KRESSER INSTITUTE
FOR FUNCTIONAL AND EVOLUTIONARY MEDICINE

Blood Chem Hyperglycemia Etiology & Diagnosis Review

CAUSES OF HYPERGLYCEMIA

- Industrialized diet
- Physical inactivity
- Sleep deprivation
- Chronic Stress
- Environmental toxins
- Disrupted gut microbiota

Hyperglycemia is a risk factor for many other serious diseases, including cardiovascular disease, nerve damage, kidney damage, diabetic retinopathy, bone and joint problems, skin problems, and periodontal infections.

Current reference ranges for markers related to blood sugar are too high on the upper end. Many studies have shown that even high-normal blood sugar, according to the current lab reference ranges, is associated with a significantly higher risk of diabetes, heart disease, and other conditions, so we need to identify and address blood sugar issues early.

PRIMARY HYPERGLYCEMIA MARKERS

Marker	Value
Glucose (fasting)	High
Hemoglobin A1c	High
Fructosamine	High
Post-meal glucose (GlycoMark, OGTT, glucometer)	High (Low for GlycoMark)
Triglycerides	High
HDL	Low
Triglycerides:HDL	High

SECONDARY HYPERGLYCEMIA MARKERS

Marker	Value
Uric acid	High
Fasting insulin	High
ALT	High
AST	High
LDH	Low
GGT	High

FASTING GLUCOSE

- Measures the concentration of glucose in the blood after an eight- to 12-hour fast.
- Fasting glucose varies a lot from day to day and is affected by multiple factors, including recent food intake, sample storage, high intraindividual variability, acute stress, and diurnal variations.
- Drugs that influence glucose metabolism include corticosteroids, fibrates, cyclosporine, beta-blockers, methoxazole, thiazide diuretics, and thyroid hormones, among many others.

Fasting glucose is the least sensitive marker for predicting future diabetes and heart disease. This is due to the first- and second-phase insulin response.

- First-phase insulin response is the early release of stored insulin by beta cells immediately when you eat a meal. If blood sugar rises above 100 mg/dL, the beta cells release more insulin into the blood.
- In a healthy person, it keeps blood sugar from rising too high.
- After completing the first phase, the beta cells pause. If blood sugar is still not below 100 mg/dL 10 to 20 minutes later, they push out another smaller second-phase insulin response.
- In a healthy person, this should bring blood sugar back down to the starting level that it was at before a meal within 1 to 1-1/2 hours after the meal has finished.

- As blood sugar control worsens, it may take 4 to 5 hours for beta cells to make enough insulin to bring blood sugar back down to a fasted level after a meal.
- During the day, this may never happen because glucose increases after the next meal before glucose from the previous meal has been cleared out.
- Blood sugar may only return to normal at night after sleeping 7 to 8 hours without eating. This allows enough time for the impaired second-phase response to get blood sugar down and 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.
- You need to look at postmeal glucose and A1c to get a complete picture.

WHAT IS "NORMAL" FASTING GLUCOSE?

- 80 mg/dL = average fasting glucose levels in healthy people.
- <85 mg/dL = cardiovascular disease risk progressively increases with fasting glucose.
- Conventional range is 65-99 mg/dL.
- Functional range is 75-85 mg/dL.
- Fasting glucose is highly variable; we're looking for patterns, not individual markers.
- Look at multiple markers of metabolic function, including fasting glucose and A1c.
- Many factors affect blood sugar. For example, high iron can cause high blood sugar.

High fasting glucose with normal A1c and postprandial glucose could indicate a defect in basal insulin secretion.

HEMOGLOBIN A1C

- Theory behind the A1c test:
    - 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 average measure of blood sugar over a three-month period with greater focus on the most recent six weeks.
- The number reported in the A1c indicates the percentage of hemoglobin that has become glycated, or stuck, to sugar.
- A1c has a closer association with cardiovascular disease than fasting glucose.
- A1c is considered to be a more stable marker.
- The biological variability is lower than fasting glucose and oral glucose tolerance test.

Hemoglobin A1c downsides

- Some people's A1c results are always a little higher or lower than their fasting glucose or postmeal glucose numbers would predict.
    - This is likely due to the fact that several factors can influence red blood cells.
- Anything that affects red blood cells and hemoglobin, such as anemia, dehydration, and genetic disorders, will skew A1c results.
- Two-hour postmeal blood sugar and impaired glucose tolerance are stronger predictors of heart disease than A1c.
- There is a wide range of red blood cell survival time, which affects A1c levels and makes them less accurate in individuals.

This is a partial list - please see presentation video or transcript PDF for a more comprehensive list.

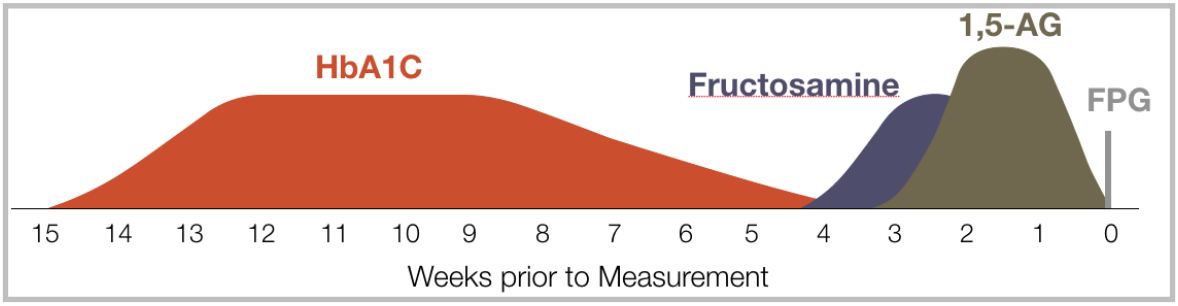
On a population basis, a truly normal A1c is 4.6 to 5.3%, but we treat individuals, not populations.

As with fasting glucose, we need to consider other markers to determine the relevance of A1c. Mean corpuscular Volume (MCV) can be useful in interpreting A1c values.

- Red blood cells start out large and decrease in size over their lifespan.
- 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.

Fructosamine

- During the glycation of serum proteins such as albumin, the aldimine intermediate can be reconverted to glucose and protein or form into a fructosamine derivative.
- 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 below.



Fructosamine can detect changes in blood glucose before they show up in A1c.

POSTMEAL BLOOD SUGAR OR POSTPRANDIAL BLOOD SUGAR

- 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 the pathophysiology behind diabetes better than any other glycemic marker.
- Normal blood glucose levels two hours after a glucose load indicate good beta cell capacity.
- High two-hour postprandial glucose level indicates an impairment of beta cell function.
- Postprandial glucose is superior to fasting glucose or A1c in predicting cardiovascular disease outcomes.

THREE WAYS TO MEASURE PPG

1. Oral glucose tolerance test
    a. Patient fasts, then is given 75 g of glucose dissolved in water.
    b. 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, this indicates prediabetes. If blood sugar above 199 mg/dL two hours later, this indicates diabetes.
    c. Advantage: It is highly validated, and there is tons of research correlating it with clinical outcomes.
    d. Disadvantage is it's artificial. I don't know anyone who drinks a pure solution of 75 g of glucose outside of this OGTT setting.
    e. 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.

2. Glucometer testing
    a. Tests blood sugar just before and then one, two, and three hours after a meal.
    b. Advantages
        i. Convenient
        ii. Better reflection of response to actual meals that that patient is eating
        iii. Objective way of determining carbohydrate tolerance
        iv. Better compliance and also fewer adverse reactions in patients
    c. Cons
        i. It's not validated to the same degree as OGTT.
        ii. Glucometers are notoriously variable in accuracy and consistency. Overall, I prefer using glucometers to OGTT because we're looking for patterns. A single reading is not super important. We also consider other markers such as fasting glucose, A1c, etc.

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

Caveats to this kind of testing

- Even reliable glucometers have about a 10 percent margin of error, so a reading of 100 mg/dL could be anything between 90 and 110, but this is okay because what we're doing here is trying to identify patterns.
- If the patient normally eats a low-carb diet, postmeal glucose readings on the third day following the simple carbohydrate challenge will be abnormally high.
- 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.

3. GlycoMark
    a. Measures the 1,5-anhydroglucitol molecule in the blood.
    b. One- to two-week measure related to average daily maximum blood glucose.
    c. For people with well-controlled blood sugar, 1,5-AG is stored at a steady state in the tissues and the bloodstream, which keeps blood levels of 1,5-AG high and produces a high GlycoMark score.
    d. For people with blood glucose averaging over 180 mg/dL a day, 1,5-AG is low.
    e. This is an inverse marker. High 1,5-AG indicates normal or well-controlled blood sugar, and low 1,5-AG indicates high blood sugar.
    f. This test has advantages over a test such as A1c because it shows glycemic variability and blood sugar spikes.
    g. Spikes are better predictors of cardiovascular disease and other complications, and are more damaging than just a high average A1c level.

OTHER MARKERS OF METABOLIC DYSFUNCTION AND DYSGLYCEMIA

Triglycerides

- Triglycerides are one of the major lipids found in the serum.
- Elevated in conditions characterized by abnormal blood sugar such as obesity and type 2 diabetes.

High-density lipoprotein (HDL)

- So-called good cholesterol.
- Low levels of HDL are observed in patients with insulin resistance, obesity, and type 2 diabetes.
- The ratio of triglycerides to HDL is one of the best-studied markers of metabolic dysfunction. It should be below 2 optimally.

ALT, AST, and **GGT** are enzymes that may be out of range in dysglycemic conditions. GGT is an enzyme responsible for the extracellular catabolism of glutathione, and high GGT may be linked to increased oxidative stress and beta cell destruction.

Uric acid
Studies have shown significant associations between increased uric acid and metabolic syndrome such as obesity, type 2 diabetes, hypertension, and gout.