

## Iron Overload - Part Three

Be careful in assuming that high ferritin is always related to iron overload. Ferritin is also an acute-phase reactant that is elevated in the inflammatory response, so if you see elevated ferritin with normal iron saturation and UIBC, further investigation is often required.

As discussed in the iron deficiency presentation, soluble transferrin receptor can be helpful in distinguishing high ferritin due to iron overload and iron ferritin due to inflammation. Soluble transferrin receptor decreases with reduced cellular need for iron, and unlike ferritin, it's not affected by inflammation. You can just use the reported lab range. I've also provided a functional range that is just a little bit smaller. We don't have enough data for an evidence-based, you know, peer-reviewed, evidence-based functional range, but I think empirically it makes sense to narrow the range a little bit based on what we know from all of the other ranges for the other iron markers.

**Other useful markers** for distinguishing between **iron overload and inflammation**

**CRP**

**A1-Acid  
Glycoprotein**

Other markers that can be helpful in distinguishing between iron overload and inflammation include C-reactive protein and A1-acid glycoprotein. These are also acute-phase reactants that are elevated in the inflammatory response. A1-acid glycoprotein in particular is known to be elevated in chronic inflammatory conditions. If ferritin, CRP, and A1-acid glycoprotein are high but other iron markers are normal on the initial test and the retest, and especially if ferritin doesn't decrease significantly after a blood donation, inflammation would be the likeliest cause.

TESTS	RESULT	FLAG	UNITS	REFERENCE INTERVAL
Iron, Serum	209	High	ug/dL	27 - 159
<u>Iron Saturation</u>	<u>78</u>	<u>Alert</u>	%	15 - 55
Ferritin, Serum	86		ng/mL	15 - 150
Vitamin B12	1083	High	pg/mL	211 - 946
Vitamin D, 25-Hydroxy	29.1	Low	ng/mL	30.0 - 100.0
CBC, Platelet Ct, and Diff				
WBC	3.7		x10E3/uL	3.4 - 10.8
RBC	4.28		x10E6/uL	3.77 - 5.28
Hemoglobin	14.5		g/dL	11.1 - 15.9
Hematocrit	43.1		%	34.0 - 46.6
<b>MCV</b>	<b>101</b>	<b>High</b>	fL	79 - 97
<b>MCH</b>	<b>33.9</b>	<b>High</b>	pg	26.6 - 33.0
MCHC	33.6		g/dL	31.5 - 35.7
RDW	12.3		%	12.3 - 15.4
Platelets	158		x10E3/uL	150 - 379
Neutrophils	50		%	
Lymphs	36		%	
Monocytes	9		%	
Eos	5		%	
Basos	0		%	
Neutrophils (Absolute)	1.8		x10E3/uL	1.4 - 7.0
Lymphs (Absolute)	1.4		x10E3/uL	0.7 - 3.1
Monocytes(Absolute)	0.3		x10E3/uL	0.1 - 0.9
Eos (Absolute)	0.2		x10E3/uL	0.0 - 0.4
Baso (Absolute)	0.0		x10E3/uL	0.0 - 0.2
Immature Granulocytes	0		%	
Immature Grans (Abs)	0.0		x10E3/uL	0.0 - 0.1

In addition to the markers we just discussed, red blood cell indices such as hemoglobin and mean corpuscular volume may also be elevated in iron overload. This is more true with hemochromatosis than with mild or functional iron overload, however. High MCV and hemoglobin levels are thought to reflect increased iron uptake and hemoglobin synthesis by immature erythroid cells. Generally, MCV and hemoglobin will fall with treatment along with the rest of the iron markers.

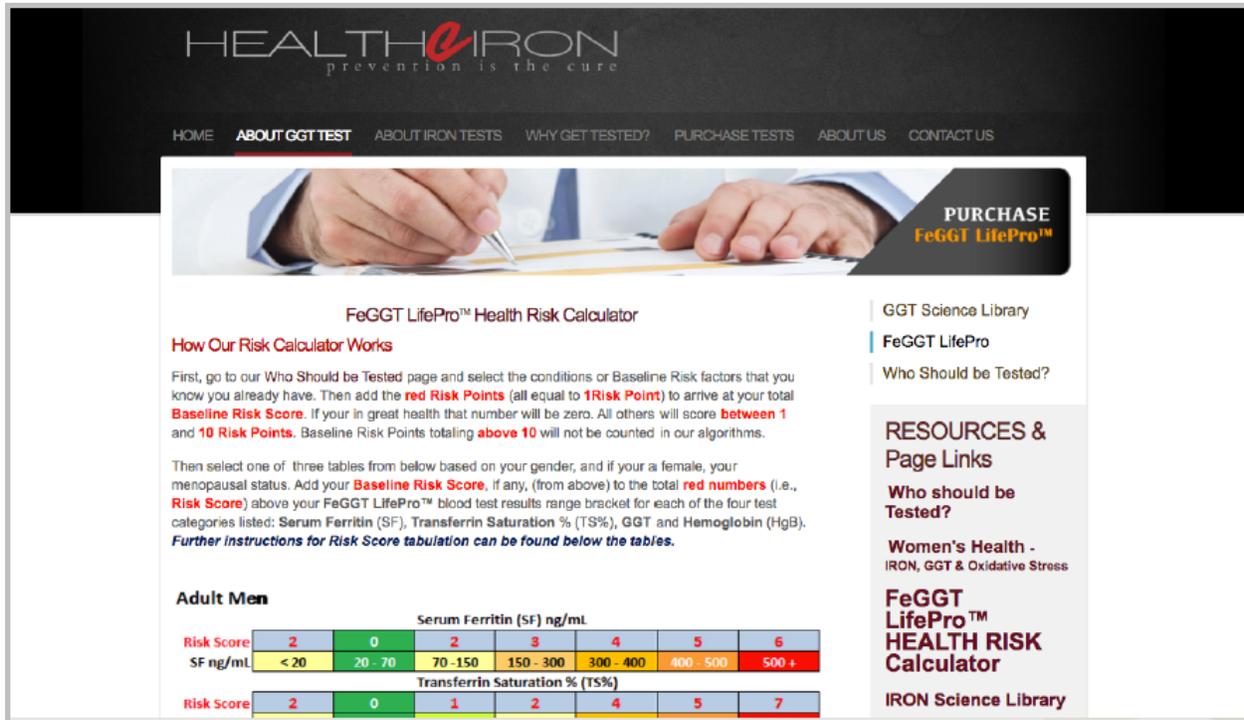
## Biochemical iron parameters in the VB population stratified for presence or absence of MetS

	Metabolic Syndrome NO (n=1,087)	Metabolic Syndrome YES (n=304)	Unadjusted P	Sex- and age- Adjusted P
Age (years)	53.1±18.6	65.6±12.2	<0.001	
Male Sex (%)	44.6	43.1	636	
S-Iron (µg/l)	97.7±34.9	95.6±31.9	342	721
Transferrin (mg/dl)	243.4±44.1	233.5±40.6	<0.001	46
Transferrin saturation (%)	29±11	30±12	510	575
Ferritin* (µg/l)	61 (58-65)	102 (92-112)	<0.001	<0.001
Hepcidin* (nmol/l)	4.3 (3.9-4.7)	8.0 (7.0-9.1)	<0.001	<0.001
Hepcidin undetectable (n/%)	140/12.9%	12/3.9%	<0.001	<0.001
Hepcidin/Ferritin* Ratio (nmol/µgx1000)	70.4 (65.2-76.0)	77.8 (68.5-88.3)	222	93
Hb (g/dl)	14.3±1.5	14.6±1.5	3	<0.001

\* Variables not normally distributed were log-transformed and expressed as geometric means with 95% CIs.

Source: <http://www.ncbi.nlm.nih.gov/pubmed/23144745>

Recently, the Iron Disorders Institute developed a new scoring system for iron overload called the **FeGGT LifePro**, and I've put a representation of it here on this slide, and we'll also link to where you can get more information. The FeGGT score recognizes the important role of the regulatory hormone hepcidin, which we talked about earlier, in promoting macrophage iron loading, atherosclerosis, and other adverse consequences. It's predicated on research showing that numerous diseases and medical conditions develop when both iron and GGT are in the upper normal ranges and above.



**HEALTH eIRON**  
prevention is the cure

HOME ABOUT GGT TEST ABOUT IRON TESTS WHY GET TESTED? PURCHASE TESTS ABOUT US CONTACT US

**PURCHASE FeGGT LifePro™**

**FeGGT LifePro™ Health Risk Calculator**

**How Our Risk Calculator Works**

First, go to our [Who Should be Tested](#) page and select the conditions or Baseline Risk factors that you know you already have. Then add the **red Risk Points** (all equal to **1Risk Point**) to arrive at your total **Baseline Risk Score**. If you're in great health that number will be zero. All others will score **between 1 and 10 Risk Points**. Baseline Risk Points totaling **above 10** will not be counted in our algorithms.

Then select one of three tables from below based on your gender, and if you're a female, your menopausal status. Add your **Baseline Risk Score**, if any, (from above) to the total **red numbers** (i.e., **Risk Score**) above your FeGGT LifePro™ blood test results range bracket for each of the four test categories listed: Serum Ferritin (SF), Transferrin Saturation % (TS%), GGT and Hemoglobin (Hgb). **Further instructions for Risk Score tabulation can be found below the tables.**

**Adult Men**

	Serum Ferritin (SF) ng/ml						
<b>Risk Score</b>	2	0	2	3	4	5	6
<b>SF ng/ml</b>	< 20	20 - 70	70 - 150	150 - 300	300 - 400	400 - 500	500 +

	Transferrin Saturation % (TS%)						
<b>Risk Score</b>	2	0	1	2	4	5	7

GGT Science Library  
FeGGT LifePro  
Who Should be Tested?

**RESOURCES & Page Links**

**Who should be Tested?**

Women's Health - IRON, GGT & Oxidative Stress

**FeGGT LifePro™ HEALTH RISK Calculator**

IRON Science Library

The FeGGT LifePro score includes ferritin, transferrin saturation, GGT, and hemoglobin, and these are all markers that are included on the case review blood panel that I'm teaching. We'll discuss GGT in more detail later. It's a liver enzyme that has traditionally been measured to detect liver health and function and alcohol consumption, but in recent years, elevated GGT measurements have proven to be effective early warning signs of other health risks such as atherosclerosis, stroke, type 2 diabetes, kidney disease, and cancer.

When GGT concentrations exceeded the lowest 25 to 35 percent of normal population ranges, disease risk grew in proportion to increases in GGT. People faced increased disease risk once GGT rose above the low-normal range for their gender in a linear fashion. The higher the GGT concentration, the greater the risk of future disease and premature mortality, even when GGT levels were still well within the normal laboratory range. I just want to reiterate that here. This data suggests that any time GGT is above even low-normal, not high-normal, just low-normal, you see a linear increase in disease risk. This is hardly known at all in the conventional model, at least from what I've seen.

So why is GGT so strongly correlated with increased disease risks? One of its roles is to reconstitute glutathione, the body's master antioxidant. When GGT concentrations are above low-normal ranges, excess GGT can catabolize or degrade glutathione, which causes critical glutathione depletion. When glutathione is depleted, oxidative stress occurs, and this leads to a vicious cycle of irreversible cell, tissue, and DNA damage. Blood donation or a phlebotomy can reduce GGT and other risk markers associated with liver diseases and insulin resistance.

## Framingham Heart Study (US)

**3,544 participants - mean age 44.5 years**  
**GGT Population median Divided Mortality Study**  
 (upper panel data is adjusted for all known CVD risk factors)

<b>Women</b> with GGT <b>below</b> the median	<b>Women</b> with GGT <b>above</b> the median
<b>Men</b> with GGT <b>below</b> the median	<b>Men</b> with GGT <b>above</b> the median
Cohort Distribution: 50%	Cohort Distribution: 50%
<b>Normal Risk</b>	<b>Normal Risk +71%</b>
<i>(Lower panel data is adjusted for age and sex only)</i>	
<b>Normal Risk</b>	<b>Normal Risk +119%</b>

**Source:** <http://www.healthiron.com/Websites/healthiron/images/a.Serum%20gamma-glutamyl%20transferase%20and%20risk%20of%20heart%20failure%20in%20the%20community.pdf>

Now, I've put a study up here on this slide, the famous Framingham Heart Study, which I'm sure you're aware of. There were 3,544 participants with an average age of 44½ years. Then there has been a lot of reanalysis of the Framingham heart data, and this is one of those reanalyses. It's called the GGT Population Median Divided Mortality Study. What they found is that both women and men with GGT below the median had a normal risk of cardiovascular disease, but women with GGT above the median had a 71 percent higher risk of cardiovascular disease, and men with GGT above the median had a 119 percent higher risk of cardiovascular disease.

## Calculating FeGGT baseline risk score

Add up total # of points based on **metabolic syndrome risk factors**

Risk factor	Point
Waist circumference >40 in (men) or >35 in (women)	1
Systolic BP >130 or diastolic BP > 85mm	1
Fasting glucose >100 mg/dL	1
Triglycerides >150 mg/dL	1
HDL <40 mg/dL (men) or 50 mg/dL (women)	1

Here's how the FeGGT LifePro risk calculator works. You first establish a baseline risk score starting with the table on this slide, listing risk factors for metabolic syndrome. The maximum score here would be 5, so you would look at waist circumference, over 40 in men or over 35 in women, systolic blood pressure over 130 or diastolic blood pressure over 85, fasting glucose over 100 mg/dL, triglycerides over 150 mg/dL, and then HDL below 40 mg/dL in men or below 50 mg/dL in women.

## Calculating **FeGGT** baseline risk score

Add up total # of points based on **conditions (with max score of 5)**

Condition	Point
<b>Atherosclerosis or CHD</b>	1
<b>Any liver disease</b>	1
<b>Pre-diabetes or diabetes</b>	1
<b>Hip, knee, or ankle replacement before 65 years old</b>	1
<b>Loss of libido or impotence before age 60</b>	1
<b>Premature menopause (natural or surgical)</b>	1
<b>Unusual fatigue, weakness or depression</b>	1

Then you give each patient an additional point for each condition that he has listed here in this table, so atherosclerosis or coronary heart disease would be one; any liver disease would be another; prediabetes or diabetes; hip, knee, or ankle replacement before 65 years of age; loss of libido or impotence before age 60; premature menopause, whether it's natural or surgical; and then unusual fatigue, weakness, or depression.

Then you add these points to the points from the risk factors on the last slide, and you come up with a total baseline risk score. Now, the maximum total baseline risk score is 10, even if they have more points, so it tops out at 10.

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## Adult Men

Serum Ferritin (SF) ng/mL							
<b>Risk Score</b>	2	0	2	3	4	5	6
<b>SF ng/mL</b>	<20	20-70	70-150	150-300	300-400	400-500	500+
Transferrin Saturation % (TS%)							
<b>Risk Score</b>	2	0	1	2	4	5	7
<b>TS%</b>	<20	20-35	35-45	45-55	55-65	65-85	85+
Gamma Glutamyl Transferase (GGT) U/L							
<b>Risk Score</b>	0	1	2	3	5	6	9
<b>GGT U/L</b>	<12	12-15	15-25	25-35	35-50	50-100	100+
Hemoglobin (Hgb) g/dL							
<b>Risk Score</b>	2		0			3	
<b>Hgb g/dL</b>	<11		11-17			17+	

## Adult Pre-Menopausal Women

Serum Ferritin (SF) ng/mL							
<b>Risk Score</b>	2	0	2	3	4	5	6
<b>SF ng/mL</b>	<15	15-50	50-80	80-120	120-175	175-250	250+
Transferrin Saturation % (TS%)							
<b>Risk Score</b>	2	0	1	2	4	5	7
<b>TS%</b>	<18	18-35	35-45	45-55	55-65	65-85	85+
Gamma Glutamyl Transferase (GGT) U/L							
<b>Risk Score</b>	0	1	2	3	5	6	9
<b>GGT U/L</b>	<9	9-13	13-20	20-33	33-45	45-80	80+
Hemoglobin (Hgb) g/dL							
<b>Risk Score</b>	2		0			3	
<b>Hgb g/dL</b>	<11		10-17			17+	

## Adult Post-Menopausal Women

Serum Ferritin (SF) ng/mL							
<b>Risk Score</b>	2	0	2	3	4	5	6
<b>SF ng/mL</b>	<20	20-60	60-125	125-175	175-225	225-350	350+
Transferrin Saturation % (TS%)							
<b>Risk Score</b>	2	0	1	2	4	5	7
<b>TS%</b>	<18	18-35	35-45	45-55	55-65	65-85	85+
Gamma Glutamyl Transferase (GGT) U/L							
<b>Risk Score</b>	0	1	2	3	5	6	9
<b>GGT U/L</b>	<10	10-15	15-22	22-35	35-45	45-90	90+
Hemoglobin (Hgb) g/dL							
<b>Risk Score</b>	2		0			3	
<b>Hgb g/dL</b>	<11		10-17			17+	

Once you have the patient’s baseline risk score, you would add the number of points in these tables on this slide, which we’ll provide a handout of, based on their lab values to that score for their total FeGGT LifePro score. You would choose which table to use to calculate this score based on their gender, and if they are female, based on their menopausal status.

## FeGGT LifePro™ Risk Score Tabulation

Total Risk Score	Risk Level
<b>0 - 5</b>	Low
<b>6 - 10</b>	Moderate
<b>11 - 15</b>	High
<b>16 - 20</b>	Very High
<b>≥ 21</b>	Extreme

Okay, now let’s talk a little bit about interpreting the FeGGT LifePro score. So, as you can see in the table on this slide, a score of 0 to 5 is low, 6 to 10 is moderate, 11 to 15 is high, 16 to 20 is very high, and over 21 is extreme, but there are a few things to be aware of in addition. Those who have really high blood test scores who are in midlife and younger will have relatively worse outcomes when compared to age-matched peers who have high lifestyle and family history risk scores, so this just means that the serum markers are more important in predicting risk in general than the lifestyle and family history. For people who have relatively high blood iron scores, whether you’re talking about serum ferritin, transferrin saturation, or both, the blood test results including some baseline risk factors can be expected to improve rapidly as iron reduction is achieved. This suggests that the high iron scores contribute significantly to the FeGGT LifePro score and are also among the most modifiable factor.

For people with high GGT, you want to emphasize a nutrient-dense, polyphenol-rich diet that is high in glutathione, and you may want to supplement with glutathione as well, because as we discussed, one of the ways that high GGT causes problems is it degrades glutathione. A lot of people suffer from glutathione deficiency as it is.

People with FeGGT LifePro scores of 5 or above combined with one iron score of 3 or above, either serum ferritin or transferrin saturation, should add two risk points to their FeGGT LifePro score. So, this suggests that even if you have a relatively low FeGGT score, but you have an iron score that is very high, you'd be at higher risk of chronic disease and mortality even if your baseline risk scores, you know, lifestyle and family history scores, are zero because iron is a pro-oxidant that causes oxidative damage, and nearly every chronic disease that we know of has an element of oxidative damage.

Those people with the overall highest risk scores can expect to achieve the greatest improvement in risk scores by adhering to a healthy diet regimen and, when indicated, reducing their iron levels, so those are the two most important things, as we'll talk about in the treatment section in the next presentation. Those with high baseline risk scores but iron scores of zero must focus on reducing their baseline risks, so, in other words, in those cases the high GGT score is not due to iron overload. It's due to their baseline risk factors such as diabetes, so obviously, in those cases, you have to address those issues to make an improvement in the score.

We'll look at a few examples of this in the next section. I think that will make it easier to understand, and if you're worried about the calculation, which can be a little time consuming, I've made **an online calculator** where you can just input the risk factors and the blood markers and then get the score automatically calculated, and we'll put a link to that in the resources section.