Ortho Science Bytes:
Diagnostic Testing for Type I/II Diabetes and Associated Complications

Key Takeaways from a discussion with Amy L. Pyle-Eilola, PhD, DABCC, FACB

DISCLAIMER

The following slides contain excerpts from the responses to questions discussed in the podcast episode and were created by the podcast moderator, Andrea Ott-Vasconi. Please refer to the podcast recording and transcript for the full responses to the questions.

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What are the causes of type 1 and type 2 diabetes?

- Type 1 diabetes results from autoimmune destruction of the beta cells of the pancreas. Individuals are not able to make insulin to regulate their blood sugar.

- Type 2 diabetes comes about as the body develops resistance to insulin or the beta cells of the pancreas fail to secrete enough insulin. Generally speaking, type 2 diabetes develops secondary to dietary, genetic, and other lifestyle factors.

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

- The American Diabetes Association (ADA) has stipulated four tests to choose from for the screening and diagnosis of type 2 diabetes:
  - random plasma glucose
  - fasting plasma glucose
  - two-hour glucose tolerance test
  - Hemoglobin A1c

- Because of the simplicity of collection and interpretation, hemoglobin A1c is now probably the most widely used test for screening for diabetes.

Are there differences in the screening criteria for type 2 diabetes for children vs. adults?

- 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 for children, too.

- For type 1 diabetes, routine screening is not recommended because the disease prevalence is fairly low, with the exception of individuals who have a first degree relative with type 1 diabetes. Instead of screening, patients with symptoms of type 1 diabetes are tested. Symptoms include polydipsia (excessive thirst), polyuria (excessive urination), weight loss, and hyperglycemia.

What are some of the important factors to consider when screening for type 2 diabetes?

- For a two-hour glucose tolerance test, an individual must have consumed a sufficient amount of carbohydrates for at least 3 days prior to the test.
- A1c testing: anything that alters the lifespan of a red cell will alter the time that A1c can form, leading to results that do not 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, recent blood loss, and/or transfusion.
- Hemoglobinopathies: if an individual has one copy of a variant hemoglobin, A1c can usually still be measured accurately. If an individual has two copies of a variant hemoglobin, he/she does not have any hemoglobin A, only the hemoglobin variant. That result can't be correlated to an average blood glucose.
- Ethnicity: 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.
- 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, which reports the glycation of all hemoglobins present, not just hemoglobin A.

What are some of the challenges you've seen with interpreting A1c values, for example, low values?

- Most of the challenges with A1c results are from hemoglobin variants.
- An issue that arises occasionally is a low hemoglobin A1c. 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 low A1c results, 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. In another case, the low A1c was attributed to advanced liver disease. However, Dr. Pyle-Eilola conducted a recent review of a year's worth of A1c cases from her lab and found about 1% of the total A1c results were below 4.5%. After reviewing most of those cases, none of the patients had liver failure or a restrictive diet that would cause hypoglycemia. So this really remains a mystery to laboratorians.

What additional tests are used in the diagnosis of type 1 diabetes beyond what has already been discussed?

- Because type 1 diabetes is an autoimmune disease, testing for autoantibodies associated with type 1 diabetes can help diagnose type 1 diabetes.

- 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 a condition known as diabetic ketoacidosis or DKA, and is life-threatening if not addressed. From the lab perspective, there are three ketones which can be measured, acetone, 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.

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

- Complications associated with prolonged diabetes 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.

Additional Resources:

- American Diabetes Association Practice Guidelines Resources: https://professional.diabetes.org/content-page/practice-guidelines-resources
- Centers for Disease Control and Prevention (CDC): HbA1c Performance in African Descent Populations in the United States with Normal Glucose Tolerance, Prediabetes, or Diabetes: A Scoping Review: https://www.cdc.gov/pcd/issues/2021/20_0365.htm
- Low HbA1c: What is a lab director to do? : https://www.aacc.org/science-and-research/scientific-shorts/2021/low-hb-a1c-what-is-a-lab-director-to-do
- Journal article: What Clinical Laboratorians Should Do in Response to Extremely Low Hemoglobin A1c Results: https://academic.oup.com/labmed/article/48/1/89/2687769
- International Diabetes Federation: https://worlddiabetesday.org/

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