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Islet autoantibodies and type 1 diabetes: does the evidence support screening?

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Guest:
Dr. Boris Calderon is an Assistant Professor of Pathology & Immunology at Washington University School of Medicine in Saint Louis.

Bob Barrett: This is the podcast from *Clinical Chemistry*. I'm Bob Barrett. Type 1 diabetes is a chronic progressive autoimmune disorder with complex, polygenic susceptibility. Environmental factors which are poorly defined also contribute to the pathogenesis. This disease is characterized by lymphocyte infiltration into the islets of Langerhans in the pancreas, leading to inflammation and selective destruction of the insulin-producing beta cells resulting in hyperglycemia.

In the March 2014 issue of *Clinical Chemistry*, a perspective article examined islet autoantibodies and type 1 diabetes, and if evidence supports screening for these autoantibodies. The authors were Dr. Boris Calderon and David Sacks. Today, we're joined by Dr. Calderon. He's an Assistant Professor of Pathology & Immunology at Washington University School of Medicine in Saint Louis, Missouri. And doctor, tell us why you think the editors of *Clinical Chemistry* wanted to do a perspective article based on the recent study evaluating seroconversion to multiple anti-islet autoantibodies, and the subsequent risk of progression to diabetes in children.

Dr. Boris Calderon: Well, Bob, the main reason of this perspective article is the increasing prevalence of type 1 diabetes, which is an autoimmune disease that leads to the destruction of the insulin-producing cells that reside in the islets of Langerhans of the pancreas.

Now, this disease mainly affects the pediatric population between two and eighteen years, but it can also develop in adults, especially in the late 30s. Now, in the United States, the prevalence of type 1 diabetes under the age of 20 rose by 20% in the last decade. So, this means that more than 30,000 people in the United States are diagnosed annually with type 1 diabetes. Also, this disease involves a strong genetic predisposition of the major histocompatibility complex class II, which is also known by the genetic name, IDDM1.

The rate of type 1 diabetes varies among individuals due to other genetic and environmental components. So currently, there are no accurate diagnostic methods to evaluate the risk of developing type 1 diabetes. And the current diagnosis for type 1 diabetes is based on the end result of the disease, which is the detection of elevated blood glucose. Because of this, there is a great need to identify individuals at high risk that will go on to develop diabetes if more symptoms occur, and when immunotherapy may be possible to either prevent or delay the disease.

Now, current research has shown that approximately 85% of the patients with type 1 diabetes have circulating anti-islet cell antibodies. And the majority also has detectable anti-insulin antibodies before receiving therapy. Now, taking this into consideration, it becomes feasible to evaluate the risk of developing type 1 diabetes by assessing the presence of autoantibodies in high risk individuals.

Now, this study discussed in the perspective article has provided the most complete screening profile for type 1 diabetes in a high risk population of more than 13,000 subjects followed from birth until adulthood. Their results provided us with substantial information regarding the progression to type 1 diabetes, in a high risk individual after autoantibodies' seroconversion. Now, however, there are several limitations that need further evaluation for this screening method to actually move forward.

Bob Barrett: Well, tell us about these limitations that need that evaluation.

Dr. Boris Calderon: Well, in the discussed study, which I've mentioned before, included more than 13,000 subjects at high risk for type 1 diabetes, 8% of the subjects seroconverted to multiple or a single antibody. Now, from all the seroconverted individuals, 38% developed diabetes. The sensitivity was high in individuals with multiple antibodies, but lower when a single antibody was present. Now, on top of this, the low prevalence of type 1 diabetes yields a very low positive predictive value.

Now, the second limitation is the fact that in this study, a small group of autoantibody negative individuals did go on to develop diabetes, which questions if autoantibodies are the end-all of screening for type 1 diabetes.

The third limitation is the time interval from seroconversion to the onset of diabetes, which varies dramatically in the discussed study, ranging from weeks after birth to even more than 15 years. So this becomes a significant problem

concerning the frequency of analysis to assess the risk of developing diabetes.

The fourth limitation is actually the lack of autoantibody standardization since autoantibody measurements have varied considerably among laboratories due to the lack of consensus between methods of detection. And because of this, there is actually an ongoing effort by the Islet Autoantibody Standardization Program to fix the problem. However, the most important limitation at this time is the lack of preventive therapy upon the identification of a high risk individual.

Bob Barrett: Dr. Calderon, as the director of the diagnostic lab, do you think we're going to see changes in the way we screen for the risk of type 1 diabetes in the pediatric population anytime soon?

Dr. Boris Calderon: Well, since insulin at this moment is the only treatment available for type 1 diabetes, the benefit of screening may allow the prevention of other complications such as diabetic ketoacidosis, as well as allowing an early initiation of insulin therapy.

Now, at this moment, and in the near future, if autoantibody diagnosis for type 1 diabetes becomes common, it should be centralized to reference laboratories to maintain harmonization.

Bob Barrett: So who should we screen for type 1 diabetes risk?

Dr. Boris Calderon: Screening should be only performed on high risk individuals, having the IDDM1, the disposition gene, which with that, it already cuts 60% of general population, as well as also having first degree relatives with type 1 diabetes.

Bob Barrett: Well, finally, doctor, regarding the gap between seroconversion and the onset of type 1 diabetes, how frequently should high risk individuals be assessed?

Dr. Boris Calderon: Well, under the high risks scenario for type 1 diabetes, screening should be at least twice in the first year, and then every one to three years to identify those at risk of developing type 1 diabetes in the near future. And hopefully, gain the benefit of upcoming preventive therapies to inhibit the progression of this disease. In the meantime, risk assessment should be focused for early insulin treatment and to reduce the cases of diabetic ketoacidosis.

Bob Barrett: Dr. Boris Calderon is an Assistant Professor of Pathology & Immunology at Washington University School of Medicine in Saint Louis. He's been our guest in this podcast on

autoantibodies and type 1 diabetes from *Clinical Chemistry*. I'm Bob Barrett. Thanks for listening.