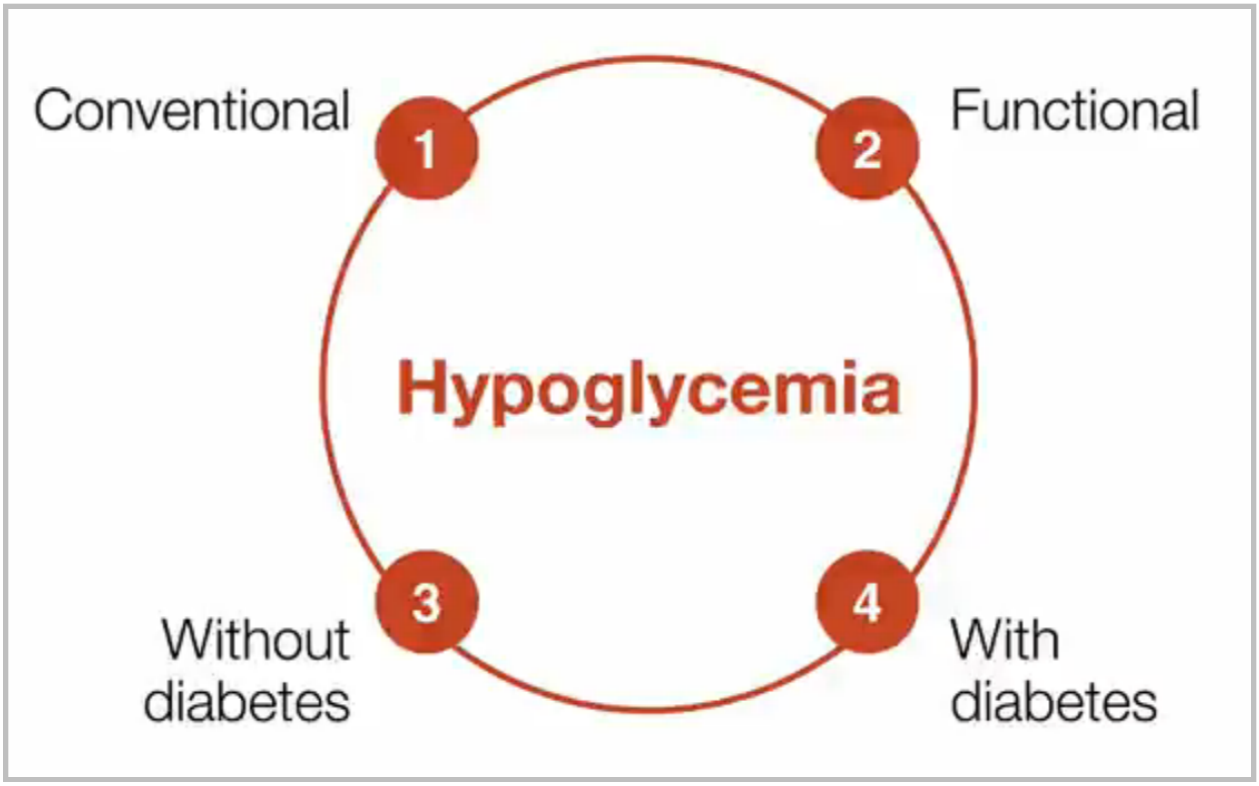
KRESSER INSTITUTE
FOR FUNCTIONAL AND EVOLUTIONARY MEDICINE

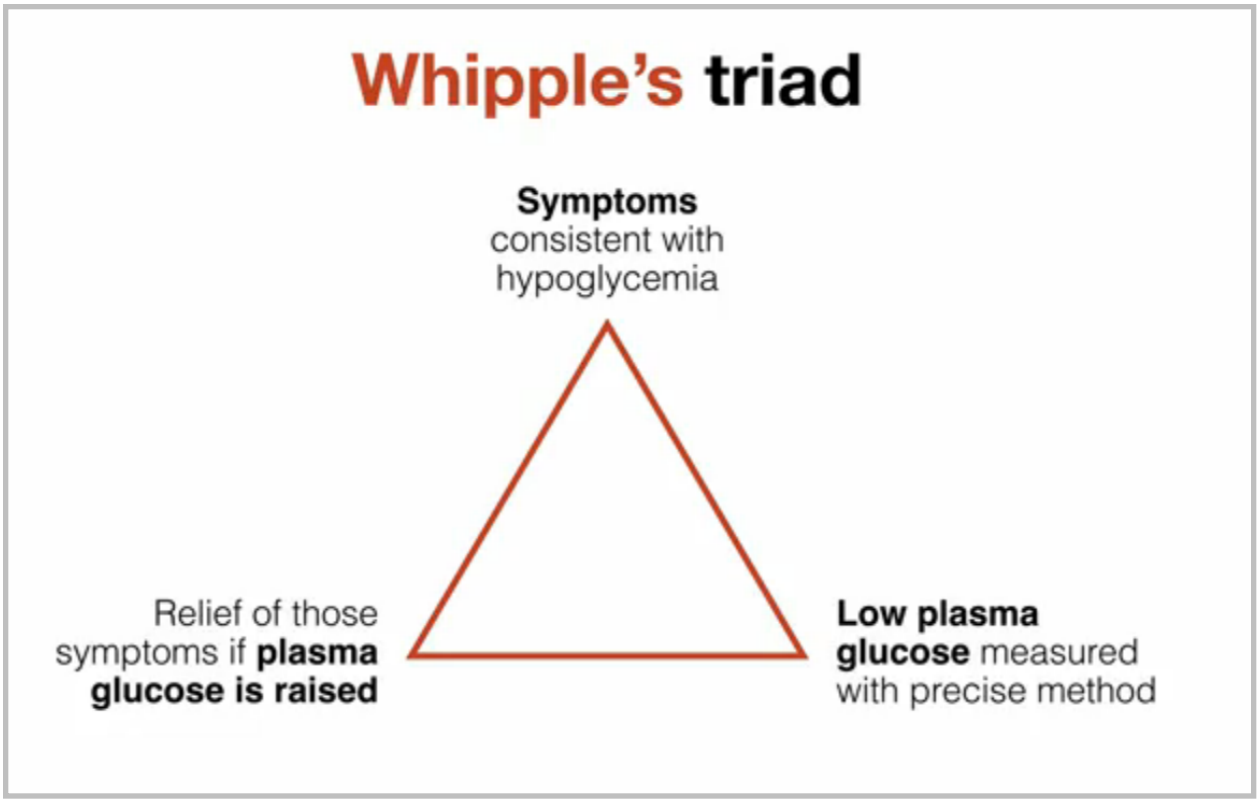
Hypoglycemia – Part One

Hey, everyone. In this presentation, we're going to talk about hypoglycemia, or low blood sugar. I'm going to break this down into a few categories.

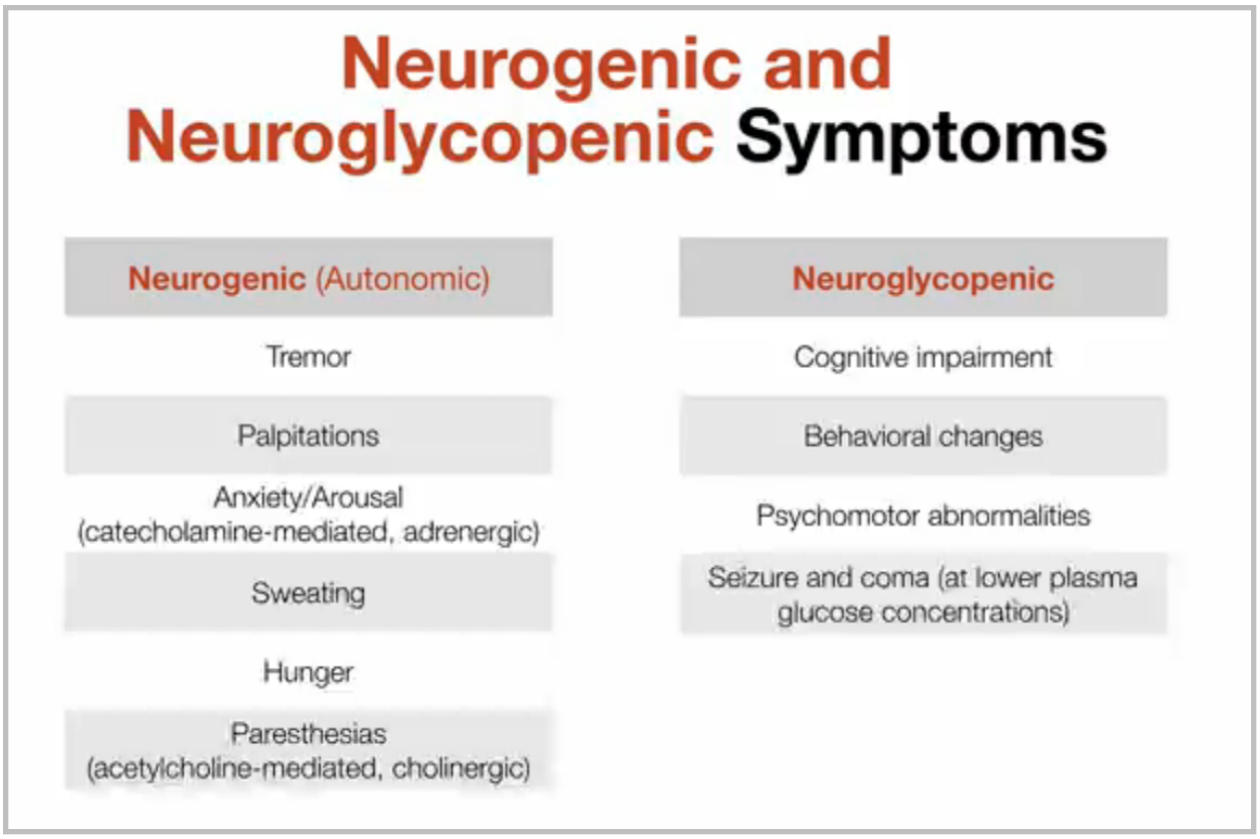


First, we'll discuss the conventional interpretation of hypoglycemia, and under that umbrella, I'll break it further down into hypoglycemia in patients without diabetes and hypoglycemia in patients with diabetes or other high blood sugar disorders. Then, I'll talk about subclinical or functional hypoglycemia, which is where a patient doesn't meet the conventional definition for hypoglycemia but has symptoms that are consistent with and respond to interventions that regulate low blood sugar.

In any case, true hypoglycemia is far less common in clinical practice than hyperglycemia is. In fact, in almost 10 years of practice, I've only had about two to three patients with overt hypoglycemia who didn't also have diabetes and hyperglycemia. This section will have very few case studies as a result compared to other sections.

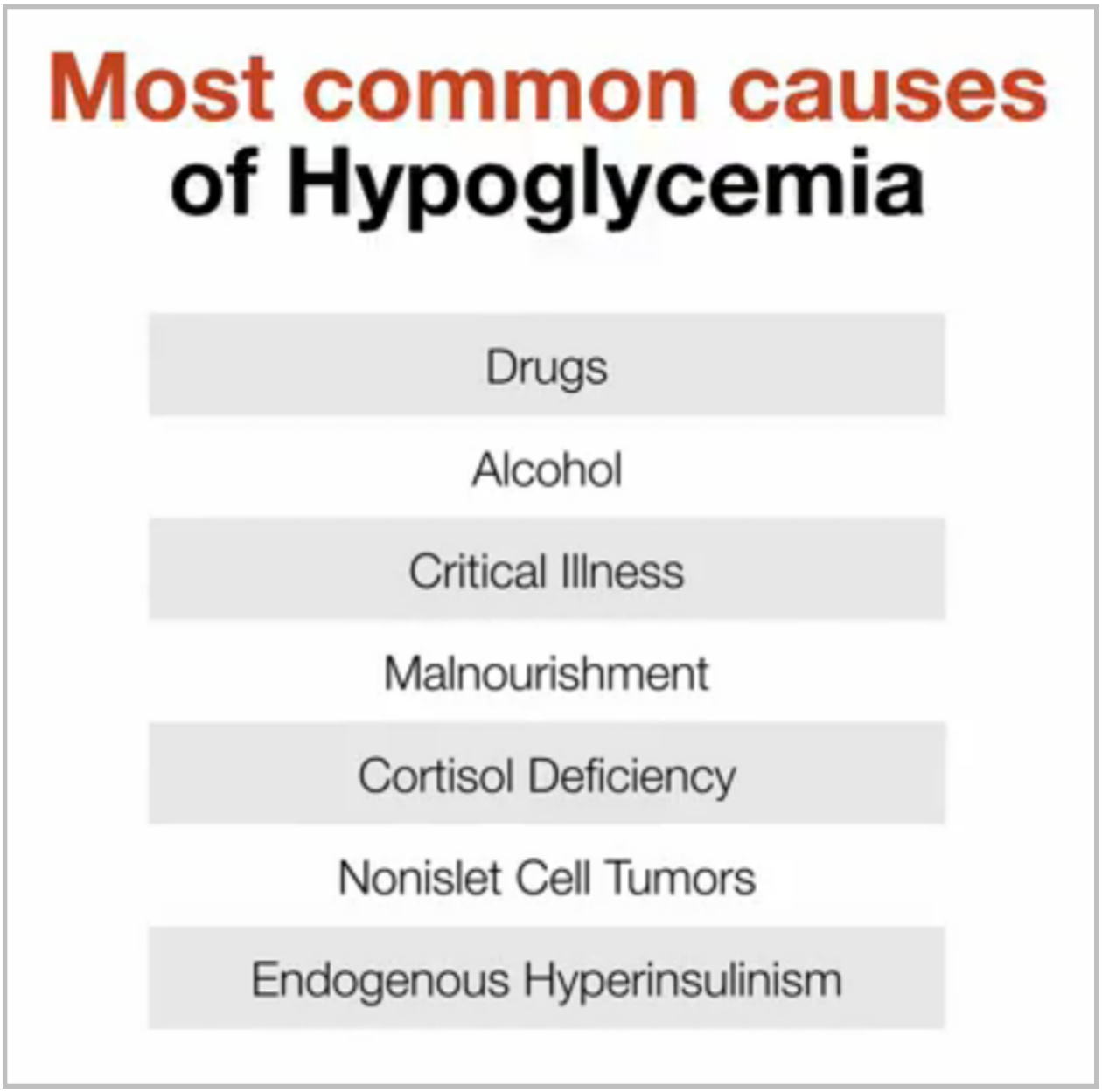


In order for a patient without diabetes to be diagnosed with hypoglycemia in the conventional setting, he has to meet criteria known as Whipple's triad. This includes, number one, symptoms consistent with hypoglycemia; number two, low plasma glucose measured with a precise method, meaning not a glucometer, when symptoms are present; and number three, relief of those symptoms if plasma glucose is raised. If the patient is not symptomatic during testing, you may need to recreate the conditions in which hypoglycemia would appear by doing a prolonged supervised fast. This is the most reliable test for hypoglycemia in a food-deprived state. In the conventional setting, a single measurement of low glucose below 65 mg/dL, which is the lower end of the lab reference range, isn't enough to diagnose hypoglycemia unless it's extremely low, such as below 40 mg/dL. The patient must have Whipple's triad in order to meet the definition of hypoglycemia.



The symptoms of hypoglycemia are diverse and nonspecific. They're primarily broken into two categories: neurogenic, or autonomic, and neuroglycopenic. Neurogenic symptoms include tremor, palpitations, anxiety, and arousal, which are catecholamine-mediated and adrenergic; and then sweating, hunger, and paresthesias, which are acetylcholine-mediated and cholinergic. Neuroglycopenic symptoms include cognitive impairment, behavioral changes, psychomotor abnormalities, and, at lower plasma glucose concentrations, seizure and coma.

Hypoglycemia may also be asymptomatic due to what is known as hypoglycemia unawareness. This is thought to be the result of reduced sympathoadrenal responses to a given degree of hypoglycemia. Patients who have only sympathoadrenal symptoms such as anxiety, weakness, tremor, perspiration, or palpitations but normal fasting or concurrent glucose are not diagnosed with hypoglycemia in the conventional setting, though we may consider them to have hypoglycemia in the functional setting, which we'll talk about later.



In patients without diabetes, the most common causes of hypoglycemia according to the conventional model are certain medications. For example, in a systemic review of almost 450 studies describing drug-induced hypoglycemia, there were 164 different drugs associated with low blood sugar. The drugs that were most commonly associated were quinolones, pentamidine, quinine, beta-blockers, angiotensin-converting enzyme inhibitor, and IgF-1. So note that this evidence was judged to be poor quality, but you should still do a thorough review of patients' medications during the case review and intake process to be sure one of them isn't contributing.

Next is alcohol. Alcohol-induced hypoglycemia typically follows a several-day alcohol binge with limited ingestion of food. In my experience, this is not common in patients who seek out functional medicine care, but it's something to be aware of.

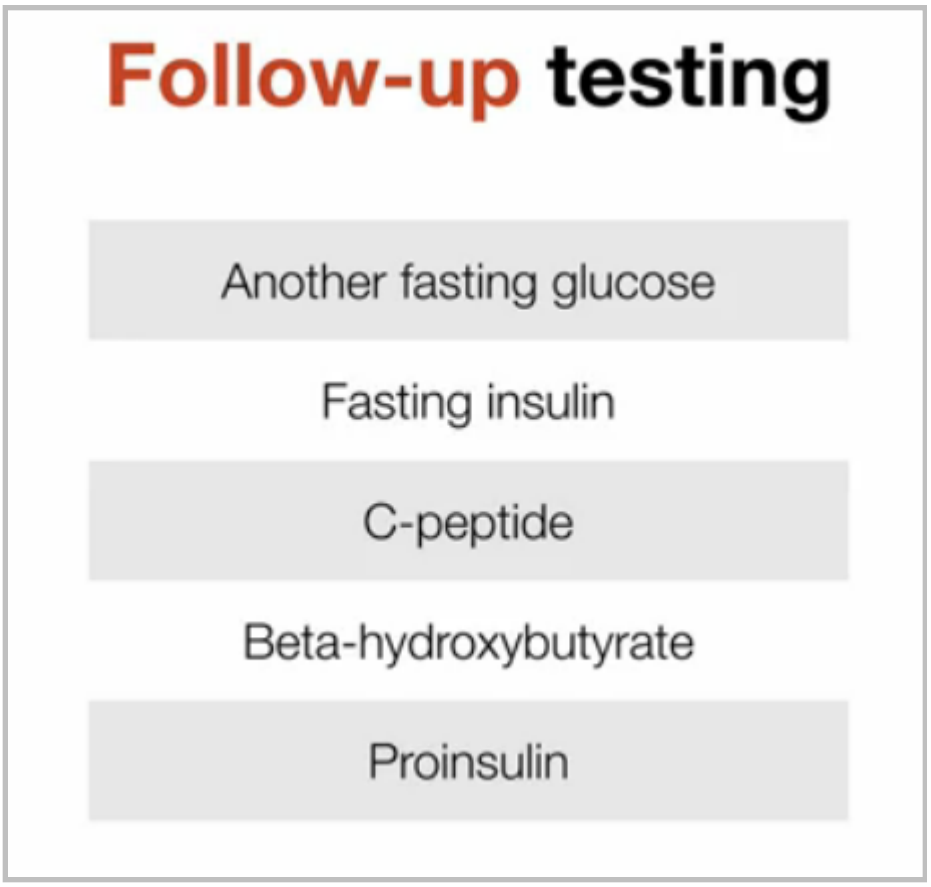
Next is critical illness. Hypoglycemia can occur in critical illnesses such as septic shock and renal insufficiency, again uncommon in a functional medicine setting.

Malnourishment, inadequate food intake or absorption due to gastrointestinal conditions, limits the substrate for gluconeogenesis and glycogenolysis. Anorexia nervosa and eating disorders can also be associated with hypoglycemia.

Next is cortisol deficiency. In the conventional model, they're speaking about Addison's primarily, but in functional medicine, we're also looking at hypocortisolism that is not as extreme due to HPA axis dysregulation.

Non-islet cell tumors: severe hypoglycemia has been observed in a small number of patients with non-islet cell tumors. This is again rare. You're unlikely to see this.

Then finally endogenous hyperinsulinism, which is also caused by a beta cell tumor, a functional beta cell disorder, or insulin autoimmune hypoglycemia, and I have seen a few cases of autoimmune hypoglycemia where the body is actually attacking insulin.



In patients without diabetes that meet Whipple's triad, follow-up testing should include the laboratory assays on this slide, so I would do another fasting glucose, fasting insulin, C-peptide, beta-hydroxybutyrate, and proinsulin.

Interpretation of hypoglycemia follow-up tests

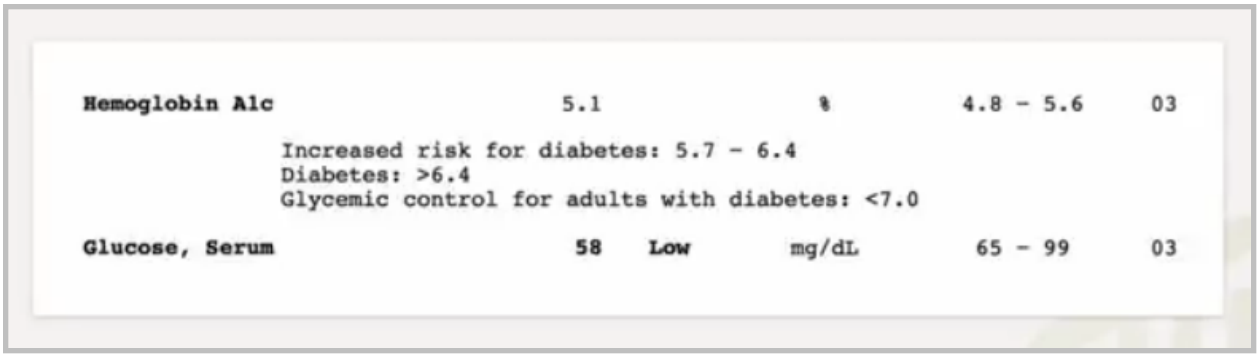
Symptoms, signs, or both	Glucose (mg/dL)/ (mmol/L)	Insulin (microU/mL)/ (pmol/L)	C-peptide (nmol/L)/ (ng/mL)	Proinsulin (pmol/L)	Beta-hydroxybuty-rate (mmol/L)	Glucose increase after glucagon (mg/dL)/ (mmol/L)	Circulating oral hypoglycemic agent	Antibody to insulin	Diagnostic interpretation
No	<55/3	<3/20.8	<0.2/0.6	<5	>2.7	<25/1.4	No	No	Normal
Yes	<55	> >3	<0.2	<5	≤2.7	>25	No	Neg (Pos)	Exogenous insulin
Yes	<55	≥3	≥0.2	≥5	≤2.7	>25	No	Neg	Insulinoma, NIPHS, PGBH
Yes	<55	≥3	≥0.2	≥5	≤2.7	>25	Yes	Neg	Oral hypoglycemic agent
Yes	<55	> >3	> >0.2*	> >5*	≤2.7	>25	No	Pos	Insulin autoimmune
Yes	<55	<3	<0.2	<5	≤2.7	>25	No	Neg	IGF**
Yes	<55	<3	<0.2	<5	>2.7	<25	No	Neg	Not insulin (or IGF)-mediated

* Free C-peptide and proinsulin concentrations are low, ** Increased pro-IGF-II, free IGF-II, IGF-II/IGF-I ratio

Adapted from: http://www.uptodate.com/contents/hypoglycemia-in-adults-without-diabetes-mellitus-diagnostic-approach

The table on this slide lists the interpretation of the follow-up tests, and we will provide this as a handout because it's obviously pretty busy. If the patient does meet Whipple's triad, and he is positive on these follow-up tests, he should be referred to an endocrinologist for a more complete evaluation unless this is something that you do and are familiar with. You can still treat them with functional medicine, but it's probably helpful to clarify what the pathology is, especially if it's one of the more rare causes that we talked about on the last slide.

Evaluation of low fasting glucose and hypoglycemia in children is a little different. One of the primary possible causes in kids is mitochondrial dysfunction or mitochondrial disease. If you see Whipple's triad and low fasting glucose in children without type 1 diabetes who aren't taking insulin, you need to consider this as a possibility.



Hemoglobin A1c 5.1 % 4.8 - 5.6 03

Increased risk for diabetes: 5.7 - 6.4
Diabetes: >6.4
Glycemic control for adults with diabetes: <7.0

Glucose, Serum 58 **Low** mg/dL 65 - 99 03

The lab result on this slide was from a three-year-old patient presenting with fatigue; food intolerances; occasional muscle aches and weakness, particularly in her legs; stomach aches; and

dark circles under eyes. She weighed 38 pounds and was approximately 42 inches tall, which put her in the 75th percentile for weight and the 91st percentile for height. Her cognitive and social development were normal. Her parents noted that she often complained about being too tired to walk up hills or stairs and that she was prone to intense tantrums and mood swings. They reported that she was susceptible to upper respiratory infections and had a cold or cough for most of the previous winter. Now, this isn't true mitochondrial disease probably because the symptoms may be more severe, but there is a growing number of researchers and clinicians who believe that functional mitochondrial dysfunction is not only a possibility, but it's actually a lot more common than we have recognized so far, and this is something that we may discuss in more detail in future Kresser Institute trainings.

Testing for mitochondrial disorders or dysfunction is complex, and it's beyond the scope this ADAPT Level One framework. However, I'm going to briefly show you what I did to give you an overview.

TESTS	RESULT	FLAG	UNITS	REFERENCE INTERVAL	LAB
Lactic Acid, Plasma	11.4		mg/dL	4.5 - 19.8	03
Pyruvic Acid, Blood	**0.1**	**Low**	mg/dL	0.3 - 0.7	01

Organic Acid Analysis, Urine

Organic Acid Interpretation 01

Analysis of this urine specimen revealed a normal pattern of organic acids.
Organic acid analysis may fail to detect certain disorders which are characterized by minimal or intermittent metabolite excretion. If a specific disorder is suspected, consider submitting a repeat specimen.
Specimens collected during an acute metabolic crisis may be more informative than specimens collected when the patient is well.

Contact: 02

Adviye Ayper Tolun, MS, PhD, FACMG
Director, Biochemical Genetics

To discuss these results or other testing for inborn errors of metabolism, please contact our Biochemical Geneticists at 1-800-345-GENE(4363), LabCorp Genetics Customer Service, RTP, NC.

Methodology: 01

Urine organic acids were obtained by solvent extraction and oximated with hydroxylamine hydrochloride. TMS derivatives were separated and identified by GC/MS. (Shapira E, Blitzer MG, Miller JB, and Africk DK: Biochemical Genetics: A Laboratory Manual.Oxford University Press, 1989.)

Follow-up markers include direct markers of mitochondrial dysfunction such as lactate, pyruvate, the lactate-to-pyruvate ratio, ubiquinone, alanine, alanine-to-lysine ratio, and acylcarnitine. There is a full acylcarnitine profile. Then indirect markers such as creatine kinase, carnitine, aspartate aminotransferase, or AST, alanine, aminotransferase, or ALT, and then ammonium and organic acids in the urine. As you can see on this slide, her pyruvate was low, and her lactate was normal, making the ratio of lactate to pyruvate elevated. Typically, in mitochondrial dysfunction, you'll see elevated lactate and normal pyruvate or even elevated pyruvate with a high lactate-to-pyruvate ratio, and that indicates mitochondrial dysfunction. Low pyruvate with normal lactate is a different story. It's

more suggestive of mitochondrial hyperfunction. The mitochondria are sucking in pyruvate at an elevated rate, and she has more mitochondrial potential than normal. This phasic mitochondrial overfunction is more common in kids now, and it's been defined as the cell danger response by Robert Naviaux at UCSD, and I've included a link to a paper about it in the resources section.

One important note: pyruvate is very unstable and has to be drawn into percolate tubes that instantly precipitate protein, so it's really difficult to get an accurate pyruvate reading even at a LabCorp or Quest draw site. They're often not aware of that, so you have to instruct the lab to make sure to use those percolate tubes in order to get the accurate reading.

TESTS	RESULT	FLAG	UNITS	REFERENCE INTERVAL	LAB
Acylcarnitine Profile, Plasma					
C2	9.27		umol/L	2.79 - 16.23	01
C3	0.38		umol/L	0.14 - 0.85	01
C3-Dicarboxylic	0.07		umol/L	0.00 - 0.08	01
C4	0.14		umol/L	0.05 - 0.39	01
C4-Hydroxy	0.04		umol/L	0.00 - 0.22	01
C5	0.09		umol/L	0.04 - 0.29	01
C5:1	0.00		umol/L	0.00 - 0.02	01
C5-Hydroxy	0.04		umol/L	0.01 - 0.08	01
C5-Dicarboxylic	0.05		umol/L	0.01 - 0.08	01
C6	0.04		umol/L	0.01 - 0.13	01
C8	0.15		umol/L	0.02 - 0.26	01
C10	0.18		umol/L	0.01 - 0.36	01
C10:1	0.09		umol/L	0.02 - 0.31	01
C10:2	0.02		umol/L	0.00 - 0.05	01
C12	0.07		umol/L	0.01 - 0.21	01
C14	0.04		umol/L	0.01 - 0.09	01
C14:1	0.06		umol/L	0.01 - 0.23	01
C14:2	0.02		umol/L	0.00 - 0.13	01
C14-Hydroxy	0.01		umol/L	0.00 - 0.02	01
C16	0.11		umol/L	0.03 - 0.15	01
C16:1	0.03		umol/L	0.00 - 0.05	01
C16:1-Hydroxy	0.01		umol/L	0.00 - 0.02	01
C16-Hydroxy	0.00		umol/L	0.00 - 0.02	01
C18	**0.08**	**High**	umol/L	0.01 - 0.06	01
C18:1	**0.31**	**High**	umol/L	0.03 - 0.21	01
C18:2	0.10		umol/L	0.02 - 0.11	01
C18-Hydroxy	0.00		umol/L	0.00 - 0.01	01
C18:1-Hydroxy	0.00		umol/L	0.00 - 0.01	01
C18:2-Hydroxy	0.00		umol/L	0.00 - 0.01	01
Interpretation					02
Plasma acylcarnitine analysis revealed an essentially normal pattern. Minimal variations from the reference range were noted for some species, however these are not suggestive of an inborn error of					

This is her acylcarnitine profile. She has high C18 and high C18:1, but this is not suggestive of an inborn error of metabolism or frank mitochondrial disease, so this was a good sign. I and other clinicians and researchers believe that functional mitochondrial dysfunction that is not due to an inborn error of metabolism may be caused by things such as heavy metal toxicity, mold, or chronic inflammatory response syndrome, and it did turn out that this patient was living in a moldy house and had CIRS, or chronic inflammatory response syndrome. Once she was removed from exposure and treated with cholestyramine, her labs and symptoms normalized within two months.