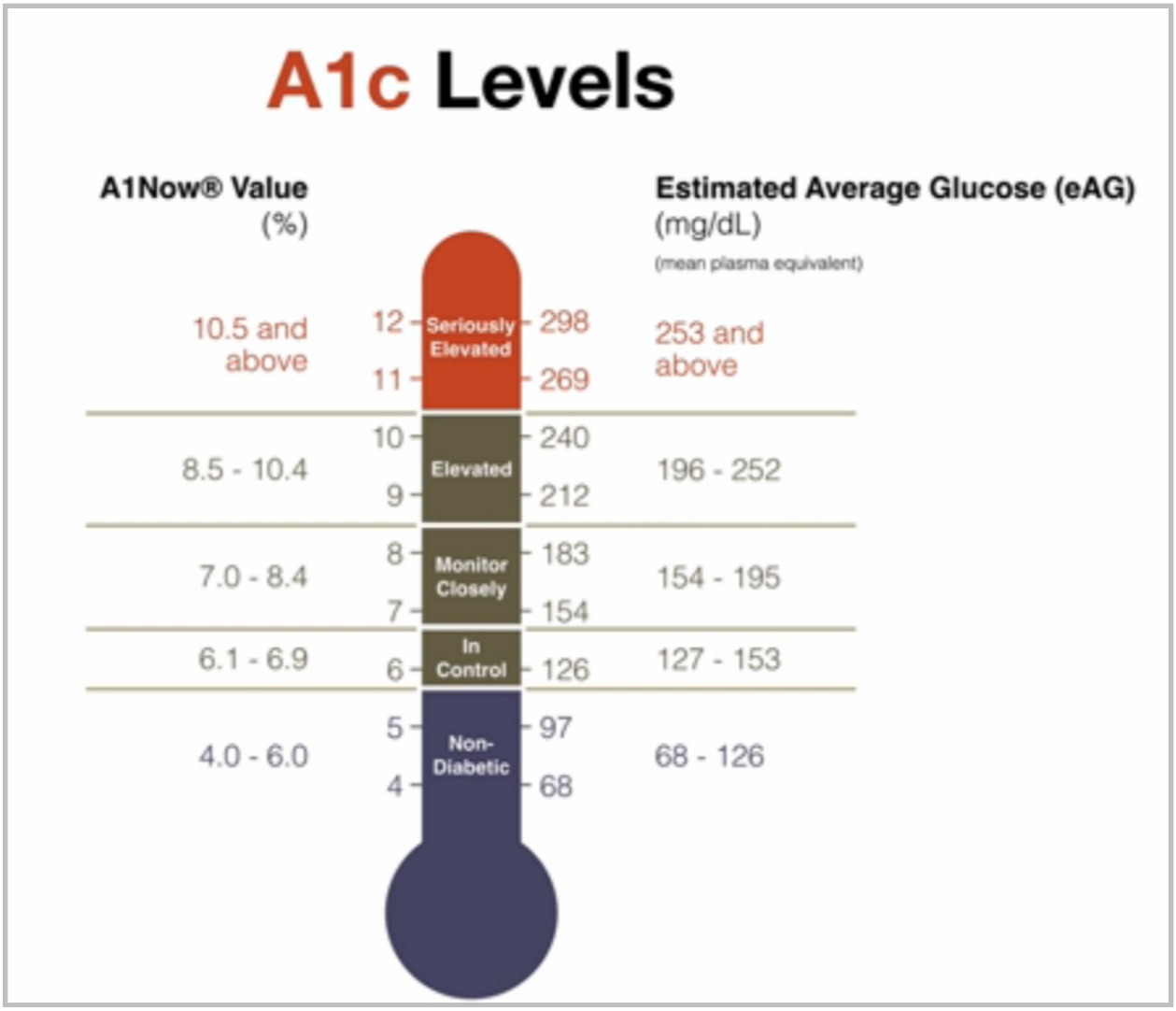
KRESSER INSTITUTE
FOR FUNCTIONAL AND EVOLUTIONARY MEDICINE

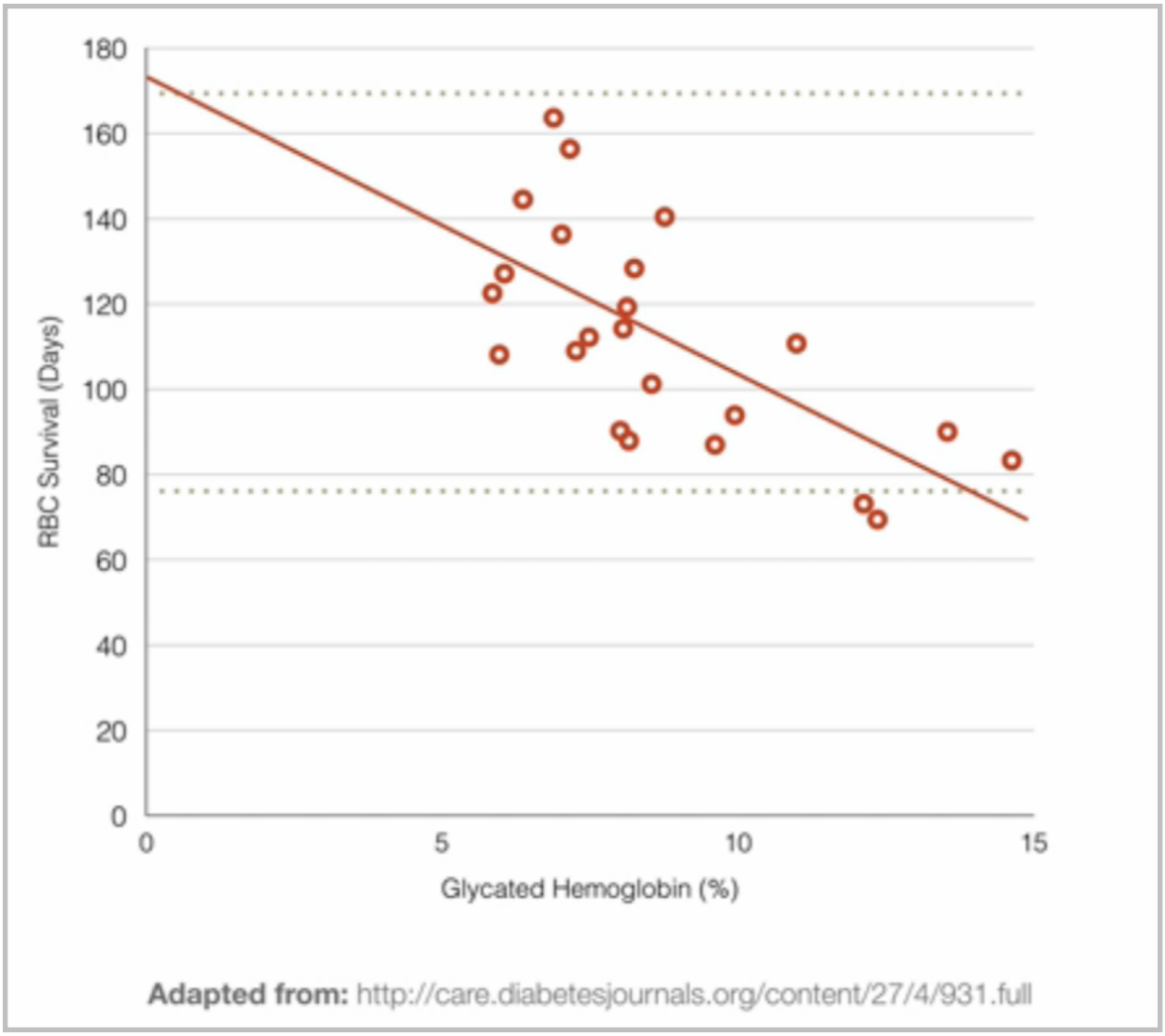
Hyperglycemia I - Part Three

Let's talk a little bit more about A1c and average glucose. A1c has some advantages as a marker for diabetes. Fasting and post-meal glucose gauge just a moment of a single day.



Even two random measurements of fasting glucose and post-meal glucose may miss a chronic blood sugar problem. A1c represents an average measure of blood sugar over a three-month period with greater focus on the most recent six weeks. The measurement of A1c equals the assessment of hundreds or virtually thousands of fasting glucose levels and also captures postprandial glucose peaks. In this sense, it can detect chronic hyperglycemia even when two random measurements of fasting glucose and post-meal glucose cannot. Finally, some studies suggest A1c is more tightly associated with blood sugar complications than fasting blood sugar.

A1c also has some downsides. While it's a good way to measure blood sugar in large population studies, it's not as accurate for individuals. An A1c of 5.1 percent maps to an average blood sugar of about 100 mg/dL, but some people's A1c results are always a little higher than their fasting glucose and OGTT or post-meal glucose numbers would predict, and other people's are always a little lower. This is probably due to the fact that several factors can influence red blood cells. A1c is a measure of how much hemoglobin and red blood cells are bonded, or glycated, to glucose. Anything that affects red blood cells and hemoglobin, such as anemia, dehydration, and genetic disorders, will skew A1c results.



Adapted from: http://care.diabetesjournals.org/content/27/4/931.full

Sugar has a tendency to stick to stuff. Anyone who has cooked with sugar can tell you that. In our body, sugar also sticks, especially to proteins. The theory behind the A1c test is that our red blood cells live an average of three months, so if we measure the amount of sugar stuck to these cells, which is what the hemoglobin A1c test does, it will give us an idea of how much sugar has been in the blood over the previous three months.

The number reported in the A1c test result, let's say of 5.2, indicates the percentage, so 5.2 percent of hemoglobin that has become glycated, or stuck, to sugar. While this sounds good in theory, the reality is not so black and white. The main problem is there is actually a wide variation in how long red blood cells survive in different people. For example, one study showed that red blood cells live longer than average at normal blood sugars. Researchers found that the lifetime of hemoglobin cells of diabetics turned over in as few as 81 days, while they lived as long as 146 days in nondiabetics. On the other hand, if someone is diabetic, his red blood cells live shorter lives than nondiabetics, which means that diabetics and those with high blood sugar will test with falsely low A1c levels.

Reasons to prefer A1c compared with plasma glucose determination for diagnosing diabetes
Chronic hyperglycemia is captured by A1c but not by FPG (even when repeated twice)
Microangiopathic complications (retinopathy) are associated with A1c as strongly as with FPG
A1c is better related to cardiovascular disease than FPG
Fasting is not needed for A1c assessment
No acute perturbations (e.g., stress, diet, exercise, smoking) affect A1c
A1c has a greater pre-analytical stability than blood glucose
A1c has an analytical variability not inferior to blood glucose
Standardization of A1c assay is not inferior to blood glucose assay
Biological variability of A1c is lower than FPG and 2-h OGTT PG
Individual susceptibility to protein glycation might be caught by A1c
A1c can be used concomitantly for diagnosing and initiating diabetes monitoring
Diabetes assessment with A1c assay is not necessarily greater than with glucose assessment

Reasons not to prefer A1c compared with plasma glucose determination for diagnosing diabetes
Diabetes is clinically defined by high blood glucose and not by glycation of proteins
A1c is a poor marker of important pathophysiological abnormalities featuring diabetes
A1c has a poor sensitivity in diabetes diagnosis and would change the epidemiology of diabetes
2-h glucose level and IGT are stronger predictors of CVD than A1c
Fasting is not essential to identify perturbation in glucose metabolism
Standardization of A1c assay is poor, even in Western countries, and standardization of glucose assay would be easier to implement
In many subjects, A1c assay is unreliable and cannot be used
A1c has significant differences in various ethnic groups, which are poorly understood and characterized
Within-days biological variability of plasma glucose might unveil disturbance of glucose metabolism
Individual susceptibility to glycation of hemoglobin is not relevant to diabetes diagnosis
Using the same biomarker for diagnosing and monitoring diabetes might have negative effects
Cost of the assay: glucose is unquestionably cheaper than A1c, and A1c assay is not available on a large scale in most of the countries
A1c levels vary not only according to glycemia, but also to erythrocyte turnover rates (e.g., hemoglobinopathies, malaria, anemia, blood loss) as well as other factors
Correlation between A1c and FPG is -0.85%, which means that as many as 30% of the variation in FPG is not explained by A1c and vice versa
Nothing is known about changes in A1c during the development of diabetes
A1c levels of 6.0-6.5% do not predict diabetes as effectively as FPG and 2-h PG (OGTT)
Sensitivity of A1c to detect diabetes defined by the OGTT is <50%; thus, the majority of diabetic individuals will remain undiagnosed if A1c is used
The levels of A1c predicting future retinopathy, nephropathy, etc., in the population is not well established (<6.5%?)
No diabetes prevention trials have selected their populations based on A1c
Using A1c will delay the diagnosis of diabetes in ~60% of incident cases

I've listed some pros and cons of A1c on this slide, and it's from a study, a great paper that I believe the full text is available for free with, and we'll put a link to that in the resources section so you can check out that paper and these full tables because it's really busy on this slide and difficult to read. I'm not going to go through all these, but I'm going to pick out a few highlights. As mentioned, some of the pros of A1c compared to fasting glucose are that chronic high blood sugar can be captured by A1c but not by fasting glucose, in some cases even when repeated twice in certain people. A1c has a closer association with cardiovascular disease than fasting glucose. A1c is considered to be a more stable marker, so from an analytical perspective, it's better than fasting

glucose. It's more standardized. The biological variability is lower than fasting glucose and oral glucose tolerance test.

The downsides of A1c: Two-hour post-meal blood sugar and impaired glucose tolerance are stronger predictors of heart disease than A1c. In many people with conditions such as anemia, A1c will not be an accurate marker. There is quite a wide range of red blood cell survival time, which affects A1c levels and makes them less accurate in individuals. Even though A1c is more standardized as a marker than fasting glucose, that's not saying much because the standardization of A1c is poor even in the developed world. Levels of A1c predicting future retinopathy and neuropathy in a population are not well established, and using A1c would delay the diagnosis of diabetes in about 60 percent of cases. So definitely some strengths and weaknesses. It's a good marker to include in the workup, but it's not—just like fasting glucose—something that we can rely on as a single marker. I often see a lot of patients and clinicians putting far too much stock in A1c readings without looking at the other markers in the panel.

So having said all that, what is a normal A1c? As you might surmise, it's difficult to answer that question given all the caveats for interpreting A1c in individuals, but at a population level, a truly normal A1c is between 4.6 and 5.3 percent. A number of studies show that A1c levels below the diabetic range are associated with cardiovascular disease. One study showed that A1c levels lower than 5 percent had the lowest rates of CVD and that a 1 percent increase to 6 percent significantly increased CVD risk.

Another study showed an even tighter correlation between A1c and cardiovascular disease, indicating a linear increase in CVD as A1c rose above 4.6 percent, a level that corresponds to a fasting blood sugar of just 86 mg/dL. Yet another study showed that the risk of heart disease in people without diabetes doubles for every percentage point increase in A1c above 4.6 percent, so if someone goes from 4.6 percent A1c to 5.6 percent A1c, his heart disease risk doubles. Studies also consistently show that A1c levels that are considered normal by many groups and labs fail to predict future diabetes. For example, one study found that using the American Diabetes Association criteria of an A1c of 6 percent as a cutoff missed 70 percent of individuals with

diabetes, 71 to 84 percent of individuals with dysglycemia, and 82 to 94 percent of individuals with pre-diabetes.

So how do we make sense of this data on A1c? Population data is helpful, but as you know, in functional medicine and in any kind of medicine, we don't treat populations. We treat individuals. As we've seen, there are many factors that influence A1c levels in a given person. As with fasting glucose, we need to consider other markers to determine the relevance of A1c. If A1c is high but fasting glucose and post-meal glucose throughout the day are normal, it's less likely to be significant because A1c is a marker of average blood sugar. If blood sugar is low in the fasted state and low in the post-meal state, there is no way it could be high on average, and this would be a sign where A1c might be high because the patient has abnormally long-lived red blood cells, or he has some other condition that affects A1c levels.

MCV is another marker that can be useful in interpreting A1c values. MCV is mean corpuscular volume. Red blood cells start out large and decrease in size over their lifespan, kind of a Benjamin Button phenomenon. If A1c is high and MCV is high-normal, this indicates that an elevated A1c is not due to long-lived red blood cells. If A1c is high and MCV is normal or low, it suggests that high A1c could be due to long-lived red blood cells.

Marker	Value	Functional Range	Lab Range
Glucose	90	75 – 90	65 - 99
Hemoglobin A1c	5.8	4.4 – 5.4	4.8 - 5.6
Uric Acid	6.1	3.2 - 5.5	2.5 - 7.1
BUN	9	13 – 18	6 - 20
Creatinine	0.71	0.85 – 1.1	0.57 - 1
BUN/Creatinine Ratio	13	9 – 23	9 - 23
Sodium	138	135 – 140	134 - 144
Potassium	4.2	4.0 – 4.5	3.5 - 5.2
Chloride	101	100 – 106	97 - 108
C02	20	25 – 30	18 - 28
Calcium	9.0	9.2 – 10.1	8.7 - 10.2
Phosphorus	3.5	3.5 – 4.0	2.5 - 4.5
Magnesium	2.0	2.0 – 2.6	1.6 - 2.6
Protein, total	6.8	6.9 – 7.4	6.0 - 8.5
Albumin	4.4	4.0 – 5.0	3.5 - 5.5
Globulin	2.4	2.4 – 2.8	1.5 - 4.5
A/G ratio	1.8	1.5 – 2.0	1.1 - 2.5
Bilirubin, total	0.3	0.1 – 1.2	0.0 - 1.2
Alkaline Phosphatase	63	42 – 107	39 - 117
LDH	147	140 - 180	119 - 226
AST	20	10 - 30	0 - 40
ALT	16	10 - 22	0 - 32
GGT	9	0 - 28	0 - 60
TIBC	247	250 – 350	250 - 450
UIBC	215	150 - 375	150 - 375
Iron	32	85 – 135	35 - 155
Iron saturation	13	15 – 45	15 - 55
Ferritin	26	15 - 120	15 - 150
Cholesterol, total	121	150 – 250	100 - 199
Triglycerides	26	50 – 100	0 - 149
HDL	87	55 – 85	> 39
LDL	29	0 – 175	0 - 99
T. Chol / HDL Ratio	1.4	< 3	0 - 4.4
Triglycerides / HDL Ratio	0.30	< 2	< 3.8
TSH	2.100	0.5 – 2.5	0.45 - 4.50
T4, total	8.2	6.0 – 12	4.5 - 12.0
T3 Uptake	29	28 - 35	24 - 39
T3, Total	118	100 – 180	71 - 180
Vitamin D, 25-hydroxy	73.3	35 - 60	30.0 - 100.0

Blood Chemistry Report	JENNIFER HARVEY		7/7/15
Marker	**Value**	**Functional Range**	**Lab Range**
WBC	9.6	5.0 – 8.0	3.4 - 10.8
RBC	4.97	4.4 – 4.9	3.77 - 5.28
Hemoglobin	14.7	13.5 - 14.5	11.1 - 15.9
Hematocrit	45	37 - 44	34.0 - 46.6
MCV	91	85 – 92	79 - 97
MCH	29.6	27.7 – 32.0	26.6 - 33.0
MCHC	32.7	32 – 35	31.5 - 35.7
RDW	13.6	11.5 – 15.0	12.3 - 15.4
Platelets	326	150 – 415	150 - 379
Neutrophils	72	40 – 60	
Lymphocytes	17	25 – 40	
Monocytes	10	4.0 – 7.0	
Eosinophils	1	0.0 – 3.0	
Basophils	0	0.0 – 3.0	
Additional Tests:			
T3, Free	3.1	2.5 - 4.0	2 - 4.4
T4, Free	1.42	1 - 1.5	0.82 - 1.77
Thyroid – TPO Ab			0 - 34
Thyroid – TGA			0 - 0.9
CRP-hs	6.35	< 1.0	0.00 - 3.00
Homocysteine	6.7	< 7.0	0.0 - 15.0
Vitamin B-12	652	450 – 2000	211 - 946
Copper	103		72 - 166
Zinc	92		56 - 134
Zinc / Copper Ratio	0.89	> 0.85	
Serum Methylmalonic Acid (MMA)	57	0 - 325	0 - 378

The results on this slide are from a 33-year-old female with a chief complaint of decreased stress tolerance. She also had brain fog, anxiety, and bloating despite clean diet and recent miscarriage. Her fasting blood glucose is a little high in the functional range, and this particular blood chemistry result template was when my functional range was broader than it is now, which is why it is marked as normal, but it was still within the normal lab range. Note that her A1c is high at 5.8 percent, and her MCV is normal. We did additional blood testing, and all of her markers for blood sugar were normal. In this case, I would assume that her A1c was falsely elevated, and if you look at her iron levels, you'll see that they are low, and you'll see that her red blood cell indices are also a little out of whack. This is actually a somewhat complicated picture in terms of what is happening with her iron and her red blood cell indices, but we know that those changes in those markers, the function that those markers indicate can be one of the things that alters A1c levels and makes them unreliable. In this case, I would say A1c is probably not reliable.