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Decoding Diabetes Diversity: A Study on Heterogeneity and Endotypes in T1D

Dr. Buse:
Welcome to *Diabetes Discourse* on ReachMD. I'm Dr. John Buse, and joining us to talk about her study focusing on heterogeneity and endotypes in type 1 diabetes is Dr. Maria Redondo. She's a Professor of Pediatrics in the Division of Pediatric Diabetes and Endocrinology at Baylor College of Medicine in Texas.

Maria, thanks so much for speaking with me today.

Dr. Redondo:
Thank you so much. It's really my pleasure. I'm very happy to be able to talk with you all today.

Dr. Buse:
I read your review on heterogeneity in type 1 diabetes with great interest. Most clinicians have thought of type 1 diabetes as being fairly monolithic, even though we've often noted that there are some patients who respond differently to care. Can you tell us about the general pathophysiology of type 1 diabetes and the various approaches that you've used to define heterogeneity to just sort of get us on the same baseline with regards to what we'll talk about later?

Dr. Redondo:
Yeah, absolutely. So what we know of type 1 diabetes today is that there is a genetic predisposition, so in most people, there are some genes that are known to make someone more predisposed to developing this disease. And then in addition, there's something coming from the environment that, so far, seems to be a virus. And then in these people with this particular makeup, it triggers an autoimmune response directed against some of the antigens and some of the proteins that are in the islets where the insulin, of course, is produced, so then that process happens actually way before the person develops the clinical symptoms of type 1 diabetes. And we know that it's happening because there's those islet antibodies that are measurable in the blood of most people who will develop type 1 diabetes. And then at some point, that autoimmune attack that is destroying beta cells ends up causing such a loss that the system cannot maintain normal glucose; so basically, there's less insulin being produced than insulin that is needed to maintain euglycemia, and that's when type 1 diabetes happens.

So this process is very heterogeneous, way more than we were thinking before. So, for example, we know that age has a huge effect. Children who develop diabetes very early have a much more aggressive disease. It progresses much faster. They are left without any cells that make insulin that can be appreciated in the histopathology samples that are, for example, being collected by the IMPORT study. And then as opposed to that, people who develop diabetes later—adolescents and young adults—we know adults who present with type 1 diabetes have a much smaller process. They do not always end up losing completely the ability to make insulin. And even in the case of what we called in the kind of recent past LADA, latent autoimmune diabetes in adults or slowly progressive autoimmune diabetes, they can actually have even at some time where insulin is not needed. So they present with diabetes. They don't need insulin. Many times, they are actually misdiagnosed with type 2 diabetes, but in fact, they have those autoimmune markers that is type 1 diabetes, and then that process continues, and they ultimately develop insulin dependence.

Dr. Buse:
In your paper, you talk about type 1 diabetes endotype 1 and type 1 diabetes endotype 2, and it's based on some pretty sophisticated markers that I don't think most clinicians use, like T-cell markers and specific genotypes. How do you think clinicians should be thinking about this specifically in their day-to-day practice?

Dr. Redondo:
So an adult who presents with diabetes does not automatically have type 2 diabetes. It's the most common, but type 1 is something that we need to keep in the back of our minds. To me, that's the most pragmatic aspect at this point. But I think that very soon we'll see new treatments—teplizumab is now the one that is FDA approved to prevent the progression to type 1 diabetes, and then there's some drugs, some agents such as verapamil that has been shown to slow down the loss of beta cell function after the onset. APG has also shown that. So there's different response, and there are some markers—genetic markers, age, and some other characteristics—that are telling us that some things work better in some people than in others. So I think that not quite yet, but very soon we will be able to tailor those newer treatments to the specific characteristics of the person, so I think that for the clinician, it's just kind of keeping that in mind that that is coming, and hopefully, we'll be able to tailor treatment better.

Dr. Buse:
So you mentioned before about latent autoimmune diabetes in adults, or LADA. I think many, many people have heard about that. But one thing that you wrote about in the paper that I don't think we think about as much is what you described as slowly progressive insulin-dependent diabetes. Can you tell us about the distinction that you're trying to make there?

Dr. Redondo:
So as we said before, there's a huge effect of age. Many people who develop type 1 diabetes later have a slower process where their loss of beta cell function happens over the course of years, and they hover around the threshold where you need insulin for longer time. And that is what we call slowly progressive autoimmune diabetes in adults, which actually also happens in children, and we have seen that. And I think that is very similar to what is also called latent autoimmune diabetes in adults.

So at the end of the day, as physicians we know that we are faced with a person that may have not just a single disease, but different pathogenic mechanisms going on. One is the autoimmune process that is slowly distracting beta cells slowly in this particular case of older adults and, in addition, all of the type 2 diabetes components. And then our goal is, of course, to be able to address all of those pathogenic mechanisms from a diagnostic standpoint, but also from prevention as we think about how to prevent that type 1 diabetes from developing and from progressing and then, hopefully, as we think also for treatment of disease once that person has developed diabetes.

Dr. Buse:
For those just tuning in, you're listening to *Diabetes Discourse* on ReachMD. I'm Dr. John Buse, and today I'm speaking with Dr. Maria Redondo about her study on the heterogeneity and endotypes in type 1 diabetes.

How about the term type 1.5 diabetes? What's the meaning there?

Dr. Redondo:
So many times it is used as a synonym of double diabetes. So basically, this is a person that has both elements of type 1 and type 2 diabetes, and that type 1 can be not even slowly progressive but just regular type 1 diabetes, that classical picture that we see; but in addition, you have obesity, so that is contributing to the complications and even to the phenotype. For example, talking more about children maybe because that's the practice that I have, but they have higher C-peptide, so we see children who present with classical type 1 diabetes with obesity and their C-peptide is higher, right? So that is a clear case of that double diabetes having those two types that can also be called 1.5, right?

But I think that the other reason why it was applied or has been applied to the slowly progressive diabetes, which not always has that type 2 component—many times it has but not always—is because the slowly progressive autoimmune diabetes can develop so slowly that to the clinician it appears as type 2 diabetes until they realize that this person has, in fact, type 1 diabetes. To give an example, an adult who presents with diabetes— 90 percent of the diabetes in others are going to be type 2—gets classified as type 2, is given metformin, but doesn't respond well, and very quickly we see the need of adding insulin. And then going back to the drawing board, we test antibodies, and those antibodies are positive. So that is a picture of 1.5 in the sense that it looked like 2, but now I realize that it is 1. And it is definitely a different picture, right? So I think that corresponds more closely to what we call today slowly progressive type 1 diabetes, or LADA, right? Which those two terms are usually referring to the same syndrome.

Dr. Buse:
So maybe another way of thinking about it is when you have double diabetes, people will certainly respond to the type 1 diabetes therapy, but they'll also respond to the type 2 diabetes therapy. And maybe when you're thinking of it more as sort of type 1.5, they don't really respond to the type 2 diabetes therapy very well, which makes you realize that it's really type 1 diabetes and we need to focus on things like multiple daily injections of insulin or insulin pumps.

Dr. Redondo:

So the way I see it people who have type 1 diabetes and, in addition, some components of type 2 could benefit from drugs that we use for type 2 diabetes in addition to insulin, which, of course, they need because they lack insulin, right? For example, the T1D Exchange data study some time ago trying metformin in adolescents with obesity and type 1 diabetes, and A1c, which was the primary outcome, did not change; but what the authors realized is that these children improved insulin resistance, which, of course, in itself is a good thing, right? So then we did a secondary analysis and found that there are some predictors. In this case, it was leptin that was able to predict who will respond, who of those children who have type 1 and obesity will respond with a decrease of insulin resistance by taking metformin. So I think that's a good example of how we have to start thinking about a person who has classical type 1 but in addition has obesity-induced insulin resistance—that is another pathogenic mechanism that may deserve treatment, for example, with metformin.

Dr. Buse:
I think the sort of newest emerging area is around the GLP-1 receptor agonists and what to do in the patient with double diabetes, type 1 diabetes, obesity dyslipidemia hypertension, non-alcoholic steatohepatitis, and heart failure chronic kidney disease. Where I have had patients who responded fabulously to the GLP-1 receptor agonists and all those sort of metabolic type 2 diabetes aspects as they lost weight, we often have trouble getting coverage for treating their type 1 diabetes with these drugs. And, actually, because I do think they have double diabetes, I've taken to diagnosing them with both type 1 and type 2 diabetes and sometimes that has helped with the discussion with insurance companies. In pediatrics, is that an area that you are starting to embrace?

Dr. Redondo:
Yeah, absolutely. I mean, obviously, in pediatrics we are late adopters number one, because many of the drugs are not approved in younger children, but we have adolescents, so there are adolescents who many times are even at the age where these agents can be used. I think that traditionally, we are kind of reluctant to use additional medications, but I think that is all true. First of all, GLP-1 agonists have really shown to have some beneficial effects on the beta cell. And today, we know that type 1 diabetes is not just a disease where the immune system is wrongly attacking a completely healthy beta cell. That is not the case. The beta cell already has some abnormalities. And these agents really are promising in terms of increasing the health of the beta cell.

Dr. Buse:
This has been a really interesting conversation. I'd like to thank my guest, Dr. Maria Redondo, for sharing her findings on heterogeneity and endotypes in type 1 diabetes. Maria, it was really great speaking with you today.

Dr. Redondo:
Thank you very much, John.

Dr. Buse:
For ReachMD, I'm Dr. John Buse. To access this and other episodes from our series, visit *Diabetes Discourse* on ReachMD.com, where you can Be Part of the Knowledge. Thanks for listening.