Transcript Details
This is a transcript of an educational program. Details about the program and additional media formats for the program are accessible by visiting: https://reachmd.com/programs/diabetes-discourse/exploring-precision-medicine-in-the-treatment-of-diabetes/14210/

ReachMD
www.reachmd.com
info@reachmd.com
(866) 423-7849

Exploring Precision Medicine in the Treatment of Diabetes

Dr. Buse:
With therapeutic advances continuing to emerge, diabetes treatment has changed over the years. Incorporating precision medicine into treatment may change the way clinicians approach the management of patients with diabetes altogether.

Welcome to *Diabetes Discourse* on ReachMD. I'm Dr. John Buse. And joining me to explore the potential role of precision medicine in diabetes treatment is Dr. Jose Florez, a professor at Harvard Medical School. He's also the Chief of the Endocrine Division and Diabetes Unit at the Massachusetts General Hospital, and he holds the John T. Potts Jr., MD Endowed Chair in Medicine.

Dr. Florez, thanks for joining me today.

Dr. Florez:
My pleasure to join.

Dr. Buse:
Well, Jose, we're old friends. You're one of the premiere people in genetics and diabetes. Can you start us off with what precision medicine means to you? And how can people start to think about applying this to diabetes treatment?

Dr. Florez:
Absolutely. Precision medicine is about making sure that when we make prescription decisions we are applying the right treatment to the person at the time that the person needs it. And in particular for diabetes, we have so many options, particularly in recent years, and the way that the algorithms that you and others have developed are applied to people, they are based on things like comorbidities. They are based on things like cost and side effects and so on, but seldom are they based on the specific pathophysiology that leads to the person's form of diabetes. So I may prescribe something because they have coronary disease or they have renal disease or they are afraid of falls and hypoglycemia, but I'm seldom evaluating the patient from the point of view of the patient's physiology and saying can I apply the medication that really addresses the particular pathway that is deranged in this person's manifestation of diabetes. So that's the nextincrement that we need to make.

Dr. Buse:
That's really quite clear. So, what is the next thing we need in order to be able to start implementing precision medicine into diabetes treatment?

Dr. Florez:
Oh, yeah, so there's a number of things that really need to come into place. So one is we need a better understanding of the subtypes of type 2 diabetes. If you think about it, if a person's hyperglycemia, which is the end result of many pathophysiological processes—if that hyperglycemia is not caused by autoimmune destruction of beta cells, which we call type 1, or is not caused by single-gene defects, most typically MODY, then we call it type 2 diabetes.

But there's many different ways to get to hyperglycemia beyond those two: autoimmune destruction of beta cells or single-gene defects. And so, type 2 diabetes really is a conglomerate. It's a diagnosis of exclusion, and it's very heterogeneous, and so the first thing that we need to do is to really develop ways in which we can categorize people with type 2 diabetes in a much more granular way, and that can be genetics, but it might also be biomarkers, for example, C peptide levels or response, things like BMI, etc. There needs to be a much more sophisticated way of coming up with the subtypes of type 2 diabetes. That's number one. Then number two, we need to study the various agents at our disposal and see which of the drugs work better in a specific subgroup of people, so we need to do the studies that will show that people respond better or worse depending on their subtypes that they have and the metabolic state at the time.

© 2023 ReachMD

Dr. Buse:
Well, it seems like you've largely framed this on omics, but isn't it possible that you could take a diet history and see that some people are getting 70 percent of their calories from carbohydrates and other people are getting 20 percent of their calories from carbohydrates and that there might be, you know, for instance, acarbose might work better in the people that are eating lots of carbohydrates? Is that legitimate precision medicine to look at lifestyle factors or social determinants of health?

Dr. Florez:
Absolutely. Absolutely. No, you make a very good point. You know, each person is not simply the endogenous factors that lead to the person's physiology or metabolic state but also the external circumstances in terms of lifestyle, in terms of diet, in terms of exercise, in terms of pollution, etc., so absolutely. The question then is for the methods that we have to collect that information, you mentioned the dietary questionnaire, how accurate are those methods? And maybe we can come up with some metabolite that you measure in serum that is indicative of the person's diet and that captures that information maybe more accurately.

So I think, you know, we need to apply these technologies that are now available to us that capture entire axes of biology and then see what is the most parsimonious and cost-effective measurement, whether it's a behavioral measurement or a biochemical measurement, that really collects that particular axis of the person's biology, but, you know, maybe there is nothing that we can measure that is better than a dietary questionnaire or than an actigraphy record or than a CGM or things of that sort.

Dr. Buse:
Great. So, can you give us a real example of precision medicine at work in clinical practice today?

Dr. Florez:
Yes. So, in diabetes it's fairly clear when we come to the monogenic type of the disease. So, we typically, as endocrinologists or primary care physicians, when somebody comes with diabetes, our first decision point is making sure they don't have either type 1 or type 2 because we know that for type 1 they need insulin, as their major defect is complete absence of insulin production, but there are some cases that may be a little confusing. And when we look at maturity-onset diabetes of the young, which is diabetes that manifests itself in the first few decades of life, say, you know, before age 20 or 30, in a lean patient with a strong family history, but with a nonketotic presentation, meaning they don't need insulin up front, they don't have DKA, that typically is the clinical criterion for maturity-onset diabetes of the young, or MODY, caused by single-gene defects in a number of genes.

Now, if you don't go through that exercise and you assume that because the patient is young has type 1 diabetes, you will be prescribing insulin, and if you think that because the patient is maybe a little older and they don't have DKA and their antibodies are negative that they have type 2, you'll be prescribing metformin because that's what the algorithms call for. Now, it turns out that if you have mutations in the transcription factors that operate in the beta cell that give you MODY, the best medication for you has been demonstrated as a sulfonylurea. And so, in either case, whether you make the mistake of assigning type 1 and prescribe insulin or type 2 and prescribe metformin, you're not giving the patient the medication that works best for them, which is a sulfonylurea. If, on the other hand, they have a mutation in glucokinase, which is basically the Glucostat of the organism is the enzyme in the beta cell that regulates insulin secretion on the basis of glucose concentration, people who have mutations in glucokinase don't need any treatment unless they happen to be pregnant, and then there's a more complicated algorithm you follow.

So, making the diagnosis of MODY diabetes, whether it's transcription factor MODY which requires a sulfonylurea or glucokinase MODY that essentially requires no treatment, is essential to make sure that the patient receives the therapy that corresponds to their type of disease.

Dr. Buse:
Thank you. 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. Jose Florez about precision medicine in diabetes.

Switching gears a bit here, Jose, what are some of the benefits of utilizing precision medicine in diabetes care?

Dr. Florez:
All of us who treat people with type 2 diabetes, we see that we end up escalating therapy, you know, and we start with metformin up front, and then there's, you know, the consensus guidelines that have been developed by the professional societies that tell us, based on the patient's comorbidities, do we add a GLP-1 receptor agonist, do we add an SGLT2 inhibitor, at what point do we incorporate insulin, but essentially, it is an escalation. And what we also do see, we know that up to 25 to 30 percent of our patients will fail metformin therapy within the first five years, as shown by the ADOPT study. And then in young people, it's even a lot worse. 50 percent fail metformin therapy within five years as shown in the TODAY study.

© 2023 ReachMD

So we are prescribing medications that don't always work, and then we are adding therapy upon therapy with a consequent cost to the healthcare system in addition to potential for side effects when you have polypharmacy. So, would it be a lot better to know exactly what medication is going to work best for a particular patient and then keep them on that single medication or a couple of medications so that their beta cells survive the longest and their physiology is maintained as close to the normal range as possible? It would prevent the potential development of side effects when you have polypharmacy, it would save dollars to the healthcare system, and it would save frustration from the clinician and the patient, when they are being treated with ineffective medications.

So I think that's the aspiration for diabetes, better treatment that is better tolerated, that is most effective and that leads to the—to prevent the complications that assail people with diabetes.

Dr. Buse:
So let's take it just a step further. As you imagine the primary care provider of the future, how is this really going to work?

Dr. Florez:
Well, so, obviously, there are many people with type 2 diabetes, and not everybody is going to be doing any omics, so what needs to happen is that we need to make it simple at the point of care for any practitioner and affordable, sustainable, not only in the United States, not only in people who are well-insured, but really in resource-poor settings. So I think the way I would imagine is that as we do these studies, we will hopefully come up with a profile that characterizes the subtype of the person's diabetes that is relatively inexpensive and affordable. Say, for example, genetics. So, genetics, if you think about it getting the person's inherited germline sequence only needs to happen once in the person's lifetime. It is easily accessible from peripheral blood. You can either sequence or genotype the DNA. And then you have a trove of information that can be stored in the person's medical record and be there for the person's lifetime, not only for diabetes but for any disease.

And so I think given the continuing reduction in sequencing costs, it is not too far-fetched to imagine that at some point everybody will have genomic information as part of the medical record. And so that information is already stored, and then we do the studies that show that a particular genetic profile is going to predict enhanced response to a drug. Then, when those studies are done, then that will be captured in the person's medical record. So the practitioner really only needs to do is to make the diagnosis of diabetes, and then the algorithm would spit out the treatment decision that the physician or the clinician needs to implement at that point. I think that is the dream, you know, where things like genomic information is obtained in everyone and is stored, and then we are doing the studies in the background that show that a particular genetic profile can alter treatment.

I think, you know, within a decade that's the kind of thing that you can imagine in healthcare systems, at least in the developed world.

Dr. Buse:
Well, you know, it's interesting to also think about the possibility of perhaps investing more in omics and then really trying to understand prevention strategies from an omics perspective. You know, as more drugs become generic, the real possibility is there I would imagine as well. But this has been fascinating. We're just about out of time. Before we close Jose, do you have any final takeaways you'd like to leave the audience with?

Dr. Florez:
Well, you know, I think the one maybe concern that we need to flag is the equity concern. You know, it can't really be that this is the kind of medicine that is only available to a subset of the population or a particular ethnic group because that's where the studies have been done. This is something, you know, that our DNA, our genetics, they're all of human kind's patrimony and so it really should benefit all of us. And so, when we do these studies, you know, we need to make sure that they are reproducible, that they are interpretable, that they are actionable, but also that they are sustainable and equitable.

Dr. Buse:
Thank you very much. With those final thoughts in mind, I want to thank my guest, Dr. Jose Florez, for sharing his insights on precision medicine in the treatment of diabetes. Jose, thank you for this great discussion.

Dr. Florez:
Thank you so much for inviting me. Very nice conversation, John.

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.

© 2023 ReachMD