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The Impact of RADIANT: A Deep Dive into the Study

Dr. Buse:
Welcome to *Diabetes Discourse* on ReachMD. I'm Dr. John Buse, and joining us for a discussion on the RADIANT study and its early results is Dr. Louis Philipson. Dr. Philipson is a Professor in the Department of Medicine and Pediatrics at the University of Chicago.

Lou, thanks so much for speaking with me today.

Dr. Philipson:
Oh, my pleasure. Thanks for having me.

Dr. Buse:
It's really a pleasure to get an opportunity to interview you, but in full disclosure to the audience, we go way back to being co-interns the first day of our internship, co-residents, co-fellows, co-faculty members at the University of Chicago, longstanding friends and collaborators, but getting to talk to you about the RADIANT study, which you really pioneered in a lot of ways, I think it's a great service to mankind and really an opportunity for the audience members to get involved in new discoveries with the opportunity to drive the development of new drugs and diagnostics in diabetes care.

So let's start with you telling the audience a brief reprisal of the long story of your involvement in discovering genes associated with diabetes and how that can impact the treatment and health of patients.

Dr. Philipson:
Well, interestingly enough, as always, this started with other people, our teachers. In fact, in this case literally our teachers. So back in the '90s, Graeme Bell, Ken Polonsky, and a few other people internationally, Japan, Europe, started looking at genes that caused monogenic diabetes. And without belaboring all those wonderful *Nature* and *Science* papers and everything that happened between, say, '95 and 2003, there was a remarkable outpouring of the knowledge that there are many different kinds of diabetes. But after 2003 or so, it got quiet again, and people thought these were just too rare to be worried about.

But then a remarkable thing happened thanks to the group at Exeter. So Andrew Hattersley and his group with people in Norway, France, Italy, and Japan put monogenic diabetes back on the map with neonatal diabetes, so the KCNJ11/KATP story of kids who were born with diabetes, and we got very much involved in that with one of the first cases—not the first case but one of the first cases in the United States—and so then two things happened. We started our own monogenic diabetes registry, which I'm happy to talk about some more, which now has over 4,000 people in it in over the last 15 years, and from that we started RADIANT. So RADIANT was in response to an RFA from the NIDDK to exactly identify new kinds of rare and atypical diabetes.

Dr. Buse:
Wonderful. With that background in mind, can you tell us about the RADIANT study and who you're trying to enroll? And then later, we'll get to how people in the audience could actually help enroll patients.

Dr. Philipson:
Absolutely. So that's terrific. I think at this point, as I said, we've enrolled something like 1,400 folks in RADIANT, so what we're looking for are really new kinds of what you might call subsets or subtypes of type 2 diabetes. Of course, the problem is we're not good at this. Most doctors are not good at making a diagnosis of diabetes. And going back years, that's been one of our issues is you really need to start diabetes treatment with making a diagnosis. You can't look at somebody and say this person has type 1 or type 2, or as we're doing "other," one of the many kinds of monogenic diabetes. It turns out we're not even good at making a diagnosis of type 1 diabetes because something like 10, 20 percent of the people enrolling in RADIANT who are thought to have atypical type 2 diabetes, have type

1. They still have antibodies against islet antigens that were either not looked for or missed. So we're looking for people who are not type 1, so no evidence of autoimmunity. They may not have insulin secretion, but they may have a lot of insulin secretion, and for whatever reason—and there are many—could be a syndrome, it could be something with multiple organ involvement, it could be pure diabetes, but for whatever reason a clinician says, "Gee, that's strange," and that is the signal for maybe making a referral to RADIANT.

So we don't want to be too heavily genetically biased here. One of the concerns about precision medicine in any field is that it really comes out of genomics, and unless you do sequencing, we're not interested, and that's not right. And, in fact, many of our most interesting "gee that's interesting" patients don't have a family history. And, in fact, now that we've done whole genome sequencing on a large number of these folks, we may not find a gene at all. So it could be something that is subtly genetic; it could be something acquired; it could be something that we don't understand is autoimmune or beta cell failure or extreme insulin resistance for some other reason. So I think whatever those things are—whether it's someone who's not obese or obese-plus or having odd amounts of insulin requirements or intermittent insulin requirements—that's something that's interesting.

Dr. Buse:
So bottom line atypical diabetes, something that isn't just ordinary run-of-the-mill, I've seen it a thousand times just like this.

Dr. Philipson:
Yeah. And sadly, even those, it's not like we know what causes those. I mean our friend Dr. Powers recently gave a talk, and he said, "The only thing wrong with diabetes today is that we don't know what causes type 2, and we don't know how to best treat it, so other than that, we're good." So I think we are used to seeing obesity-related diabetes. We're used to seeing people who might be young, thin, and who look like they have type 1 diabetes. And, of course, there's a certain percentage of people who are antibody-negative anyhow with type 1, so figuring that out can be challenging, and we can help do that. In RADIANT, for example, when someone is enrolled, we repeat the antibodies at a standard lab, and we also will check the type 1 genetic risk score, so that's very interesting. So that is something promulgated by Richard Oram at Exeter, which looks at anywhere depending on exactly what version of the genetic risk score, anywhere from 10 to 30 single nucleotide polymorphisms that at least show that there's a predilection to autoimmunity, and a very high score would really tell us that this is likely to be autoimmune, and we may not go ahead with that. So lots of interesting aspects here, and many genes, many syndromes have now come to our attention, so the next step is forming these special interest groups where different scientists are recruited to study the particular syndromes that are being uncovered.

Dr. Buse:
So what are the risks and benefits to people, and by extension their providers, who enroll in the RADIANT study?

Dr. Philipson:
Yeah. So that, of course, is critical. We think the risks are generally modest, but people see risks differently. So what has to happen when a clinician sends us a potential participant in the study is that first they enroll. So there's some documents, they fill out some history, and there's an initial screening process, so if they have a known form of monogenic diabetes, RADIANT is not for them. We can enroll them in some other study like our monogenic registry where we're particularly interested in following folks with known things. On the other hand, if they've had screening and a family history and nothing has come up, then we're very interested. If they have been ruled out for a bunch of other things, then we're interested. But in general, we'll help decide whether that person should be enrolled.

So the first thing that could happen, we worry about, for example, is breach of confidentiality in any study because we can do this in people from all over the country. So there are about 14 centers distributed across the United States, but the initial parts can be done anywhere over the internet, so we collect that information, we collect genetic information, so we do worry, and people are worried about breaches of confidentiality. And then once we get into the study for those people who are considered to be proper candidates for what we're trying to do, we will bring them to one of the centers for an in-person visit. So there's some cost. I mean, travel is cost and time to our volunteers, but we're reimbursing all of the travel costs and stays if there's a hotel involved. So right now, I wouldn't say there's huge risk.

Dr. Buse:
How would a patient actually get involved in the study or sign up?

Dr. Philipson:
Well, there's many different ways, but usually, they can just go to the internet. So the website atypical diabetes network.org, the participant can sign up right there. We've had great referrals from diabetes educators, from nurses occasional pharmacists, so they can refer people to that website, and they just start the process themselves without really having a referral from a medical provider.

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. Louis

Philipson from the University of Chicago about the RADIANT study.

So, Lou, given everything we've discussed so far, can you tell us about a case from RADIANT and the findings and what new it taught us about diabetes?

Dr. Philipson:
Well, we're still at a very early stage of RADIANT, so many people are going through the process now even—it took us two years of work to get the protocol really going once funding was established, and now we've been really doing that for, this is the end of the third year, beginning of the fourth year—so one paper has already been published. So that study mentioned several interesting variants that really had not been understood before. Either the gene, so this particular genetic unusual forms of diabetes—and, of course, we have a whole list of folks who don't have a gene—and so we're not ready to report that yet, but we mentioned a gene, called SMAD5, S-M-A-D 5, another gene called NF kappa B1, and even the IGF-1, so the IGF-1 receptor amongst others.

So in some cases there were links, so it wasn't completely a shock. So we knew that there were either animal models or studies of islet or target or insulin target tissues that implicated these sorts of pathways, but in most of these cases, there's never been a report of that particular change, so when one of the subjects had an insulin gene mutation. Now, in fact, our group was the first one to put insulin gene mutations back on the map a few years ago in neonatal diabetes, but since then there's been an increasing number of mutations in the insulin gene itself.

So it was not a surprise that severe neonatal diabetes was associated with insulin gene mutations, but this particular variant in the insulin gene caused a form of adult-onset diabetes, which we're seeing also increasingly, but these are among the rarest of the rare forms of atypical diabetes.

So we're very excited about the genetic forms, and there's now a whole bunch more. Every couple of weeks we get together. We have something called a discovery meeting and upwards of 20 folks. I think we had almost 30 people are on the call where geneticists and the clinician investigator discusses that particular participant in a deidentified way for the most part, although we have to have some details of the person. We review the case, the family history, and the genetic findings, and then we make suggestions as a group as to what sorts of things might happen next. So that's the most fun part of the study so far.

Dr. Buse:
Before we close, is there anything else you'd like to share with the audience?

Dr. Philipson:
Well, just that I think this whole movement to understand a better way of doing diabetes, so I think at the beginning what we're going to see more and more is an understanding that diabetes isn't one thing, it isn't two things, and it's probably many things, so you have to start with doing that. We have to be able to operationalize doing genetic testing and taking family histories right in the clinic. I mean, that has to be coin of the realm, standard clinical practice. We have to be able to get antibodies for islet antigens as standard clinical practice. So that will be themes, I think, over the next decade to better understand precision medicine, how we can do the right drug for the right person at the right time and yet have it cost-effective, so that, I think, is our vision and how RADIANT fits into that idea of the future of diabetes diagnosis and care.

Dr. Buse:
Yeah. I mean, I think that nails it really that this is the future of diabetes just happening now through baby steps trying to find our way to that future. So, Lou, thank you very much for speaking with us. This has been a really important conversation.

Dr. Philipson:
Thank you so much.

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