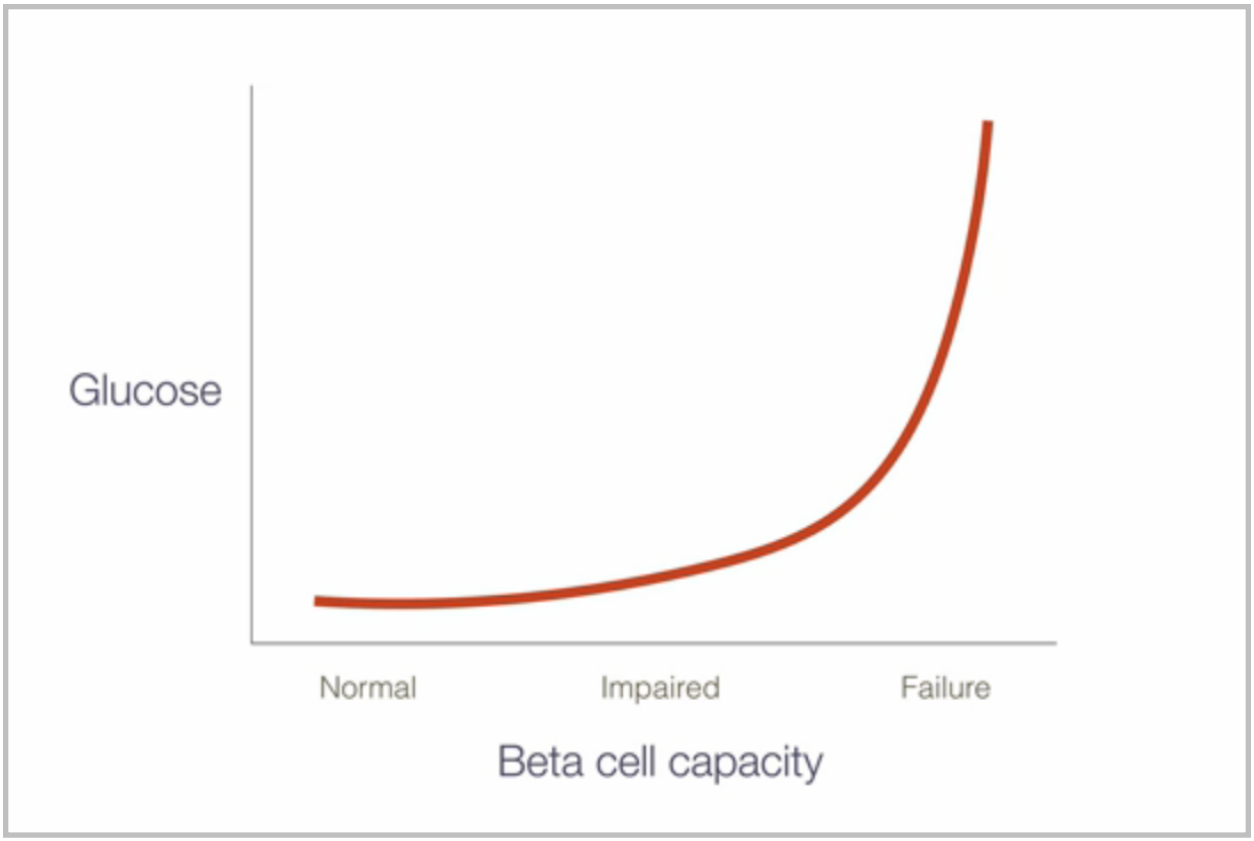
Hyperglycemia I - Part Two

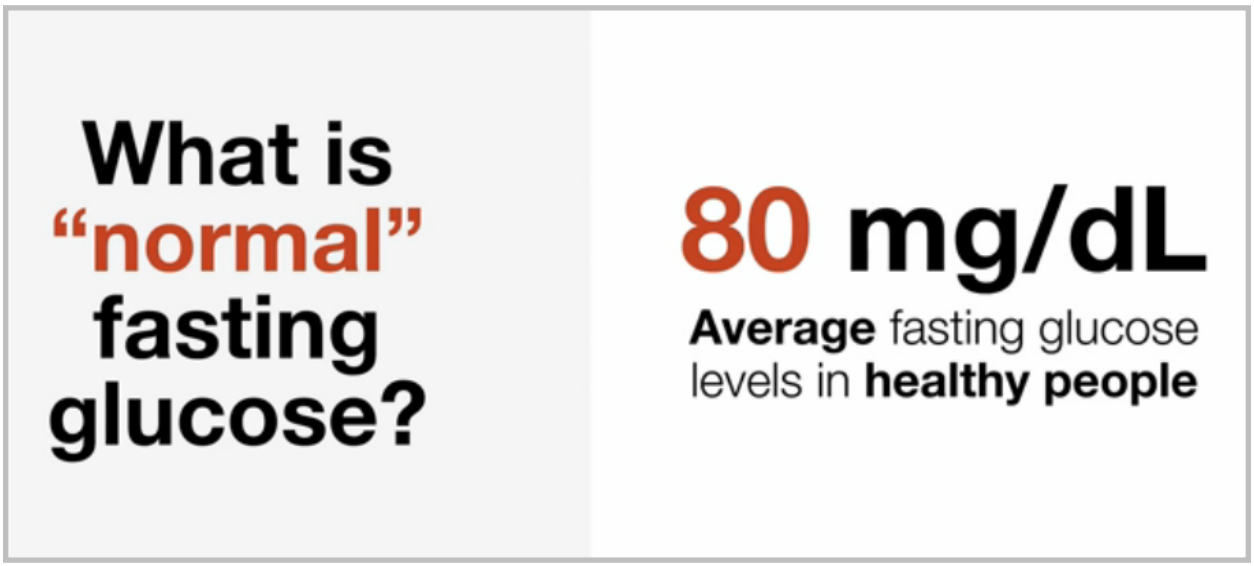
As blood sugar control worsens, the second-phase insulin response grows weaker. It may now take four to five hours for beta cells to make enough insulin to bring blood sugar back down to a fasted level after you complete eating a meal, but during the day, this may never happen because glucose is coming in from the next meal before glucose from the previous meal has been cleared out. Only at night when sleeping seven to eight hours without eating is there enough time for the impaired second-phase response to get blood sugar down low enough that the patient will wake up with normal fasting blood sugar. This is why fasting glucose can be high-normal or even completely normal in someone who is already well on the way to diabetes. If we measured their post-meal blood sugar, we'd see that it was high throughout the day, so the takeaway is that we have to look at post-meal glucose and A1c to get a complete picture of what is going on with the patient's blood sugar. You cannot rely on fasting blood sugar alone, since it's often the last marker to go out of whack, and if you do that, you'll miss a lot of patients who you could prevent the progression toward type 2 diabetes in.



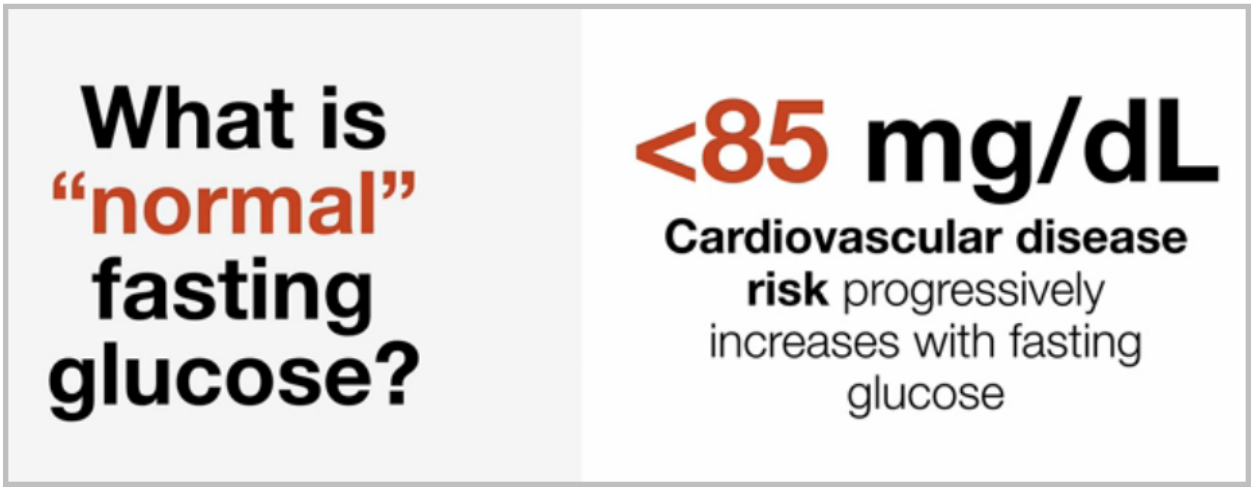
When beta cells are no longer able to keep fasting blood sugar normal, it's a sign the pancreas doesn't have enough beta cell capacity to keep up with the production of even low levels of insulin. This indicates that irreversible beta cell death has occurred. This is the start of what is know as the

fasting blood sugar death spiral. Beta cells are no longer able to provide a steady basal insulin release, and the liver interprets very low fasting insulin levels in those cases as a sign that it's time to raise blood sugar, so this starts the process of gluconeogenesis, which releases stored glucose or converts protein into glucose, either from the diet, or if there is not enough from the diet from the muscles, and then dumps large boluses of glucose into the bloodstream. This explains why fasting blood sugar deteriorates so rapidly after a certain point, and patients can see a surge of 50 mg/dL of their fasting glucose or more when this happens.

That said, in a smaller number of cases, most frequently men, fasting blood sugar is high, but A1c and post-meal glucose are normal. It is still unclear what causes this, but researchers speculate that these people may have a defect in basal insulin secretion that should take place during a fasted state and sleep. Their second-phase insulin response is still functional, which keeps post-meal blood sugars normal, but their basal or fasting insulin secretion is impaired, which leads to high fasting blood sugar. Now this isn't rare, and I've seen it quite a few times in my patient population.

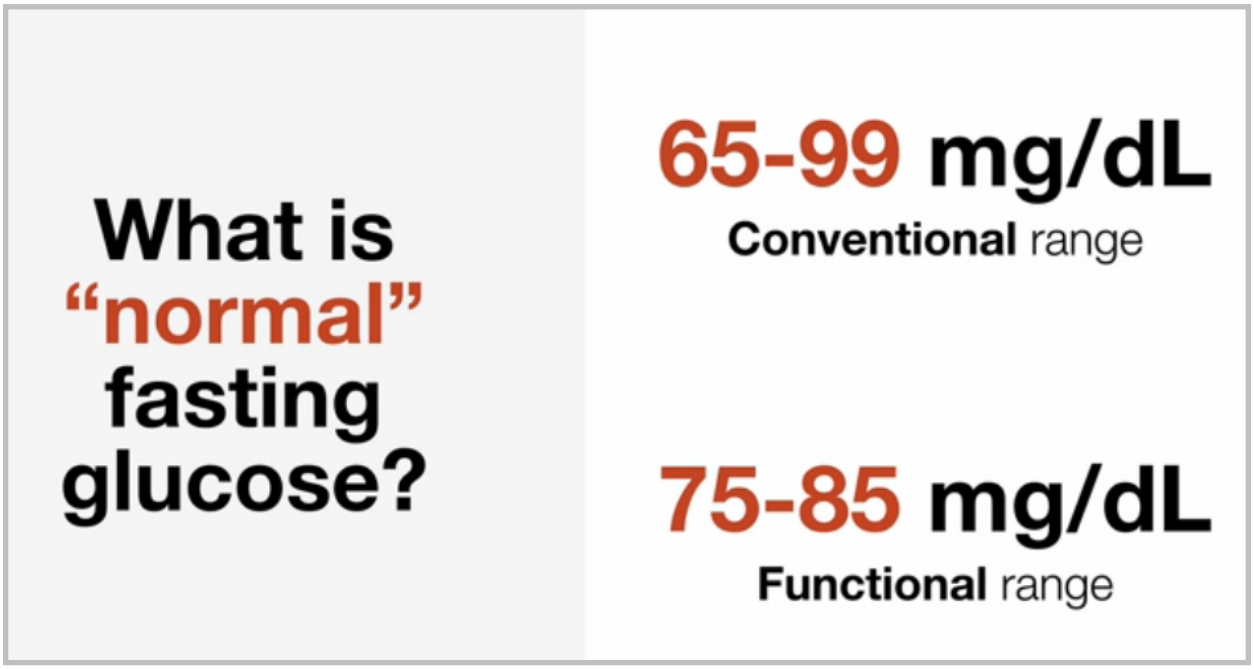


So what is a normal fasting glucose? The conventional range is 65 to 99, but I believe that that is way too broad. Average fasting glucose levels in healthy people, according to 24-hour glucose monitoring studies, are 80 mg/dL. Older women over 65 years of age with normal fasting blood sugar are 22 percent more likely to develop metabolic syndrome with a fasting glucose level of 91 to 95 and 25 percent more likely with a fasting blood sugar of over 95 mg/dL. People with fasting blood sugar in the high-normal range between 95 to 99 mg/dL had 53 percent higher cardiovascular disease risk than people with fasting glucose below 80 mg/dL in a four-and-a-half-year follow-up. Researchers in that study concluded or data suggests that a fasting glucose between 91 and 99 mg/dL is a strong independent predictor of type 2 diabetes and should be used to identify people to be further investigated and aided with preventative measures.



Other studies have shown that people with fasting glucose between 95 mg/dL and 101 mg/dL were at 36 percent higher risk of diabetes than those with fasting glucose levels below 83. Cardiovascular disease risk progressively increases as fasting glucose climbs above 85 mg/dL, and

it's a slow climb from 85 to 95, but it goes up much more quickly after that. People with fasting glucose levels above 95 mg/dL had more than three times the risk of developing future diabetes than people who had fasting glucose levels below 90 mg/dL. In a study of Chinese adults with dementia, over 80 percent had fasting glucose levels above 90 mg/dL.

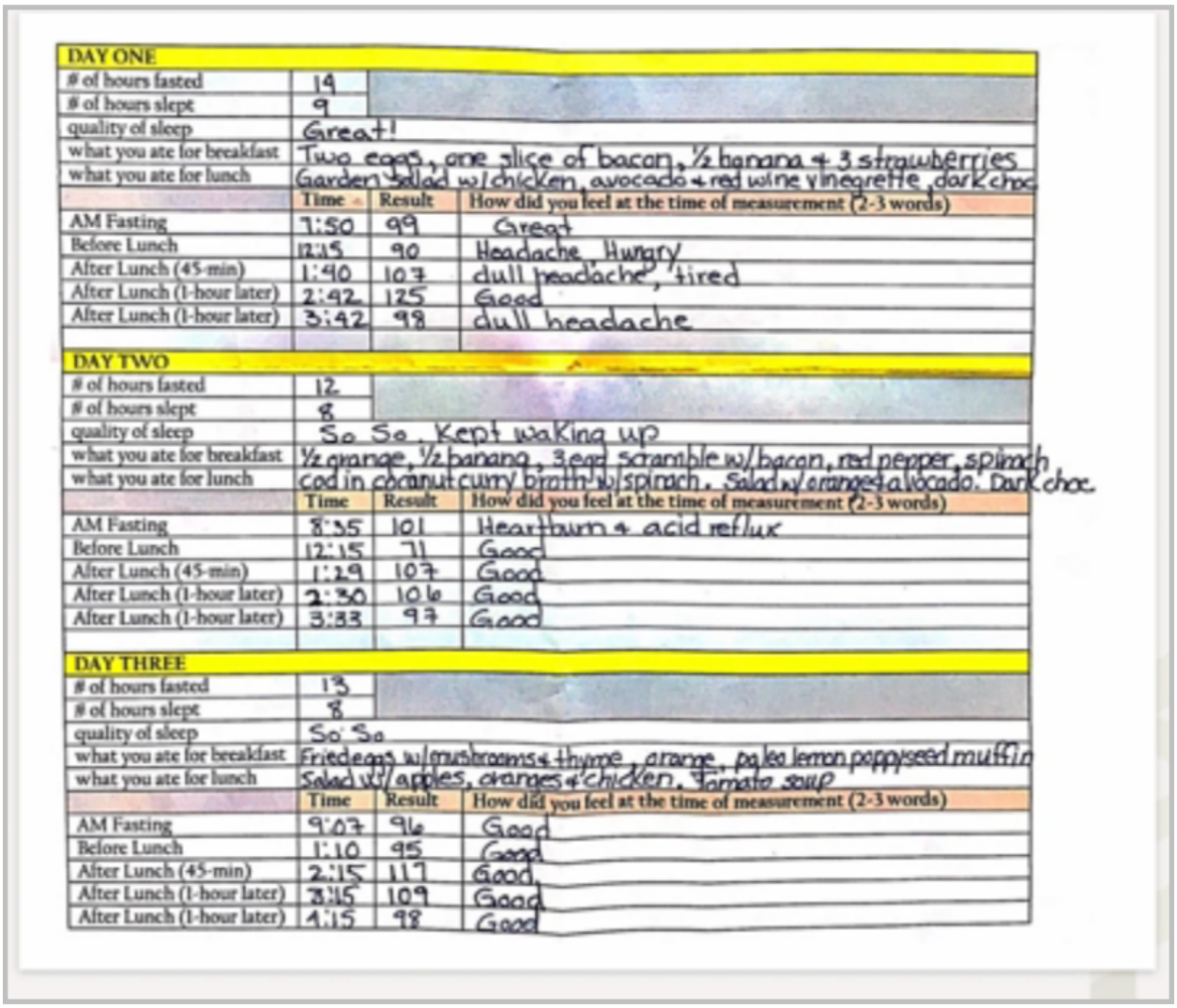


So all of this indicates why I believe that the functional range for fasting glucose should be much tighter. My range is 75 to 85, and we'll talk more about the low end of that range in the hypoglycemia section. Eighty-five is the level at which we start to see increased risk for cardiovascular disease and other diseases, though, as I mentioned, the increase in disease risk is pretty small between 85 and 95. It's still there, and it's statistically significant. Please understand that this doesn't mean that a single fasting glucose reading of 86, for example, is significant cause for concern. Remember that fasting glucose is highly variable, and that we're looking for patterns, not just individual markers. If fasting glucose is 90, and all of the other blood sugar markers are normal, it's possible the patient just didn't sleep well the night before, that they exercised before the test, or they were under considerable stress. You would want to test the fasting blood sugar again and probably a few more times before you are sure that there is a trend there.

On the other hand, if the fasting blood sugar is 86, but the hemoglobin A1c, the GlycoMark, or post-meal blood sugar testing with a glucometer and other markers indicative of blood sugar dysregulation are present, then, yes, that would be cause for concern.

Marker	Value	Functional Range	Lab Range
Glucose	100	75 - 90	65 - 99
Hemoglobin A1c	5.2	4.4 – 5.4	4.8 - 5.6
Uric Acid	7.3	3.7 – 6.0	3.7 - 8.6
BUN	12	13 – 18	6 - 24
Creatinine	0.94	0.85 – 1.1	0.76 - 1.27
Sodium	142	135 – 140	134 - 144
Potassium	4.2	4.0 – 4.5	3.5 - 5.2
Chloride	102	100 – 106	97 - 108
C02	26	25 – 30	18 - 29
Calcium	9.7	9.2 – 10.1	8.7 - 10.2
Phosphorus	2.9	3.5 – 4.0	2.5 - 4.5
Magnesium	2.0	2.0 – 2.6	1.6 - 2.6
Protein, total	6.9	6.9 – 7.4	6.0 - 8.5
Albumin	4.7	4.0 – 5.0	3.5 - 5.5
Globulin	2.2	2.4 – 2.8	1.5 - 4.5
A/G ratio	2.1	1.5 – 2.0	1.1 - 2.5
Bilirubin, total	0.5	0.1 – 1.2	0.0 - 1.2
Alkaline Phosphatase	53	42 – 107	39 - 117
LDH	130	140 - 180	121 - 224
AST	20	10 - 30	0 - 40
ALT	25	10 - 29	0 - 44
GGT	16	0 - 40	0 - 65
TIBC	262	250 – 350	250 - 450
UIBC	181	150 - 375	150 - 375
Iron	81	85 – 135	40 - 155
Iron saturation	31	15 – 45	15 - 55
Ferritin	269	30 - 150	30 - 400
Cholesterol, total	263	150 - 240	100 - 199
Triglycerides	110	50 – 100	0 - 149
HDL	48	55 – 85	> 39
LDL	193	0 – 175	0 - 99
T. Chol / HDL Ratio	5.5	< 3	0 - 5.0
Triglycerides / HDL Ratio	2.29	< 2	< 3.8
TSH	1.700	0.5 – 2.5	0.45 - 4.50
T4, total	7.5	6.0 – 12	4.5 - 12
T3 Uptake	27	30 - 38	24 - 39
T3, Total	93	100 – 180	71 - 180
Vitamin D, 25-hydroxy	41.1	35 - 60	30.0 - 100.0

So, let's look at some more examples. This patient is a 50-year-old female with a history of type 2 diabetes. Her main complaint was recalcitrant weight, stress—she was a vice president of a software company in Palo Alto—high cholesterol, and high blood sugar. As you can see, her fasting glucose is slightly high at 100, but her A1c is totally normal at 5.2.



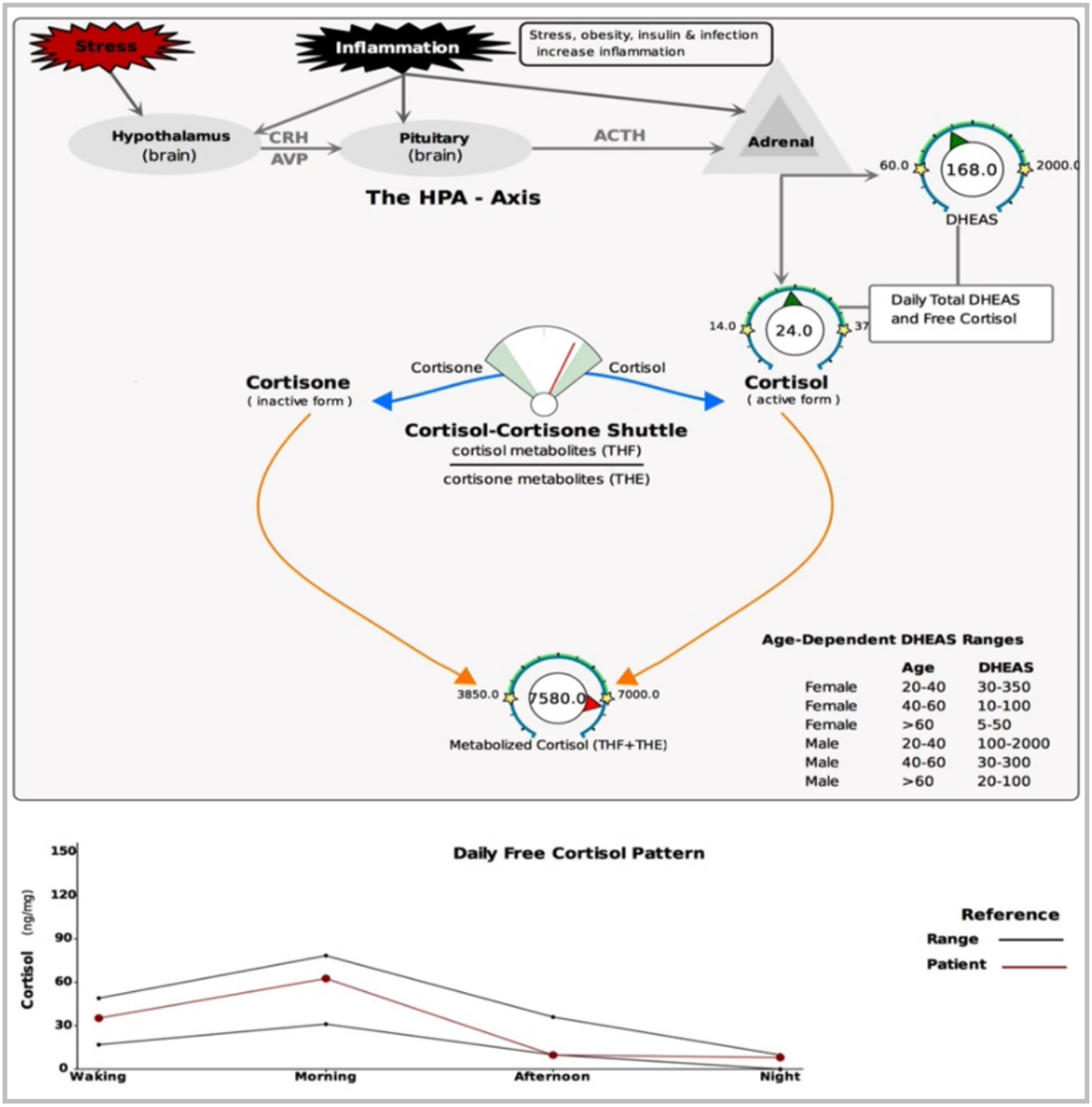
DAY ONE			
# of hours fasted	14		
# of hours slept	9		
quality of sleep	Great!		
what you ate for breakfast	Two eggs, one slice of bacon, ½ banana + 3 strawberries		
what you ate for lunch	Garden Salad w/ chicken, avocado + red wine vinegrette, dark choc		
	Time	Result	How did you feel at the time of measurement (2-3 words)
AM Fasting	7:50	99	Great
Before Lunch	12:15	90	Headache, Hungry
After Lunch (45-min)	1:40	107	dull headache, tired
After Lunch (1-hour later)	2:42	125	Good
After Lunch (1-hour later)	3:42	98	dull headache
DAY TWO			
# of hours fasted	12		
# of hours slept	8		
quality of sleep	So So. Kept waking up		
what you ate for breakfast	½ orange, ½ banana, 3 egg scramble w/ bacon, red pepper, spinach		
what you ate for lunch	cod in coconut curry broth w/ spinach. Salad w/ orange + avocado. Dark choc.		
	Time	Result	How did you feel at the time of measurement (2-3 words)
AM Fasting	8:35	101	Heartburn + acid reflux
Before Lunch	12:15	71	Good
After Lunch (45-min)	1:29	107	Good
After Lunch (1-hour later)	2:30	106	Good
After Lunch (1-hour later)	3:33	97	Good
DAY THREE			
# of hours fasted	13		
# of hours slept	8		
quality of sleep	So So		
what you ate for breakfast	Fried eggs w/ mushrooms + thyme, orange, paleo lemon poppyseed muffin		
what you ate for lunch	Salad w/ apples, oranges + chicken, Tomato soup		
	Time	Result	How did you feel at the time of measurement (2-3 words)
AM Fasting	9:07	96	Good
Before Lunch	1:10	95	Good
After Lunch (45-min)	2:15	117	Good
After Lunch (1-hour later)	3:15	109	Good
After Lunch (1-hour later)	4:15	98	Good

We did post-meal glucose testing on her, and it was also normal. You can see that she never exceeds 125 mg/dL. That was her highest reading one hour after lunch. The one-hour cutoff is 140, as we'll see later. Though her fasting blood sugars are a little bit high, all of her post-meal blood sugar levels are normal.

	Laboratory Test	Notes	High Risk	Intermediate Risk	Optimal	High Risk Range	Intermediate Risk Range	Optimal Range	Previous Results 12/8/2015
Glycemic Control	Glucose (mg/dL)				99	> 125	100-125	70 - 99	99
	HbA1c (%)				4.9	≥ 6.5	5.7 - 6.4	≤ 5.6	5.0
	Estimated Average Glucose (mg/dL) (calculated)				93.9	≥ 139.9	116.9 - 139.8	≤ 116.8	96.8
	Fructosamine (µmol/L)				295	> 346	302 - 346	< 302	288
	Glycation Gap				-1.82	> 0.77	0.45 - 0.77	< 0.45	-1.59
	Postprandial Glucose Index		8.3			> 7.9	6.0 - 7.9	< 6.0	9.0
Insulin Resistance	Leptin (ng/mL)				4	> 43	20 - 43	< 20	4
	Leptin:BMI Ratio				0.15	> 1.17	0.66 - 1.17	< 0.66	
	Adiponectin (µg/mL)		7			< 10	10 - 14	> 14	7
	Free Fatty Acid (mmol/L)				0.54	> 0.70	0.60 - 0.70	< 0.60	0.24
	Ferritin (ng/mL) *			190		> 252	147 - 252	< 147	227
	α-hydroxybutyrate (µg/mL)§		8.9			> 5.7	4.5 - 5.7	< 4.5	7.6
	Oleic Acid (µg/mL)§				49	> 79	60 - 79	< 60	20
	Linoleoyl-GPC (µg/mL)§				46.5	< 10.5	10.5 - 13.0	> 13.0	24.9
	HOMA-IR (calculated)				1.5	> 4.2	2.6 - 4.2	< 2.6	1.1
Beta Cell Function	Insulin (µU/mL)				6	≥ 12	10 - 11	3 - 9	5
	Proinsulin (pmol/L)				5	> 16	8 - 16	< 8	5
	C-peptide (ng/mL)				1.5	> 4.6	3.1 - 4.6	1.0 - 3.0	1.5
	Proinsulin:C-peptide Ratio			3.6		> 4.9	3.6 - 4.9	< 3.6	3.1
	Anti-GAD (IU/mL)				< 5	> 5 Positive		≤ 5 Negative	< 5

In this case, we went on to do an advanced metabolic and lipid panel from a lab called True Health Diagnostics*. Her A1c was even lower at 4.9. Her fructosamine, glycation gap, and estimated average glucose were all normal. Postprandial glucose index is elevated, but this marker is of questionable value. Most of her insulin resistance and beta cell function markers are normal except adiponectin, alpha-hydroxybutyrate, ferritin, and proinsulin. Her C-peptide ratio is also off, but that's a little less relevant given that both markers that it is based on are normal. Here we see a case of what I mentioned earlier where fasting glucose is high, but most other markers are normal. This could be a defect in basal insulin secretion, as we mentioned, or it could be something else such as HPA axis dysfunction, which we definitely had evidence of in this patient, and you might surmise that given she was VP of a software company in Palo Alto, but we actually did testing on her, of course.

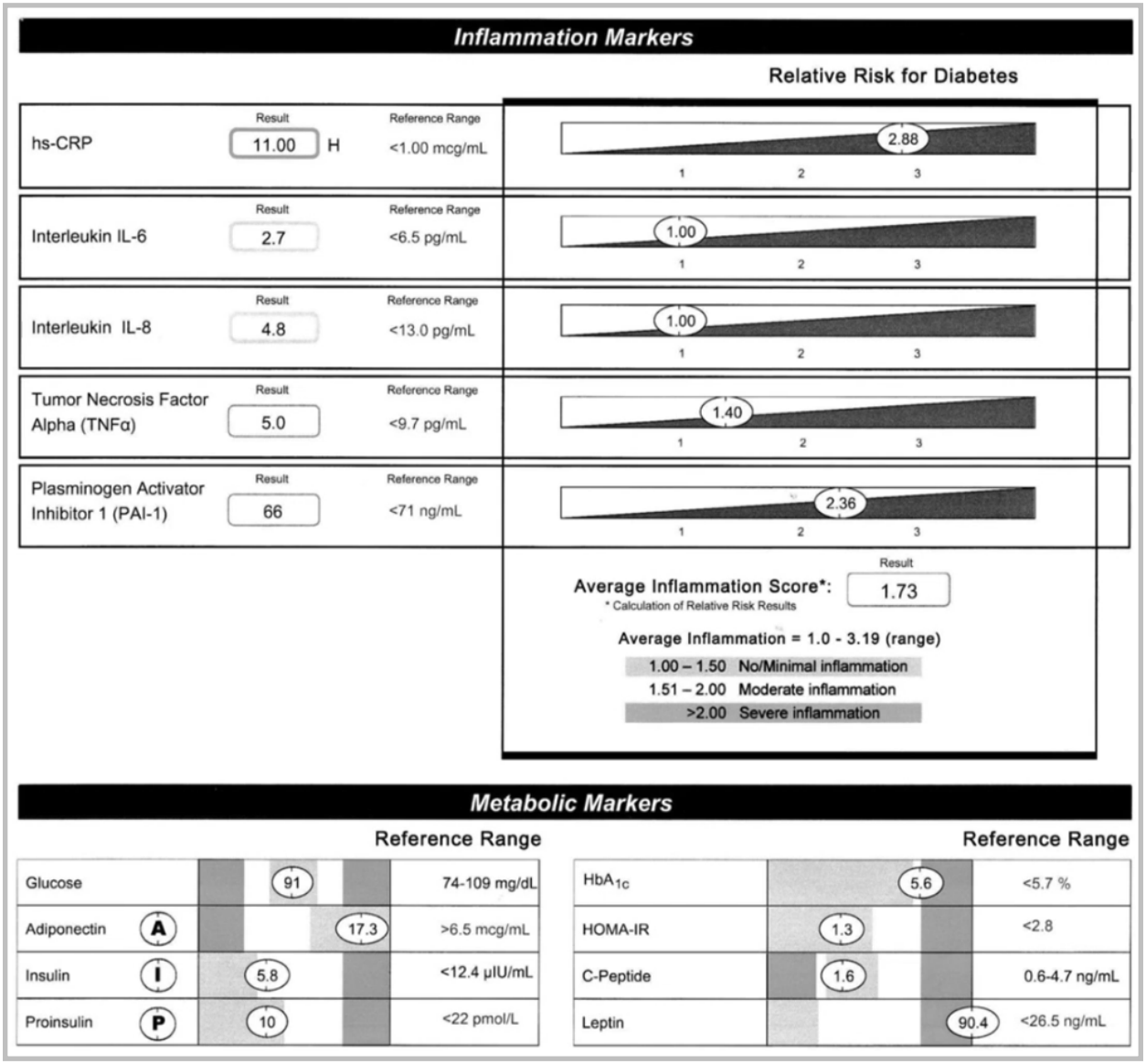
* **Note:** True Health Diagnostics is no longer in business. See **this post** for the latest updates.



You can check out her metabolized cortisol. It's very high at 7,580. Her nighttime cortisol is high as well, so this could be a case of high cortisol at night increasing her blood sugar levels overnight. She was super-stressed out, and in her case, treating her HPA axis and getting her cortisol levels down normalized her fasting glucose.

Marker	Value	Functional Range	Lab Range
Glucose	86	75 – 85	65 – 99
Hemoglobin Alc	5.7	4.4 – 5.4	4.8 – 5.6
Uric Acid	3.9	W: 3.2 – 5.5	2.5 - 7.1
BUN	14	13 – 18	6 – 24
Creatinine	0.86	0.85 – 1.1	0.57 - 1.00
Sodium	142	135 – 140	134 – 144
Potassium	4.8	4.0 – 4.5	3.5 – 5.2
Chloride	102	100 – 106	97 – 108
C02	26	25 – 30	18 - 29
Calcium	9.3	9.2 – 10.1	8.7 – 10.2
Phosphorus	3.7	3.5 – 4.0	2.5 – 4.5
Magnesium	2.5	2.0 – 2.5	1.6 – 2.6
Protein, total	6.1	6.9 – 7.4	6.0 – 8.5
Albumin	4.6	4.0 – 5.0	3.5 – 5.5
Globulin	1.5	2.4 – 2.8	1.5 – 4.5
A/G ratio	3.1	1.5 – 2.0	1.1 – 2.5
Bilirubin, total	0.5	0.1 – 1.2	0.0 - 1.2
Alkaline Phosphatase	37	42 – 107	39 - 117
LDH	167	140 - 180	0 – 214
AST	19	10 - 26	0 – 40
ALT	14	10 – 26	0 – 32
GGT	7	10 -26	0 -60
TIBC	295	250 – 350	250 – 450
UIBC	197	150 - 375	150 – 375
Iron	98	85 – 135	35 – 155
Iron saturation	33	15 – 40	15 – 55
Ferritin	112	MW 33-263	15 -150
Cholesterol, total	235	150 – 250	100 – 199
Triglycerides	53	50 – 100	0 – 149
HDL	55	55 – 85	› 39
LDL	169	0 – 175	0 – 99
Triglycerides / HDL Ratio	0.963	‹ 2	‹ 3.8
TSH	1.350	0.5 – 2.5	0.450 – 4.50
T4, total	6.3	6.0 – 12	4.5 – 12.0
T3 Uptake	29	W: 28-35	24 – 39
T3, Total	83	100 – 180	71 – 180
Vitamin D, 25-hydroxy	20.3	35 - 60	30.0 - 100.0
WBC	5.9	5.0 – 8.0	3.4 - 10.8
RBC	4.46	4.4 – 4.9	3.77 - 5.28
Hemoglobin	12.9	W: 13.5-14.5	11.1 - 15.9

Here's a different scenario. We have a normal fasting glucose at 86, although it's a little bit out of the optimal range, but we have an A1c that is high at 5.7. So this is a 54-year-old woman with Hashimoto's. Her chief complaint was brain fog, cold intolerance, postural hypotension, dizziness, weight gain, puffiness, and joint pain.



We did additional testing on her—this is the metabolic syndrome panel from Genova Diagnostics—and found elevated leptin and adiponectin as well as C-reactive protein. So, if we think of blood sugar disorders on a spectrum with normal, completely normal blood sugar on the far left and full-fledged type 2 diabetes with beta cell loss on the right, this is probably still pretty far toward the left end of the spectrum, but it's on the progression toward diabetes and getting closer to prediabetes. It's not there yet, but it's probably on the way.

As you can see with both of these cases, you need to consider the entire picture rather than relying on a single marker.

Marker	Value	Functional Range	Lab Range
Glucose	108	75 – 85	65 – 99
Hemoglobin Alc	5.9	4.4 – 5.4	4.8 – 5.6
Uric Acid	4.1	W: 3.2 – 5.5	2.5 - 7.1
BUN	21	13 – 18	6 – 24
Creatinine	0.78	0.85 – 1.1	0.57 - 1.00
Sodium	137	135 – 140	134 – 144
Potassium	4.7	4.0 – 4.5	3.5 – 5.2
Chloride	99	100 – 106	97 – 108
C02	24	25 – 30	18 - 29
Calcium	9.2	9.2 – 10.1	8.7 – 10.2
Phosphorus	3.5	3.5 – 4.0	2.5 – 4.5
Magnesium	1.9	2.0 – 2.5	1.6 – 2.6
Protein, total	6.6	6.9 – 7.4	6.0 – 8.5
Albumin	4.1	4.0 – 5.0	3.5 – 5.5
Globulin	2.5	2.4 – 2.8	1.5 – 4.5
A/G ratio	1.6	1.5 – 2.0	1.1 – 2.5
Bilirubin, total	0.3	0.1 – 1.2	0.0 - 1.2
Alkaline Phosphatase	40	42 – 107	39 - 117
LDH	132	140 - 180	0 – 214
AST	13	10 - 26	0 – 40
ALT	14	10 – 26	0 – 32
GGT	10	10 -26	0 -60
TIBC	193	250 – 350	250 – 450
UIBC	104	150 - 375	150 – 375
Iron	89	85 – 135	35 – 155
Iron saturation	46	15 – 40	15 – 55
Ferritin	160	W: 10-122	15 - 150
Cholesterol, total	287	150 – 250	100 – 199
Triglycerides	63	50 – 100	0 – 149
HDL	99	55 – 85	› 39
LDL	175	0 – 175	0 – 99
Triglycerides / HDL Ratio	0.636	‹ 2	‹ 3.8
TSH	1.850	0.5 – 2.5	0.450 – 4.50
T4, total	7.3	6.0 – 12	4.5 – 12.0
T3 Uptake	34	W: 28-35	24 – 39
T3, Total	102	100 – 180	71 – 180
Vitamin D, 25-hydroxy	61.8	35 - 60	30.0- 100.0
WBC	5.5	5.0 – 8.0	3.4 - 10.8
RBC	4.70	4.4 – 4.9	3.77 - 5.28
Hemoglobin	14.3	W: 13.5-14.5	11.1 - 15.9

Here's another result. We see elevated glucose and A1c out of the lab range. Fasting glucose is 108, and A1c is 5.9. We also see high ferritin of 160. This is a woman. Other iron markers are elevated as well. High iron is often a cause of high blood sugar, and we'll talk about this in more detail a little later.

This is a 51-year-old female with digestive issues as her main complaint such as constipation, distention, lack of bowel sensation. She also had swelling, stiffness, and pain in her extremities; frequent sinus issues; and hypothyroid symptoms. When A1c is elevated along with fasting glucose, you can be pretty certain that a blood sugar issue is present. Now, in this case, the patient had undiagnosed adult-onset type 1 diabetes, and we were able to catch it before glucose control deteriorated significantly.