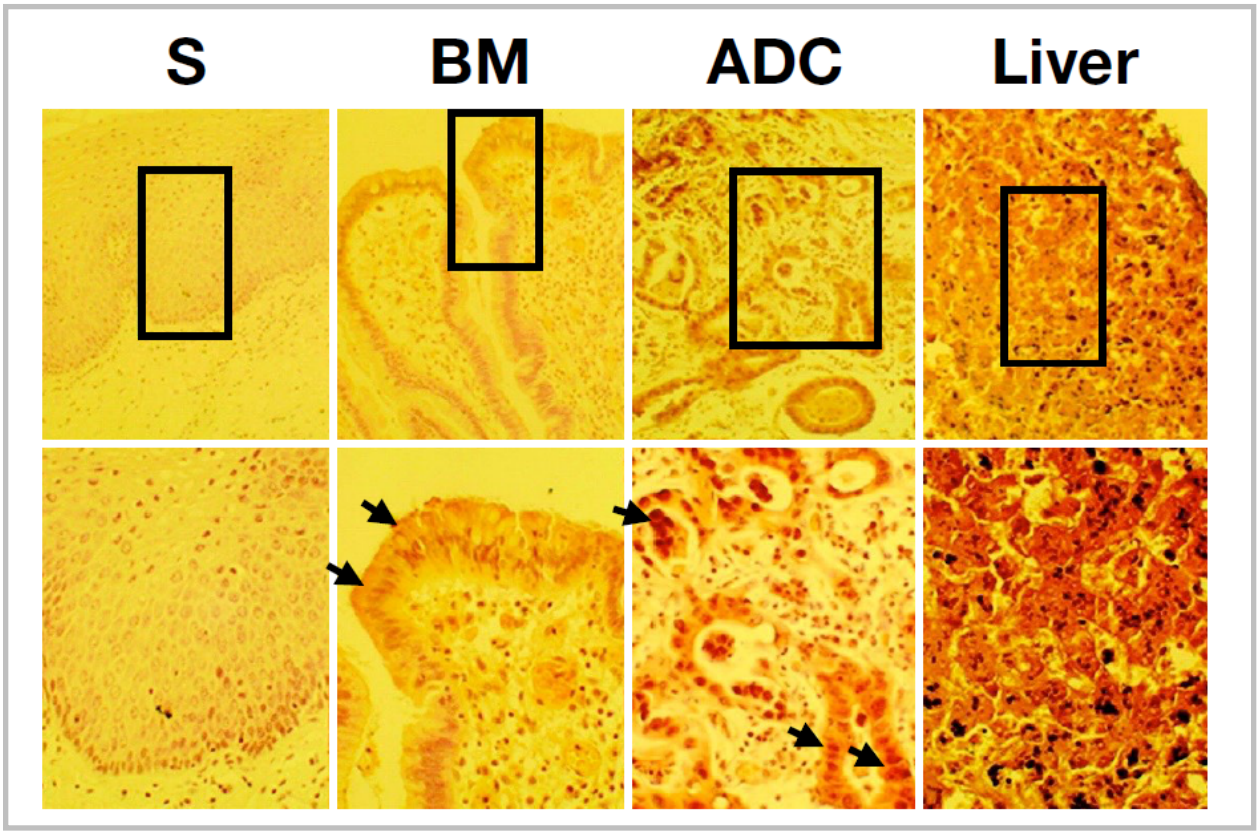
Iron Overload - Part One

Hey, everybody. In the last presentation, we talked about iron deficiency, and in this presentation, we're going to cover the other side of the coin with iron overload. We're going to spend a lot of time on etiology, pathology, and epidemiology in this particular unit, more so than in other blood chemistry modules because iron overload is so poorly understood and so often misdiagnosed. We're still going to do plenty of cases and practical application, don't worry, but you have to understand the background first.

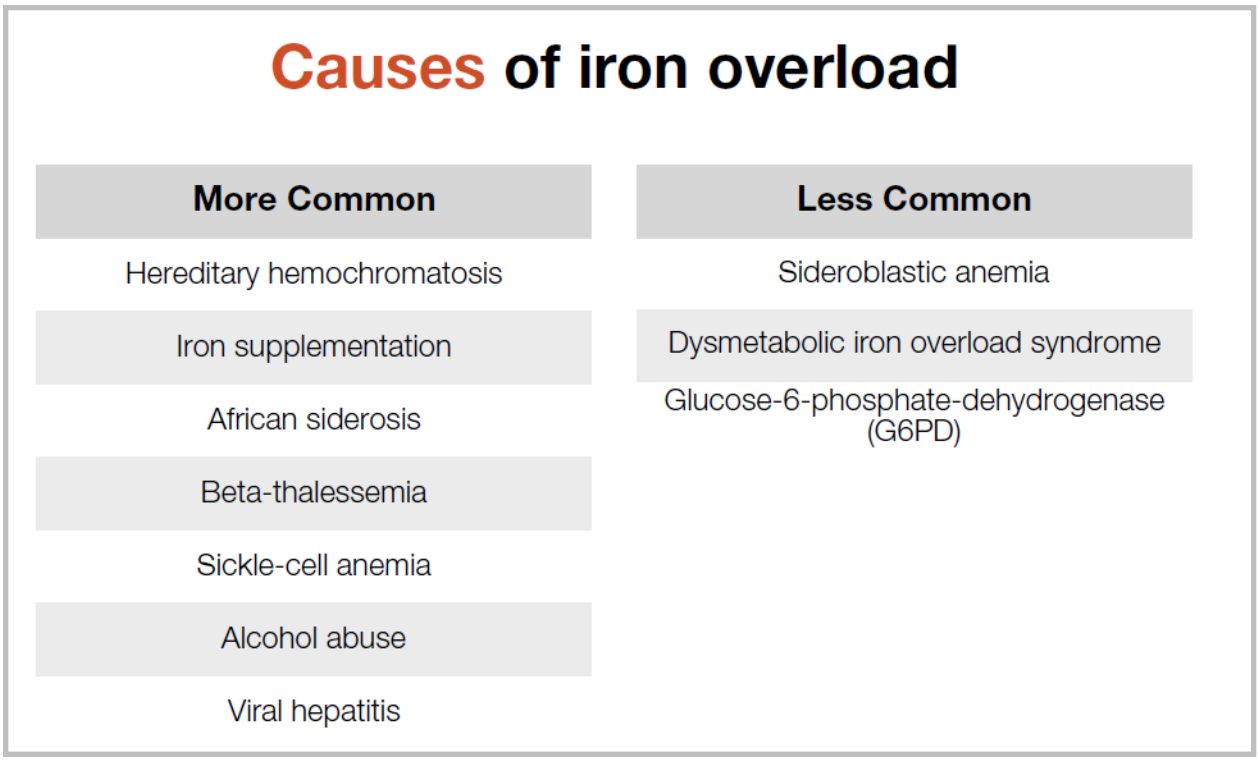
Hemochromatosis is the most well-known disorder involving iron overload. It affects between one in 200 and one in 500 individuals, depending on what study you look at and depending on what region of the world you're in, which makes it one of the most common genetic disorders, at least in North America, with a prevalence of 10 times that of cystic fibrosis. Hemochromatosis is associated with significant morbidity and mortality, yet few people have even heard of it.

Unfortunately, hemochromatosis is often misdiagnosed or simply just missed. According to a 1996 CDC survey, hemochromatosis patients have seen an average of three doctors and spent at least nine years before getting an accurate diagnosis. In my experience, it's even more than that. I've diagnosed at least 30 patients in my practice over nearly eight years, and only three of them were aware that they had it prior to my diagnosis. Iron panels are not typically included in routine lab work for reasons that I still don't understand, so both iron deficiency and iron overload are significantly underdiagnosed.

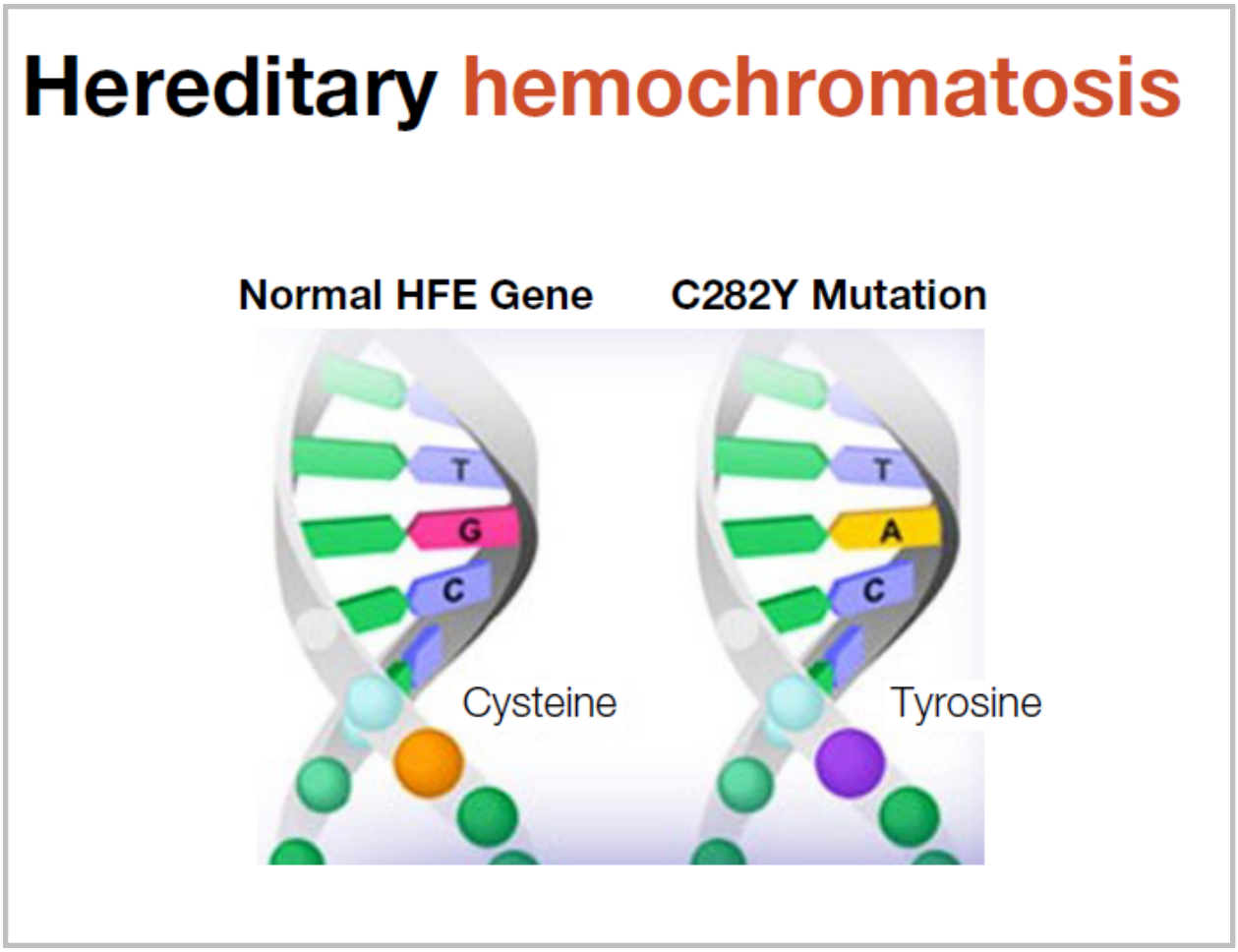
Compounding the problem, even mild iron overload, which means borderline high iron levels that are still in the lab reference range, can also cause significant problems, as we'll soon see, yet this is poorly understood in conventional medicine, so even if a doctor does run an iron panel and detects mild iron overload, he or she is likely to simply ignore it. What's more, patients who are iron deficient and even those who are not but who simply have low hemoglobin for another reason and are given iron supplements are not often told to stop, and they can develop iron overload or toxicity. This is iatrogenic iron overload, and it's quite common, in my experience.



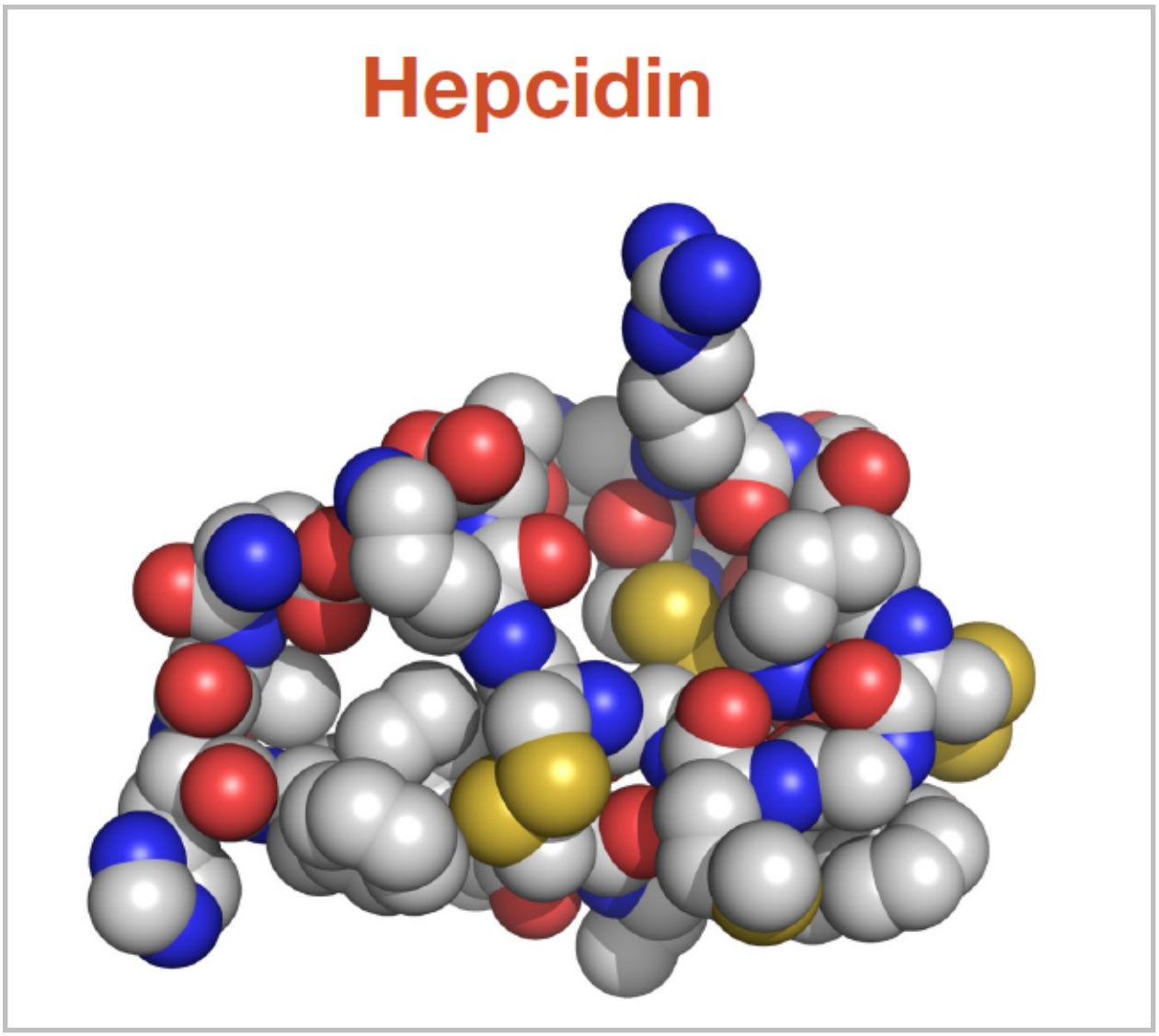
As we discussed in the last presentation, as little as 250 mg of iron can poison a small child. In a person with normal iron metabolism, excess iron is simply excreted, but when iron metabolism is impaired, excess iron from supplements and diet can accumulate in organs and tissues. This causes our organs to literally rust, especially the pancreas, liver, joints, heart, and brain.



Several conditions are known to cause iron overload. The most common causes you'll see in clinical practice are genetic mutations that contribute to excess iron storage and excess iron supplementation, but I've listed a few of the other less common causes here on this slide. These include things such as beta-thalassemia, sickle cell anemia, alcohol abuse, viral hepatitis, and glucose-6-phosphate dehydrogenase, or G6PD. You're less likely to see these in the context of a functional medicine practice, but they may pop up.



Classic hereditary hemochromatosis is an autosomal recessive disorder. It's a mutation of both copies of the HFE gene on chromosome 6. An autosomal recessive disorder means that you need two copies of the mutation to develop the disease. This is somewhat inaccurate, as we'll discover later, because heterozygous carriers can actually have problems, but this is the conventional interpretation. There are two major types of classic hereditary hemochromatosis. One is C282Y, which involves the substitution of a cysteine residue for a tyrosine residue at amino acid position 28. The second is H63D, which involves a substitution of histidine for aspartate at amino acid 63.



Since the discovery of the C282Y mutation, at least 20 other mutations of the HFE gene have been identified. Unfortunately, their effects are still poorly understood. We've also discovered mutations in other genes that can cause iron overload, including transferrin receptor 2, ferroportin 1, chromosome number 19, hepcidin, and CDA2, and these are even more poorly understood. This means that when a patient is negative for the C282Y and H63D mutations, which are the only two mutations that are typically tested for when you run an HFE gene panel, it doesn't mean that they don't have genetics that can contribute to iron overload, and unfortunately, this is also not widely known, and it contributes to the underdiagnosis of iron overload.

Prevalence of hemochromatosis mutations

Genetic pattern	Prevalence
C282Y homozygote	0.4%
C282Y heterozygote	0% - 9%
H63D homozygote	1.5%
H63D heterozygote	5 - 22%
C282Y/H63D compound	5%

Source: Hanson et al. 2001

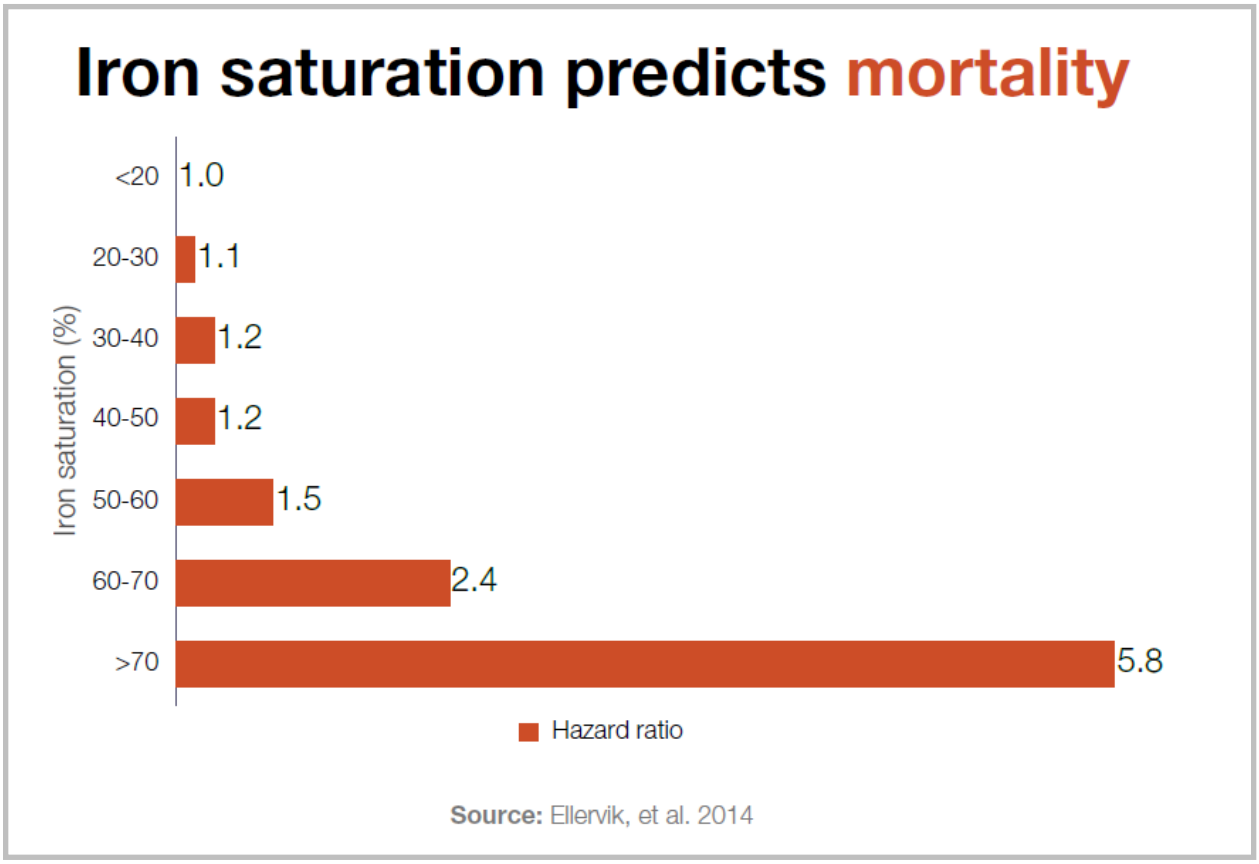
Estimates on the prevalence of hemochromatosis mutations vary geographically. According to one large review in the *American Journal of Epidemiology*, they found hemochromatosis, the classic C282 homozygotes, in about 0.4 percent of the population, or one in 200 roughly. Anywhere from 0 percent of people in Asia to 9 percent are heterozygous for the C282Y mutation. Approximately 1.5 percent are homozygous for the H63D mutation. From 5 to 22 percent are heterozygous for H63D, and then 5 percent are compound heterozygotes, meaning they have one copy of the mutated C282Y and one mutated copy of H63D. Note that these estimates vary considerably from study to study, in part because there are geographical differences, but they are mostly in these ranges.

Iron loading & increased risk of disease in carriers of HFE mutations

Clinical Condition	HFE Mutations	Clinical Observation
Iron loading (4)	CY/wt & CY/HD	Elevated ferritin & Tf sat%
Vascular disease (4)	CY/wt	2.3 - 6.6x risk for CVD
Cancer (3)	CY/wt	1.6 - 8.7x risk for cancer
Shortened life expect.	CY/wt	Increased mortality prior to age 65

Source: Weinberg 2002

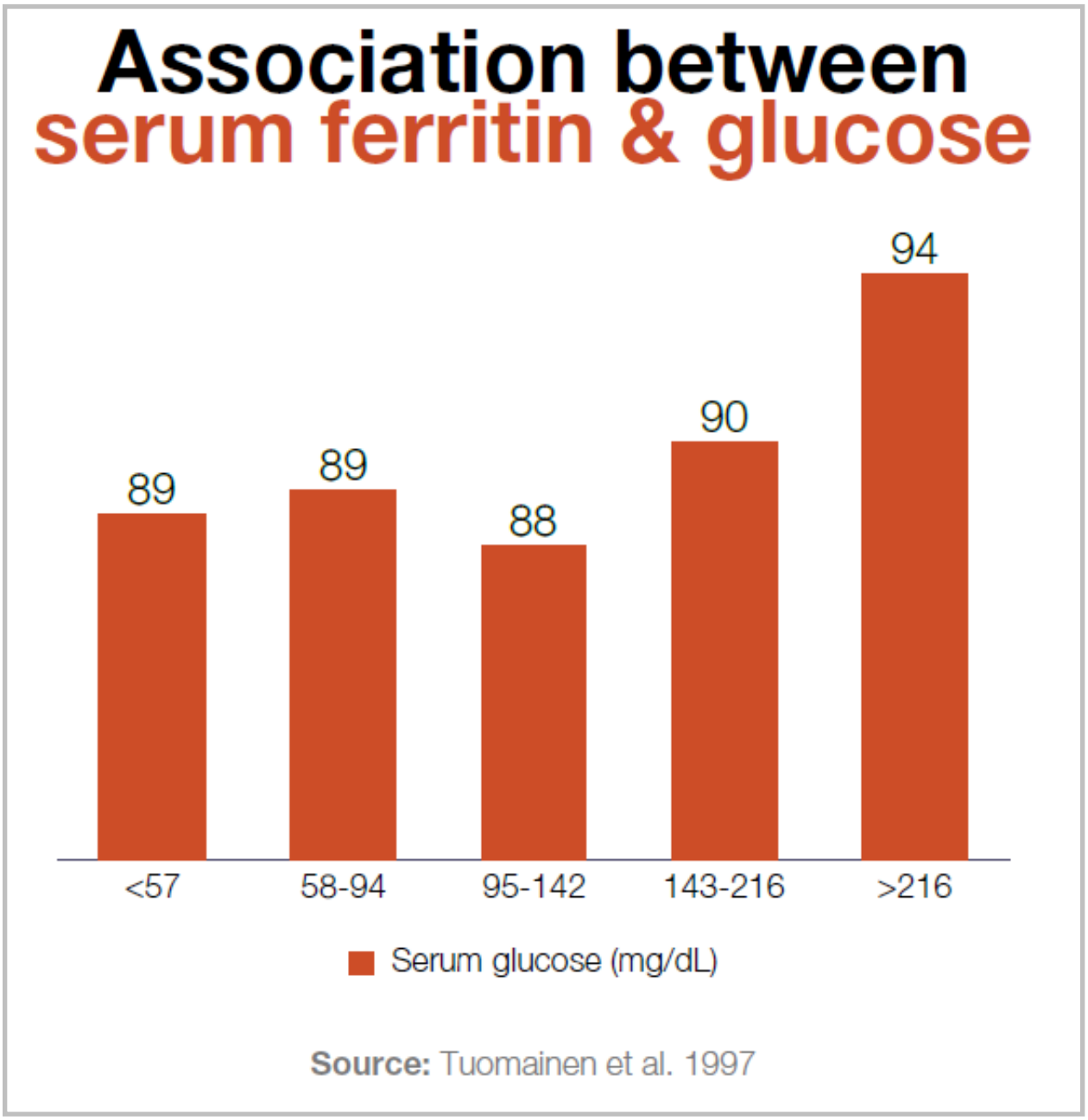
One of the most common misconceptions about iron overload is that heterozygous carriers of mutations that we just discussed are not affected. However, research over the last two decades has shown this to be clearly false. The table on this slide summarizes 11 studies correlating elevated iron indices with increased rates of clinical disease in people who are either heterozygous for these mutations or compound heterozygous for HFE mutations. Four studies showed that C282Y heterozygotes and C282Y and H63D compound heterozygotes present with elevated ferritin and transferrin saturation levels. Four studies showed that C282Y heterozygotes have between 2.3 and 6.6 times higher risk of cardiovascular disease than non-carriers. Three studies showed that C282Y heterozygotes have between 1.6 and 8.7 times higher risk for cancer, and one study showed that C282Y heterozygotes have increased risk of early mortality from all causes.



Even elevated transferrin saturation levels alone without any known genetic mutations have been shown to predict the risk of early death. In this study of nearly 85,000 Danish people with diabetes, researchers examined mortality according to baseline levels of transferrin saturation, or iron saturation. Survival was reduced in those with iron saturation above 50 percent compared to those with iron saturation below 50 percent, with median survival ages of 66 and 79 respectively, which is a huge difference, 13 years. Those with iron saturation above 50 percent had two times higher risk of early death compared to those with transferrin saturation below 50 percent. Those with iron saturation above 70 percent had an almost fivefold higher risk of early death compared to those with iron saturation below 20 percent. It's important to note that the reference range for iron saturation goes up to 55 percent in most labs, and according to this data, clearly it should be lower than that.

It's well established in the scientific literature that iron overload is associated with a long list of pathologies and diseases, including metabolic conditions affecting the liver; diabetes; metabolic syndrome; gout; cardiovascular disease; neurological issues such as Alzheimer's dementia, Parkinson's, epilepsy, and restless legs syndrome; endocrine problems such as impotence, infertility, hypogonadism, hypothyroidism, and hypoparathyroidism; immune imbalances such as asthma, inflammatory bowel disease, rheumatoid arthritis, lupus, psoriasis, gout, lung disease, and cancer; splenomegaly, and infections of all types; and then musculoskeletal disorders such as osteoporosis and osteoarthritis.

What is less well known is that even high-normal iron levels are associated with metabolic, cardiovascular, and neurodegenerative problems. For example, studies on iron overload have linked it with diabetes and impaired glucose tolerance, and this is thought to involve several mechanisms. The accumulation of iron reduces insulin production and decreases insulin sensitivity in the liver, and iron deposition in the muscles decreases glucose uptake.



Studies have shown an association between serum ferritin, which as you know is the long-term storage form of iron, and fasting glucose levels. The study on this slide was of about 1,000 Finnish

men, and it showed that as ferritin levels rose, glucose levels rose as well. The people with the highest ferritin levels—they divided the study population into quintiles—those with ferritin levels between 143 and 216 and people with ferritin levels above 216 had the highest fasting glucose levels. Now again, keep in mind that the reference range for ferritin in men goes up to 400 in most labs, so here we're talking about an observed increase in fasting glucose at levels that are well within the laboratory reference range, and you know from the hyperglycemia unit that even moderately elevated fasting glucose levels are a significant risk factor for increased morbidity and mortality.