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Getting to Know GRADE: A Comparative Study of T2D Treatment

Dr. Buse:
As the treatment landscape for type 2 diabetes continues to grow, how do you know which treatments are most effective? One study compared different treatments for type 2 diabetes over a span of seven years and what new data researchers have begun to explore, the role of islet autoimmunity in beta cell dysfunction for patients with type 2 diabetes.

Welcome to *Diabetes Discourse* on ReachMD. I'm Dr. John Buse. And joining us to share highlights from an ancillary study to the GRADE trial is Dr. Ashok Balasubramanyam, who is a professor in the Department of Endocrinology, Diabetes and Metabolism at Baylor College of Medicine.

Ashok, thanks for being here today.

Dr. Balasubramanyam:
Oh, you're most welcome, John. It's a pleasure.

Dr. Buse:
Well, to start us off, what can you tell us about the patient population included in the GRADE study?

Dr. Balasubramanyam:
Yeah. So the patient population in the GRADE study, consisted of over 5,000 people, with the entire range in age from 18 all the way up into the late 60s and 70s, and geographically spread throughout the country. And in the ancillary study that we're going to talk about, the so-called beta cell ancillary study, it was nested within this larger population. GRADE had 36 different sites from around the country that recruited subjects. 19 of those, so approximately half of those sites, also participated in the beta cell ancillary study, And if you look at the demographics, age, BMI and all other patient characteristics of the patients in the beta cell ancillary study, they are very similar to the same parameters and distributions across the entire GRADE study.

Dr. Buse:
Wonderful. And what was the rationale behind the particular study that you reported recently?

Dr. Balasubramanyam:
Well, as you know, John, diabetes, as we all know, is incredibly complex, and many of us have had the feeling for a long time that we, you know, quite hopelessly oversimplify our, approach to it by dividing it into two kinds of disease: type 1 and type 2. And we've all felt for a long time that both kinds of diabetes, and especially type 2 diabetes, is very, very heterogeneous. So one part of the goal here was to try to figure out, you know, the heterogeneity of type 2 diabetes. The other part of it was that, you know, we're all agreed that while the pathophysiology of diabetes is complex, it certainly cannot happen unless you have dysfunction or loss of insulin secretion or dysfunction of the beta cells of the islets of Langerhans, and therefore, the thought is that perhaps different kinds of events or different causes that lead to beta cell dysfunction might be a way to get at the heterogeneity of type 2 diabetes. In other words, if beta cell dysfunction is due to different causes, then each of those causes might be associated with a specific phenotype. And ultimately, by studying those two things in populations of people with type 2 diabetes, you might get a handle, number one, on the different ways in which a human being could acquire beta cell dysfunction in type 2 diabetes, and number two, perhaps be able to classify patients with type 2 diabetes better on the basis of the beta cell dysfunction etiology.

So that was kind of the motivation behind the study, and we felt that, you know, the very painstaking and careful approach to the main GRADE study really lent itself to the kind of investigations we wanted to do for several reasons: number one, a very large number of very diverse type 2 diabetes patients that we just mentioned, number two, incredibly, you know, tight control of the way people were brought

into the study in terms of the range of A1cs, the duration of diabetes, and the fact that everybody was only on a single drug at the start of the study, which is metformin. So that really helped standardize to a large extent, the baseline of these patients we wanted to study. And perhaps the thing that really motivated us was the fact that this is, perhaps, the first really large type 2 diabetes trial in which, there was a very rigorous test of beta cell function, secretory function, done repeatedly throughout the study, so that seemed like just too good an opportunity to miss.

Dr. Buse:
Wonderful. That really makes a lot of sense. So, what were your key findings regarding markers of islet autoimmunity in these patients with "type 2 diabetes?"

Dr. Balasubramanyam:
So it's been known for a while that there is at least one form of type 2 diabetes which resembles type 1 diabetes, and that is patients with adult-onset, non-insulin-requiring diabetes, are shown to have circulating autoantibodies against the islets that are usually typical of type 1 diabetes, so there's sort of an overlap syndrome between type 1 and type 2 diabetes, and we call that latent autoimmune diabetes of adults.

So, in this particular study, we not only looked at the type 1 autoimmune islet markers, but also, looked for cellular autoimmune reactivity against islets, and we tried to make the T-cell reactions against islets as specific as possible with a very broad range of controls. The one thing that that particular test, which we call the T-cell test for short, is that if you are positive for the T-cell test, you're not positive for a reactivity against a single antigen, because the way the test is done is that it could be T-cell reactivity against a whole range, a wide range of islet antigens as opposed to the type 1 diabetes antibody.

So, sorry about the long preamble, but I thought it was important to sort of set of stage for how the tests were done. And these were done on baseline fasting samples on, close to 400 patients and the assays were done for both the antibodies and the T-cell reactivity, the results were really rather astounding. We were sort of prepared for somewhere around a 10 percent frequency of LADA that is of autoantibody positivity, and it turned out that we had a positivity of about 13 percent, so slightly higher than what we've seen before, but that's not particularly shocking. What was really striking was with the T-cell or cellular reactivity. That was present in 41 percent of the patients. And the very interesting thing was there was only a very small overlap between those who were antibody-positive and those who were T-cell-positive. The overlap was only in 5 percent of patients. So, if you add it all up, it looks like over 50 percent of the patients carefully selected for having something called type 2 diabetes actually had, evidence of autoreactivity against their own islets, and most of it is in the form of a cellular reactivity and not the typical type 1 diabetes humoral autoreactivity. So that was the first major finding.

Now, since GRADE also was measuring beta cell function, and since this particular test was done at the time of the oral glucose tolerance test at baseline, which is what is used to calculate beta cell function, we wanted to see if being positive for islet autoreactivity either on humoral side or on the cellular side, the question is whether that positivity correlated in any way with beta cell function and whether it correlated with glycemic control, and it turned out that this was not the case with the antibody-positive patients, but it was very much the case for the T-cell-positive patients where the T-cell-positive patients had a significantly less or lower beta cell function and the patients who were T-cell-positive also had a significantly higher hemoglobin A1c and also had a significantly higher fasting glucose level.

Dr. Buse:
Very cool. 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. Ashok Balasubramanyam about islet autoimmunity with beta cell dysfunction in type 2 diabetes.

Ashok, let's turn to the practical application of these findings. Do you think that this is meaningful for clinicians today? And how should they apply these findings to their practice?

Dr. Balasubramanyam:
That's a great question, John. I mean, I think really a great part of our motivation in doing this study was to try to see if this can change practice in the sense of how we categorize somebody with the kind of diabetes they have when we diagnose them and then whether we can do any specific tests that tell us the cause of their beta cell function and then finally, of course, if we can then find a specific treatment that might be the most appropriate for the different kinds of beta cell dysfunction that they might have. And again, you know, the main GRADE study really lends itself to this because it's a longitudinal study with repeated beta cell function tests, and the whole globus of the main GRADE study was to see what is the optimal form of treatment beyond metformin.

Obviously, I think deciding that patients with type 2 diabetes might be T-cell-positive or T-cell-negative would be immensely helpful in many ways. Number one, since we know that people who are T-cell-positive probably have a more rapid decline in their beta cell function, clearly a test that would tell us whether they are positive or negative would prognosticate their requirement for insulin over time

because we would imagine that that would happen more rapidly, but we might also be able to find more specific treatments. So I think that, being able to classify according to T-cell reactivity and to see whether they have LADA or not, would be extremely helpful in the diagnosis, in the sort of diagnostic categorization of diabetes and hopefully also in the treatment.

Now, one problem with that in terms of making this practical is that currently the T-cell test is really very laborious. It's a three- or four-day assay. It requires a large amount of blood to be drawn. It requires cells to be separated. So one of the things we're trying to do is to figure out a more rapid way of doing the T-cell test. We might be able to sort of narrow it down to just two or three, and certainly less than a handful of specific antigens, which in combination, if one finds reactivity of a patient's T-cells against those four or five antigens, those might be almost as good as doing the complete formal test, so we're working to see if that might be a reality. If it might be much easier to translate that into a clinically viable test.

So I think that this practical application is not quite available at the moment, but I don't think it's far off. I'm being a little optimistic in saying that, but I'm hopeful that it's not far off. And if it does happen, I think it will greatly help us in being able to classify and hopefully treat diabetes, type 2 diabetes more specifically.

Dr. Buse:
This is really a very important finding, I believe. Are there any other key takeaways that you'd like to leave with our audience today?

Dr. Balasubramanyam:
So I think the kind of a word of caution, again is the fact that since we did these tests repeatedly as part of this study, we will be able to track the evolution of the islet immune reactivity, both on the cellular side and the humoral side, over the 4.5-year period that you know, each patient in the main GRADE study went through. And in the course of analyzing it. And again, it's early days, and I don't want to preempt what I hope will be a fairly, significant result we will report in the near future. There are patients who start off being T-cell or antibody-negative who then become positive over time. There are some patients who go in the opposite direction. And there's a large number of patients that stay the same. And, therefore, I think it's, it's a dynamic process, and the question will be whether our baseline findings of the correlation of being—of having this autoimmune tendency and having that correlate with beta cell function with glycemic control, does that hold up over time? Does it get worse over time? Does it get better over time? Or do people fluctuate? And if there are, in fact, different phenotypes of people, how does that affect the overall control? And again, does their response to the different classes of agents that were used in GRADE influence that evolution?

Dr. Buse:
Well, thank you. That's a great note to end on as we come to the end of today's program. I'd like to thank my guest, Dr. Ashok Balasubramanyam, for sharing insights on islet autoimmunity in type 2 diabetes. Ashok, thank you so much for speaking with me today.

Dr. Balasubramanyam:
Thank you, John. It was really a pleasure, and I really appreciate your time.

Dr. Buse:
For ReachMD, I'm Dr. John Buse. To access this episode and others from our series, visit ReachMD.com/DiabetesDiscourse where you can be Part of the Knowledge. Thanks for listening.