

## **Episode 29 Transcript: Diagnostic Testing for Type I/II Diabetes and Associated Complications**

Andrea Ott-Vasconi:

I'm Andrea Ott-Vasconi and welcome to Ortho Science BYTES. World Diabetes Day takes place each year in the month of November, created to raise awareness about the disease. Diabetes is a global health threat with the number of people living with a disease continuing to rise. Diagnostic testing is one of the major tools to help prevent and manage the disease.

With me today for a discussion on this topic is Dr. Amy Pyle-Eilola. Dr. Pyle-Eilola earned her PhD in molecular pathology from Vanderbilt University, where she also completed a post-doctoral fellowship in clinical chemistry. Dr. Pyle-Eilola currently holds multiple director positions at Nationwide Children's Hospital in Columbus, Ohio, including director of clinical chemistry. She's also an associate professor of clinical pathology at the Ohio State University. She has published multiple abstracts, papers and book chapters and has received numerous awards for her contributions to the scientific community. Thank you, Dr. Pyle-Eilola, for joining me today.

Amy Pyle-Eilola:

It's really good to be here.

Andrea Ott-Vasconi:

Thank you. First of all, can you give us a quick review of the causes of type 1 and type 2 diabetes?

Amy Pyle-Eilola:

Absolutely. And thank you again for having me. I'm really pleased to be here to discuss this important topic. So type 1 diabetes has traditionally been thought of as the diabetes of the young and as such has been referred to often as juvenile diabetes and while type 1 diabetes can develop rarely later in life, the vast majority of cases arise in childhood and adolescence. Type 1 diabetes results from autoimmune destruction of the beta cells of the pancreas, which are the cells that make insulin. So these individuals can't make insulin to regulate their blood sugar. This is treated by the use of exogenous insulin, and for this reason, type 1 diabetes has sometimes been called insulin dependent diabetes, although that's not entirely accurate. Type 2 diabetes on the other hand, comes about as the body develops resistance to insulin or the beta cells of the pancreas fail to secrete enough insulin. And so generally speaking, type 2 diabetes develops secondary to dietary, genetic, and other lifestyle factors. And most commonly it presents in adulthood, but for either type of diabetes, the primary symptom is hyperglycemia and the disorders that arise as the result of prolonged hyperglycemia.

Andrea Ott-Vasconi:

And what are the most common tests used to screen for type 2 diabetes?

Amy Pyle-Eilola:

That's a great question, and surprisingly more complicated than you'd think. The American Diabetes Association or the ADA has stipulated what tests should be used for screening and for the diagnosis of type 2 diabetes. There are four tests to choose from. These are a random plasma glucose, a fasting plasma glucose, a two-hour glucose tolerance test. And then a few years ago they added hemoglobin A1c as a screening test for type 2 diabetes. Because of the simplicity of collection and interpretation, Hemoglobin A1c is now probably the most widely used test for screening for diabetes. And a

hemoglobin of greater than or equal to 6.5% is considered indicative of diabetes. So usually when an individual goes to the doctor or maybe is even at a health screening center, they'll do one of these tests, most frequently A1C. And once one test is abnormal, the guidelines recommend a second test from that same list that will be used to establish the diagnosis of diabetes.

In addition to just being the diagnosis of diabetes, these tests can also identify something called prediabetes. This is a condition in which glucose is slightly elevated but not as much as full on diabetes. So it's important to really recognize prediabetes for two reasons. There are some symptoms associated with prediabetes, but probably more importantly, if prediabetes is recognized before it progresses to overt diabetes, that with appropriate lifestyle modification many people can avoid the progression into overt diabetes.

[Andrea Ott-Vasconi:](#)

[And are there differences in the screening criteria for type 2 diabetes for children versus adults?](#)

[Amy Pyle-Eilola:](#)

So the screening tests are basically the same. Again, A1C being the most commonly used for children or adults. What is different is the criteria for who to screen. Because there is a high prevalence of type 2 diabetes in the adult population in the United States, and also because there are significant health complications associated with untreated diabetes, screening for type 2 diabetes is common and pretty widespread. There are specific risk factors that have been defined to prompt screening, and these include but aren't limited to family history of diabetes, certain high-risk ethnic groups, history of cardiovascular disease or hypertension and obesity. And these criteria generally apply not just for adults but in children too. And as we know, there's an increase in prevalence of obesity in children, especially in the United States. And so we are seeing increased screening in children and adolescents for type 2 diabetes.

For type 1 diabetes however, routine screening is not recommended because the disease prevalence is fairly low. This is with the exception of a few individuals that have a first degree relative with type 1 diabetes. So instead of screening, we test for diabetes in patients with symptoms of type 1 diabetes. And these include polydipsia, which is excessive thirst, polyuria, which is excessive urination, weight loss, and hyperglycemia. Polyuria arises when blood glucose is above about 180 milligrams per deciliter. At that point, the glucose is excreted into the urine and when you have a lot of glucose that needs to be excreted, a lot of urine is made. And when your body makes a lot of urine, you get dehydrated and you get thirsty. And so that is why you have polyuria and polydipsia in type 1 diabetes and also in type 2 diabetes. But this is often a presenting symptom of type 1 diabetes.

So this point actually leads me to one of my favorite clinical chemistry facts. So clinical chemistry is what I do. It is the measurement of things that are dissolved in blood and body fluids. And one of the oldest tests in clinical chemistry is for diabetes. The word diabetes itself is derived from Greek, and this means passing through, which refers to a large amount of urine passed by diabetics. This is a symptom that was recognized many centuries ago. Moreover, the types of diabetes that we're talking about today are called diabetes mellitus. The mellitus means sweet. This goes back to that first clinical chemistry test when urine was tasted, and if it was sweet, it was indicative of diabetes mellitus. I'm really glad the clinical laboratory has progressed beyond those days.

[Andrea Ott-Vasconi:](#)

[I am too. What are some of the important factors to consider when screening for type 2 diabetes?](#)

Amy Pyle-Eilola:

So this actually really gets into the heart of what I do because there are numerous caveats to consider when screening for type 2 diabetes. So first of all, when an individual is presenting for a two-hour glucose tolerance test, they need to have consumed a sufficient amount of carbohydrates for at least three days prior to the test. So somebody knows the test is coming up and they decide to just go on a no carb diet for a couple days, that could actually significantly affect the results of the test and lead to some inaccuracies. So most of the rest of the caveats pertain to hemoglobin A1C. First of all, anytime we use national guidelines to determine cutoffs for disease diagnosis as we do with the ADA guidelines, laboratories need to ensure that the results are consistent across labs and methods. And to this end, an organization called NGSP was formed and they standardized hemoglobin A1C results in the US and the UK.

The NGSP has a list of methods certified to provide a sufficiently accurate A1C result, and thankfully (this wasn't always the case) at this time, the certified methods are almost universally used in the United States. In order to understand the next challenge in A1C measurements, one has to understand a little bit more about what hemoglobin A1C is. As most of us know, our red cells use hemoglobin to carry oxygen to our cells. And there are a few different kinds of hemoglobin and hemoglobin A makes up about 90% of normal hemoglobin. When any protein in circulation exposed is exposed to high concentrations of glucose, they become glycated. So that's just when the glucose molecule is basically attached to that protein. And this includes hemoglobin. So hemoglobin A1c is the glycated form of hemoglobin A. The more glucose there is in circulation, the higher your A1c.

Additionally, the time period during which A1C forms is the lifespan of a red cell, which is about four months. So factoring in the half-life of a red cell, we know that A1C reflects your blood glucose for a two to three month window. Anything that alters the lifespan of a red cell will alter the time that A1C can form, and it'll lead to results that don't accurately reflect the blood glucose for a two to three-month timeframe. Conditions which affect red cell turnover include sickle cell disease, pregnancy, glucose-6-phosphate dehydrogenase deficiency, hemodialysis, or recent blood loss, and/or transfusion. The other challenge with hemoglobin A1C is that we can only measure glycated hemoglobin A in people that have hemoglobin A. There are many hemoglobin variants known. These are also called hemoglobinopathies. If someone has one copy of a variant hemoglobin, we can still usually measure A1C accurately. But if someone has two copies of a variant hemoglobin, they don't have any hemoglobin A, only the hemoglobin variant.

And while that variant may be glycated, we can't use that result to correlate to an average blood glucose. Moreover, in certain ethnic groups, even if someone doesn't have a hemoglobinopathy, they may have altered A1C results. For example, some studies have shown that African Americans have a higher A1C result than non-Hispanic whites that have a similar result for fasting plasma glucose and glucose tolerance tests. There are also certain rare hemoglobin variants which can directly interfere with the measurement of A1C. So regardless of the cause, when A1C cannot be used, a fasting plasma glucose and glucose tolerance tests are recommended for screening and diagnosis of diabetes. For the ongoing monitoring of diabetes, which is usually performed by A1C, if someone has a hemoglobin variant that precludes the use of A1c but has normal red cell turnover, samples can be analyzed by boronate affinity chromatography. This reports the glycation of all hemoglobins present, not just hemoglobin A.

Andrea Ott-Vasconi:

And what are some of the challenges you've seen with interpreting A1C values, for example, low values?

Amy Pyle-Eilola:

That's a really good question. So most of the challenges we have with A1c's are from hemoglobin variants. Unfortunately, many clinicians don't fully understand the implications of hemoglobin variants on A1c results and will repeatedly order it on patients with hemoglobinopathies. However, another issue that arises occasionally is a low hemoglobin A1c. And what do we do with that in individuals that have a normal hemoglobin and haven't had any kind of blood loss or a red cell defect. High A1c's, we know what to do with that means they have a high blood sugar. But when an A1c is low, does that mean the individual is chronically hypoglycemic or is there some kind of interference that's causing a low A1c result that's a false result? The truth is we don't entirely know.

There are just a few case studies in the literature about this, and one turned out that the patient was actually on a profoundly restrictive diet and also taking his diabetes medications and as a result was just chronically hypoglycemic. So the A1C in that case was real. And another case, the low A1c was attributed to advanced liver disease. However, I recently reviewed a year's worth of A1c cases from my lab and saw that there was about 1% of our total A1c's that were below 4.5%. I reviewed most of these cases and none of these patients had liver failure or a restrictive diet that would cause hypoglycemia. So this really remains a mystery to laboratorians.

Andrea Ott-Vasconi:

Let's now switch the focus of the discussion to type 1 diabetes. What additional tests are used in the diagnosis of type 1 diabetes beyond what has already been discussed?

Amy Pyle-Eilola:

So just to review, the test for diagnosing type 1 diabetes are the same as type 2, so an A1c random or fasting plasma glucose and the two-hour glucose tolerance test. But once we've established a diagnosis of diabetes, the clinician must decide and determine if the diabetes is type 1 or type 2, because type 1 is an autoimmune disease. Testing for autoantibodies associated with type 1 diabetes can usually nail down a diagnosis of type 1. There are some additional tests that are important in managing type 1 diabetics, primarily urine and blood ketones. Patients with type 1 diabetes can't utilize glucose for energy, therefore the body metabolizes fats and a byproduct of that fat metabolism is ketones. The accumulation of these ketones can reach dangerous levels in uncontrolled type 1 diabetes causing acidosis, anorexia, abdominal pain, nausea and vomiting.

This condition is known as diabetic ketoacidosis or DKA, and is life threatening if not addressed. DKA is seen in about 30% to 40% of cases of new onset type 1 diabetes and can occur again if the diabetes is not well treated. DKA has been known to occur in type 2 diabetes, but it's at a much lower rate than in type 1 patients. From the lab perspective, there are three ketones, which we can measure, acetone and acetyl acetate and beta hydroxybutyric acid. Acetone and acetyl acetate are primarily present in the urine and beta hydroxybutyrate is in highest concentration in the blood. The diagnosis of DKA requires elevated urine ketones or blood beta hydroxybutyrate.

Andrea Ott-Vasconi:

And what are some of the additional complications associated with type 1 diabetes?

Amy Pyle-Eilola:

Historically, type 1 diabetes was a really terrible disease and individuals would often succumb pretty quickly after the disease onset. However, 100 years ago, exogenous insulin was introduced as a treatment for type 1 diabetics, and since then diabetics have been living much longer, which is great.

However, with longer life means prolonged diabetes, and there are some complications that go along with this. These include damage to the retinas, kidneys, and cardiovascular system. Therefore, there are certain screening tests recommended for type 1 diabetics to detect damage early. Urinary albumin is tested annually. In the initial stages of kidney injury, the filtration system of the kidney is damaged just enough that albumin can filter into the urine. Therefore, small amounts of urinary albumin can be indicative of early kidney injury and treatment can be initiated. Hyperlipidemia is also more prevalent in type 1 diabetics, so lipid screening is also performed routinely in these patients. And lastly, these individuals also receive hypertension as well as routine dilated eye exams to detect retinal changes.

Andrea Ott-Vasconi:

Thank you, Dr. Pyle-Eilola for this very insightful and informative discussion today on the important topic of diabetes. I hope everyone enjoyed this podcast episode. Make sure to review sections within the podcast description with suggested reading materials, links to learn more about diabetes, and a summary of the key takeaways from this episode. Based on today's podcast, I'll leave you with our pop quiz. What are some of the important factors to consider when screening for type 1 and type 2 diabetes? You can go back and listen again if you'd like some more details. Thank you so much for listening today. Please subscribe to Ortho Science BYTES, our monthly podcast where we'll be discussing more complex questions we face every day in our lives, brought to you by Ortho Clinical Diagnostics, pioneering advances in diagnostics for 80 years, because every test is a life. Take care.