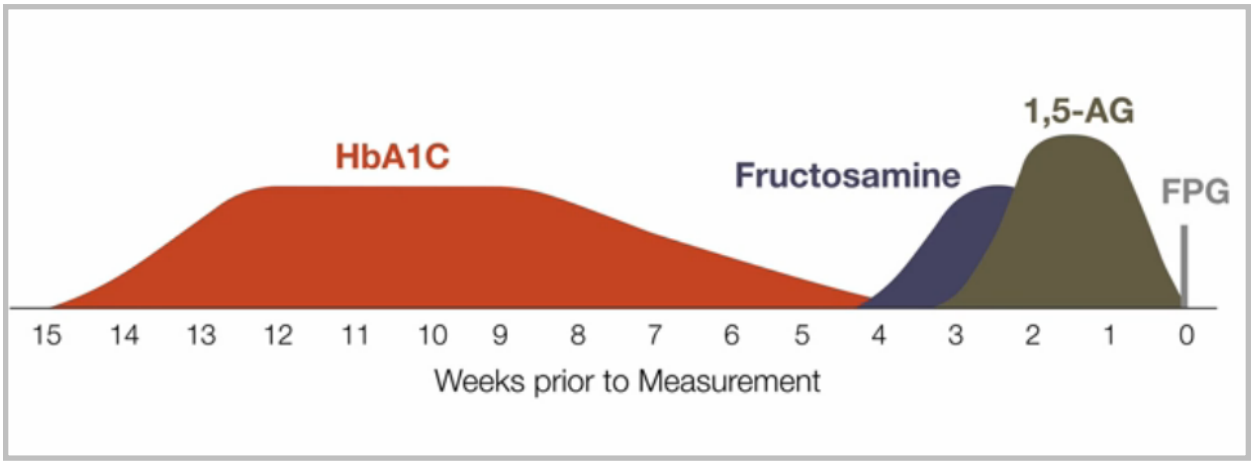
Hyperglycemia I - Part Four

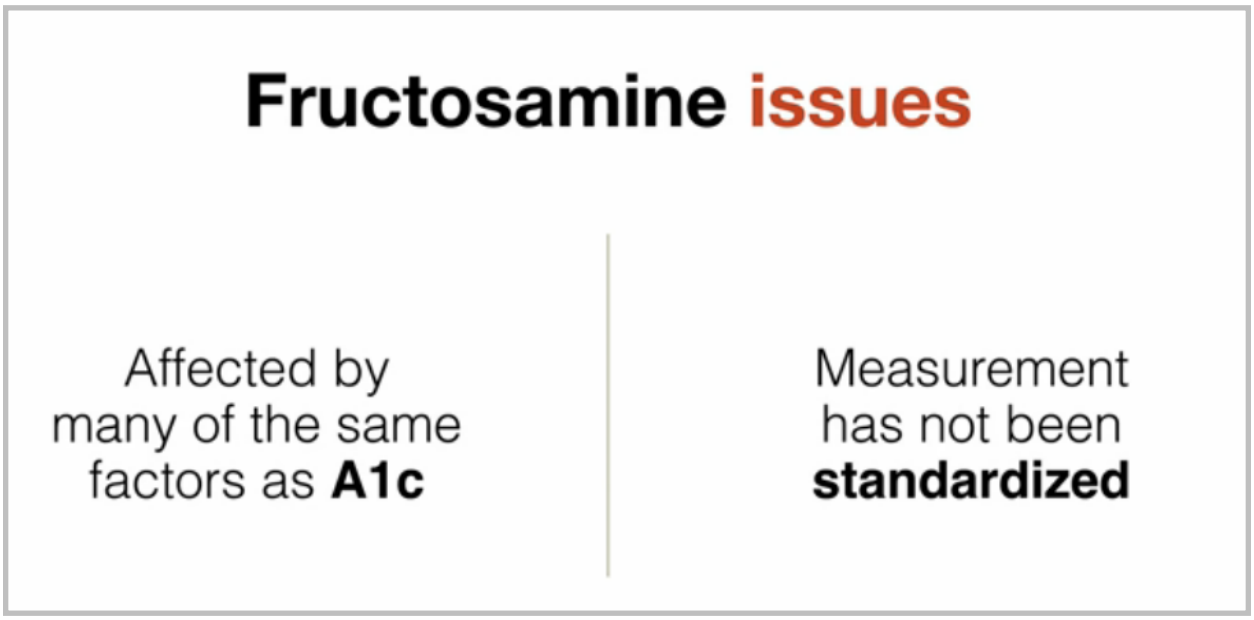
There is another option for measuring average blood sugar and clarifying A1c, and that's a marker called fructosamine.

During the glycation of serum proteins such as albumin, the aldimine intermediate can be reconverted to glucose and protein or formed into a fructosamine derivative. Because albumin is the most abundant serum protein, fructosamine is predominantly a measure of glycated albumin, though other glycated proteins such as lipoproteins and globulins can contribute to total fructosamine concentration.



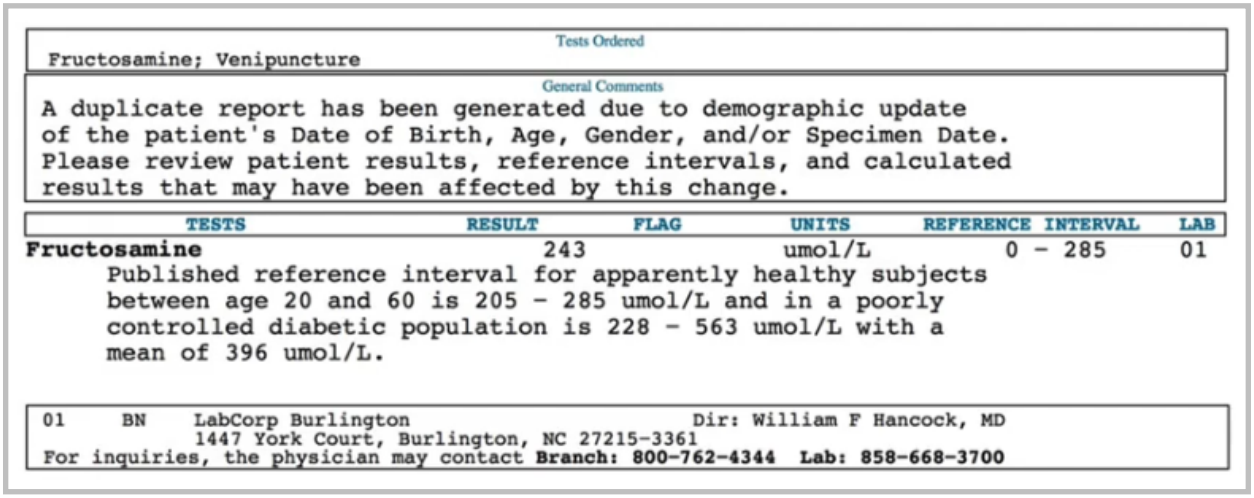
So the term fructosamine refers to all ketoamine linkages that result from glycation of serum proteins. The lifespan of hemoglobin and red blood cells is appropriately 90 to 120 days. Non-immunoglobulin serum proteins have a much lower half-life, approximately 14 to 21 days, and this means that A1c is a measurement of blood sugar control over two to three months, whereas fructosamine is a measurement of blood sugar control over the previous two weeks, and this is illustrated on the slide.

Blood levels of fructosamine exhibit a broader fluctuation than those of hemoglobin A1c, thus allowing earlier detection of rapid changes of blood sugar. It can detect changes in blood glucose before you would see them show up in A1c. Fructosamine measurement is relatively inexpensive, precise, fairly free of interferences compared to A1c, and some have argued that it is unaffected by red blood cell diseases.



However, there are a few problems with using it as an alternative to A1c. First, many of the variables that affect A1c may similarly affect fructosamine despite the different physiological compartments. The most commonly known non-glycemic factor that affects fructosamine is albumin, but other factors may include ethnicity, age, presence of kidney disease, and then vitamin B12, folate, body mass index, and thyroid status. The second problem is that fructosamine has not been standardized as a marker, and there is really no consensus on the method you use for its measurement or how to assess its threshold values.

Marker	Value	Functional Range	Lab Range
Glucose	81	75 – 90	65 - 99
Hemoglobin A1c	5.7	4.4 – 5.4	4.8 - 5.6
Uric Acid	3.9	3.2 - 5.5	2.5 - 7.1
BUN	19	13 – 18	6 - 24
Creatinine	1.00	0.85 – 1.1	0.57 - 1
Sodium	142	135 – 140	134 - 144
Potassium	4.2	4.0 – 4.5	3.5 - 5.2
Chloride	100	100 – 106	97 - 108
C02	26	25 – 30	18 - 29
Calcium	9.6	9.2 – 10.1	8.7 - 10.2
Phosphorus	4.0	3.5 – 4.0	2.5 - 4.5
Magnesium	2.5	2.0 – 2.6	1.6 - 2.6
Protein, total	7.0	6.9 – 7.4	6.0 - 8.5
Albumin	4.6	4.0 – 5.0	3.5 - 5.5
Globulin	2.4	2.4 – 2.8	1.5 - 4.5
A/G ratio	1.9	1.5 – 2.0	1.1 - 2.5
Bilirubin, total	0.4	0.1 – 1.2	0.0 - 1.2
Alkaline Phosphatase	74	42 – 107	39 - 117
LDH	191	140 - 180	119 - 226
AST	26	10 - 30	0 - 40
ALT	19	10 - 22	0 - 32
GGT	10	0 - 28	0 - 60
TIBC	331	250 – 350	250 - 450
UIBC	230	150 - 375	150 - 375
Iron	101	85 – 135	35 - 155
Iron saturation	31	15 – 40	15 - 55
Ferritin	96	MW: 30 - 150	15 - 150
Cholesterol, total	180	150 – 250	100 - 199
Triglycerides	53	50 – 100	0 - 149
HDL	69	55 – 85	> 39
LDL	100	0 – 175	0 - 99
T. Chol / HDL Ratio	2.6	< 3	0 4.4
Triglycerides / HDL Ratio	0.77	< 2	< 3.8
TSH	1.950	0.5 – 2.5	0.45 - 4.50
T4, total	5.1	6.0 – 12	4.5 - 12
T3 Uptake	30	28 - 35	24 - 39
T3, Total	92	100 – 180	71 - 180
Vitamin D, 25-hydroxy	28.1	35 - 60	30 - 100



Tests Ordered

Fructosamine; Venipuncture

General Comments

A duplicate report has been generated due to demographic update of the patient's Date of Birth, Age, Gender, and/or Specimen Date. Please review patient results, reference intervals, and calculated results that may have been affected by this change.

TESTS	RESULT	FLAG	UNITS	REFERENCE INTERVAL	LAB
Fructosamine	243		umol/L	0 - 285	01

Published reference interval for apparently healthy subjects between age 20 and 60 is 205 - 285 umol/L and in a poorly controlled diabetic population is 228 - 563 umol/L with a mean of 396 umol/L.

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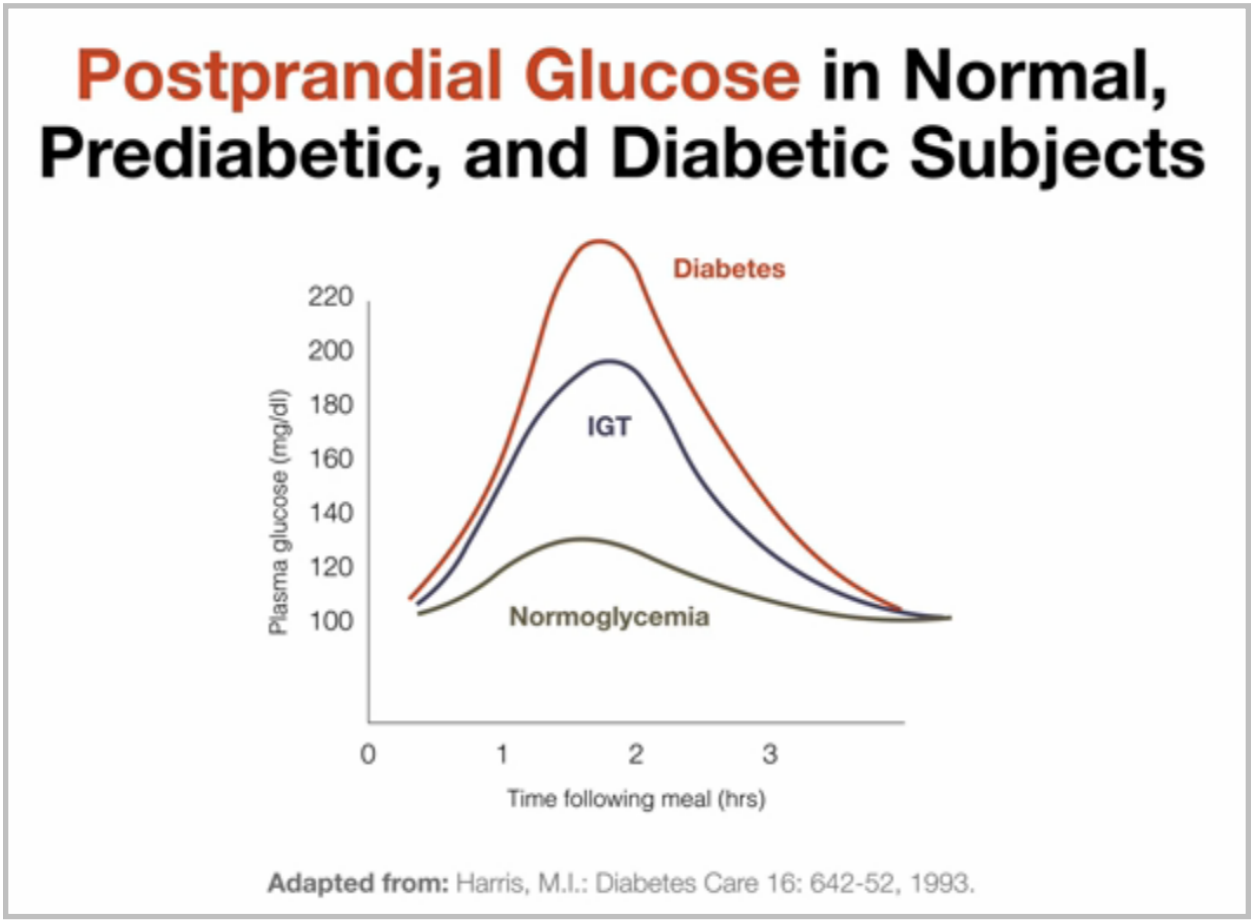
Here's an example of elevated A1c with a completely normal fasting blood sugar. MCV was also normal, but I went ahead and ran fructosamine as well. It was normal, albeit in the high end of the range. So given this and the lack of other markers of impaired glucose tolerance, it's likely that the high A1c is due to long-lived red blood cells, but, of course, it would be prudent to retest this patient's blood sugar in six months and then again in a year to make sure that you're not seeing an upward trend.

	Laboratory Test	Notes	High Risk	Intermediate Risk	Optimal	High Risk Range	Intermediate Risk Range	Optimal Range	Previous Results
Glycemic Control	Glucose (mg/dL)				90	> 125	100-125	70 - 99	
	HbA1c (%)			5.7		≥ 6.5	5.7 - 6.4	≤ 5.6	
	Estimated Average Glucose (mg/dL) (calculated)			116.9		≥ 139.9	116.9 - 139.8	≤ 116.8	
	Fructosamine (µmol/L)			327		> 346	302 - 346	< 302	
	Glycation Gap				-1.63	> 0.77	0.45 - 0.77	< 0.45	
	Postprandial Glucose Index		13.7			> 7.9	6.0 - 7.9	< 6.0	
Insulin Resistance	Leptin (ng/mL)			21		> 43	20 - 43	< 20	
	Leptin:BMI Ratio			0.88		> 1.17	0.66 - 1.17	< 0.66	
	Adiponectin (µg/mL)				21	< 10	10 - 14	> 14	
	Free Fatty Acid (mmol/L)				0.15	> 0.70	0.60 - 0.70	< 0.60	
	Ferritin (ng/mL) *				60	> 108	61 - 108	< 61	
	α-hydroxybutyrate (µg/mL)§				4.3	> 5.7	4.5 - 5.7	< 4.5	
	Oleic Acid (µg/mL)§				22	> 79	60 - 79	< 60	
	Linoleoyl-GPC (µg/mL)§				30.0	< 10.5	10.5 - 13.0	> 13.0	
	IR_i Score (calculated)				18.1	< 8.0	8.0 - 10.0	> 10.0	
	HOMA-IR (calculated)				0.8	> 4.2	2.6 - 4.2	< 2.6	
Beta Cell Function	Insulin (µU/mL)				4	≥ 12	10 - 11	3 - 9	
	Proinsulin (pmol/L)				5	> 16	8 - 16	< 8	
	C-peptide (ng/mL)				1.3	> 4.6	3.1 - 4.6	1.0 - 3.0	
	Proinsulin:C-peptide Ratio			3.7		> 4.9	3.6 - 4.9	< 3.6	
	Anti-GAD (IU/mL)				< 5	> 5 Positive		≤ 5 Negative	

Here is a different scenario. A1c of 5.7, slightly elevated; fasting glucose of 90, even though True Health Diagnostics* here marks that as normal. As you know, my range is 75 to 85, so I would mark it as a little high in the functional range or maybe intermediate risk. Check out fructosamine. It's not out of the reference range, but it is in the intermediate risk range at 327. Leptin, proinsulin, and C-peptide ratio are all also intermediate, so there is no serious problem here, but when you put all the markers together, they are starting to point in the direction of a potential issue. Again, if we think of that blood sugar spectrum from the left to the right, we're still way over toward the left, and we're in the very early stages. The good news is when you intervene at this stage, it's almost always entirely reversible. The earlier you intervene, the better chance that you'll be able to reverse it.

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



Let's move on to talk about post-meal blood sugar, or postprandial blood sugar. This measurement looks at blood sugar response to meals or a two-hour glucose challenge, in the case of the oral glucose tolerance test. These measurements reflect that pathophysiology behind diabetes better than any other glycemic marker, since they provide information on what happens in the post-meal state when glucose levels are at the highest during the day and when the health of the pancreatic beta cell is essential. Normal blood glucose levels two hours after a glucose load, whether that's from a meal or from a bolus of glucose in an OGTT, indicate good beta cell capacity, whereas a high two-hour postprandial glucose level indicates an impairment of beta cell function.

Only two-hour postprandial glucose can provide reliable information on the key pathophysiological defect of diabetes, also providing advice regarding the correct treatment to overcome it. Postprandial glucose is superior to fasting glucose or A1c in predicting cardiovascular disease outcomes. When they're analyzed together, only postprandial glucose remains statistically significant as a predictor of CVD mortality and events.

Measuring postprandial glucose in a clinical setting is somewhat challenging. There are three main ways to do it: Oral glucose tolerance test, glucometer testing, and a test called GlycoMark. The OGTT measures first- and second-stage insulin response to glucose, and you're probably familiar with how it works. The patient fasts, and then he's given 75 g of glucose dissolved in water. Then they test the patient's blood glucose one and two hours after. If the blood sugar is above 140 mg/dL two hours after the test, he has pre-diabetes. If it's above 199 mg/dL two hours later, he has got full-blown diabetes.

An advantage of oral glucose tolerance test is that it is highly validated, and there is tons of research correlating it with clinical outcomes. The disadvantage is that it's completely artificial. I don't know anyone who drinks a pure solution of 75 g of glucose outside of this OGTT setting. A 32-ounce Big Gulp from 7-Eleven has 96 g of sugar, but 55 percent of that is fructose, which produces a different effect on blood sugar. Another issue is that the OGTT can be a brutal test for someone who has impaired glucose tolerance. It can produce intense blood sugar swings that are far greater than what someone would experience from just eating a lot of carbohydrates.

There is another more realistic and convenient way to achieve a similar measurement, and that is simply using a glucometer to test your blood sugar just before and then one, two, and three hours after you eat a meal. This is called post-meal glucose testing. The advantages are that it is convenient. The patient can do it at home. It provides a better reflection of response to actual meals that that patient is eating rather than glucose. It can be used as an objective way of determining carbohydrate tolerance; more on that later. It leads to better compliance and also fewer adverse reactions in patients.

The cons are that it's not validated to the same degree as OGTT. Glucometers are notoriously variable in accuracy and consistency. For example, the international standard in 2013 advocated for an accuracy of plus or minus 15 percent. That means that if a patient gets a glucometer reading of

100, it could be as low as 85 in reality, or it could be as high as 115, and that's a pretty wide variation. It's obviously not as accurate as getting blood drawn at a lab.

I prefer, however, using glucometers to OGTT despite these caveats because we're looking for patterns. A single reading is not super-important. We're also considering other markers such as fasting glucose, A1c, and some of the others that I mentioned at the beginning of this presentation. We might do more advanced blood sugar testing from True Health Diagnostics or a Genova metabolic syndrome panel. We're just using the glucometer to get a general idea of how patients respond to meals and carbohydrate challenge over a number of days. I've seen so many people have horrible reactions to OGTT, and if a patient is on a lower-carb diet, such as a lower-carb Paleo diet, the OGTT will definitely not reflect his current blood sugar response because he's not accustomed to having a really large bolus of pure sugar like that, and he will often have a falsely elevated value.

As I mentioned, there is a wide variation in the quality of glucose meters. FreeStyle Lite is our current recommendation at the time of this recording. It's the most highly rated by Consumer Reports and diabetes patient organizations. Now, it doesn't have smartphone connectivity features, but it's more accurate and more affordable. There are some nice new ones that do have those smartphone features that automatically upload the values to your smartphone, but they, so far at least, are not as accurate as the FreeStyle Lite and some of the other lower-tech meters.

Blood Sugar Tracking Form

Instructions: Follow this link to purchase a ***FreeStyle Lite*** Meter. The page will direct you to one of the many pharmacies that offer this meter, or you can by on-line. Once you get it, test your blood sugar over a period of three days (does not need to be consecutive) as follows:

- First thing in the morning, after at least 12 hours of fasting, before breakfast
- Eat breakfast (no food between breakfast and lunch)
- Eat lunch - then test 45 minutes after you finish your last bite
- 1 hour after that (no food in between)
- 1 hour after that (no food in between)

Record what you ate for lunch on those days, as well as how you felt at the times you took the measurements.

DAY ONE			
# of hours fasted			
# of hours slept			
quality of sleep			
what you ate for breakfast			
what you ate for lunch			
	Time	Result	How did you feel at the time of measurement (2-3 words)
AM Fasting			
Before Lunch			
After Lunch (45-min)			
After Lunch (1-hour later)			
After Lunch (1-hour later)			
DAY TWO			
# of hours fasted			
# of hours slept			
quality of sleep			
what you ate for breakfast			
what you ate for lunch			
	Time	Result	How did you feel at the time of measurement (2-3 words)
AM Fasting			
Before Lunch			
After Lunch (45-min)			
After Lunch (1-hour later)			
After Lunch (1-hour later)			
DAY THREE			
# of hours fasted			
# of hours slept			
quality of sleep			
what you ate for breakfast			
what you ate for lunch			
	Time	Result	How did you feel at the time of measurement (2-3 words)
AM Fasting			
Before Lunch			
After Lunch (45-min)			
After Lunch (1-hour later)			
After Lunch (1-hour later)			

Here's the procedure that we have patients go through. It's admittedly not super-high-tech, but it leverages the higher accuracy of the FreeStyle meter. We send patients this fillable PDF blood

sugar tracking form. It has instructions at the top. We have them track their blood sugar over a three-day period. On the first two days, the process is the same. They take their blood sugar first thing in the morning after a 12-hour fast. Then they eat breakfast. They consume no food between breakfast and lunch. They do another reading just before lunch. Then they eat lunch and test 45 minutes after they finish their last bite of food. Then they test an hour after that, with no food in between, and then an hour after that with no food in between. They record what time they took their blood sugar and what the result was. They also include the number of hours they fasted and slept, the quality of their sleep. They record what they ate, and then they record how they felt at the time of the measurement.

Day three is a little bit different. On step three, instead of eating their typical lunch, we have them eat 60 to 70 g of a fast-acting carbohydrate, such as a large eight-ounce boiled potato or a cup of cooked white rice. We have them do this without a lot of fat, which would slow down the absorption of that carbohydrate. We have a patient handout with instructions for doing a post-meal blood sugar test and this fillable PDF form for recording the values. You can see it here on this slide, and it will be in the PDF generator as well.

Glucometer testing targets

Marker	Target
Fasting (before meal)	75-85
1 hour post-meal	<140
2 hour post-meal	<120
3 hour post-meal	75-85

Healthy targets for post-meal blood sugar according to the scientific literature are listed on this slide. The goal is to make sure that blood sugar doesn't consistently rise higher than 140 mg/dL an hour after a meal but does consistently drop below 120 mg/dL two hours after a meal and

returns to baseline, in other words, what it was before the meal was consumed, by three hours after a meal.

Now, as you might expect, there are a few caveats to this kind of testing as well. First, even reliable glucometers have about a 10 percent margin of error, so you need to take that into account when you interpret your results. A reading of 100 mg/dL could be anything between 90 and 110 if you had it tested in a lab, but this is okay because what we're doing here is trying to identify patterns. Second, if you normally eat a low-carb diet, post-meal glucose readings on the third day following the simple carbohydrate challenge will be abnormally high. When patients are adapted to burning fat, tolerance for carbohydrates declines, and this is why we would instruct patients to eat at least 150 g of carbohydrates for three days before an oral glucose tolerance test if they are having that test done in a lab. If the patient has been eating a low-carb diet for at least a couple of months before doing the carbohydrate challenge on day three of the test, you can subtract 10 mg/dL from your one- and two-hour readings. This will give you a rough estimate of what your results might be like if the patient had eaten more carbohydrates in the days and weeks leading up to the test. It's not precise, admittedly, but it's probably accurate enough for this kind of testing.