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Investigating Interventions: The Role of Lifestyle Changes in Preventing Diabetes

Dr. Buse:
We have known for years that patients with prediabetes can have the onset of diabetes prevented or delayed by intensive lifestyle intervention. Current guidelines suggest screening for diabetes and prediabetes in at-risk patients so over time more at-risk patients with normal tests will have a result consistent with prediabetes. What are the impacts of lifestyle interventions in this patient population?

Welcome to *Diabetes Discourse* on ReachMD. I'm Dr. John Buse. And joining us to explore prediabetes and the impacts of lifestyle interventions is Dr. Samuel Dagogo-Jack, a Professor of Medicine and Chief of the Division of Endocrinology, Diabetes and Metabolism at the University of Tennessee Health Sciences Center in Memphis.

Sam, thank you so much for joining me today.

Dr. Dagogo-Jack:
Thank you, John. My pleasure.

Dr. Buse:
As background, what are the current guidelines telling us about screening for diabetes and prediabetes? And in particular, the U.S. Preventive Services Task Force has embraced screening for diabetes and prediabetes. Is that correct, Sam?

Dr. Dagogo-Jack:
That is correct, and that could not come at any time sooner, because for decades, the ADA has drawn attention to the stages of metabolic impairment before clinical diabetes is diagnosed and more recently has been promoting the idea of screening asymptomatic people for diabetes and prediabetes, and the targeted screening has looked at people with risk factors, people who are overweight or obese, and I might add those who have a family history of type 2 diabetes. So, basically, all adults, most adults in the population should be eligible for a simple blood screening for prediabetes.

Dr. Buse:
Yeah. And, you know, to get more specific, I think the recommendations are in general people 35 to 70 with overweight or obesity and remembering that in Asian-Americans overweight is all the way down to a BMI of 23. And not a great deal of preference about using the fasting plasma glucose test or a hemoglobin A1c or an oral glucose tolerance test. Do you have any preference in clinical practice about what kind of screening test you do?

Dr. Dagogo-Jack:
The simplest would be the fasting glucose provided there was verifiable or reasonable duration of fast, somewhere between 18 and 14 hours of fast. It's cost-effective, simple. Reproducibility is better. The far end of preference would be the oral glucose tolerance test. There are arguments in favor of maybe increased yield, but the methodologic problems are not trivial, and for a wide, large-scale community screening, screening centers and community physicians, hospitals, probably are ill-equipped to go through these standardized provisos and precautions needed to get a valid, reproducible oral glucose tolerance test. And people have defaulted to the A1c as a tool that is diagnostic as to fasting conditions, that has a stronger pre- and post-analytic stability of sample and somewhat better reproducibility than OGTT. For prediabetes, however, we do have factors that can disrupt the presumed tight correlation between A1c and average blood glucose at the lower ends of the glucose range, sufficient stochastic disruption to have individuals be at risk of being overdiagnosed or underdiagnosed with prediabetes if we use just the A1c.

There are also data that certain ethnic groups are more liable to have a false flag A1c with regard to the level of blood glucose, so they

tend to have measurably higher A1c levels compared with their ambient blood glucose levels. So, if you had a group of African-Americans or Latinos, as has been published in the Diabetes Prevention Program dataset, even Asian-Americans, and then you have a comparison group of European descended, Americans, and you made sure that their blood glucose profiles were similar, fasting and two hour plasma glucose levels are similar and you compared the A1c levels, you would be chagrined to find as much as 0.4, 0.5 percent higher A1c among the non-European populations compared with European populations for the same blood glucose level. And this departure is likely to be more bothersome or troublesome in the prediabetes range because you would be more likely to label somebody with a diagnosis, and in the early stages of diabetes with A1c 6.5 being diagnostic. If you could be wrong as much as half a percentage point in an individual from a certain population, then there could also be a risk of inappropriate treatment; heaven forbid you select a glucose-lowering agent or sulfonylurea for somebody without first checking the glucose.

So my approach has always been to use the A1c as a convenient tool but does not require fasting, that when levels return at the low, marginal, borderline territories, to always recommend confirmation with actual blood glucose measurement. After all, diabetes is a disorder of glucose metabolism, not of A1c metabolism. The fact that A1c is available as a test is a convenience tool, not a replacement for the primary disorder of glucose and carbohydrate metabolism.

Dr. Buse:
Very eloquently stated. But let's dive into your study now. So the study was published recently in the BMJ Open Diabetes Research & Care. The study's name, "Pathobiology and Reversibility of Prediabetes in a Biracial Cohort." Tell me a bit about what were your primary objectives in conducting this study.

Dr. Dagogo-Jack:
The Pathobiology and Reversibility of Prediabetes in a Biracial Cohort Study, PROP ABC for short, is a spinoff from the parent study that has the acronym of POP ABC, P-O-P A-B-C, which is simply the Pathobiology of Prediabetes in a Biracial Cohort. That study was initiated back in 2006 and set as its goal the definition of the biological basis for progression from normal glycemia to prediabetes among high-risk African-American and European-American individuals. The goal was to follow them, and we did follow them, every three months for five years for the primary outcome of progression from normal to prediabetes.

So, at the end of five years, when we published our finding that race ethnicity was not a predictor of progression from normal glycemia to prediabetes among individuals that were similar in terms of parental diabetes burden, we also published several other determinants, physiological measurements, mainly insulin sensitivity, insulin secretion, adipocytokines, amino acids, metabolomics, so many things that differed between those who remained normal glycemic and those who moved on to prediabetes. We called this marker as predictors of escape from normal glycemia.

We received funding in 2012/2013 to invite the original POP ABC participants back and then continue to follow those who had not yet developed prediabetes, follow them when they change from normal to prediabetes and at the same time offer lifestyle intervention to the 30 percent or so whom we had previously ascertained to have departed from normal and arrived at the prediabetes state.

So, what we then did over the next five years was to roll into lifestyle intervention any newly occurring cases of prediabetes while already have the preexisting cohort who are prediabetic into the lifestyle itself, and we knew from my experience in the Diabetes Prevention Program, DPP, that lifestyle works. We've got about 15 percent risk reduction relative to placebo in the risk of progression from prediabetes to type 2 diabetes.

We could time the development of prediabetes to a finite duration, give or take three to six months. And since that was a unique property of our cohort, we decided to test the hypothesis whether duration of time in the prediabetes state, whether that duration was an important predictive variable as to whether lifestyle intervention would work very well or not work well at all in either reversing the prediabetes back to normal glucose regulation and/or preventing its progression to type 2 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. Samuel Dagogo-Jack about prediabetes and lifestyle interventions.

So, Sam, you've set the table. I love this paper, but you have to share the results with the audience. What happened to these people with prediabetes?

Dr. Dagogo-Jack:
So, well, as a group, they were very, very responsive to the lifestyle intervention—diet and exercise, basically, which we modified in them—and 93 percent of them did not develop type 2 diabetes. And nearly 44 percent no longer had prediabetes. They had reverted to what we call normal glucose regulation. Among these hundreds of individuals who now have opportunity to, treat with lifestyle intervention, they had prediabetes for a short period, three months, six months, or three years, three to five years, or more than five

years since we had been monitoring them since 2006 with the start of the POP ABC study. So we divided the lifestyle intervention recipients into those who had had prediabetes for the shortest duration, less than three years—in that group people had had it for as short as just three months—and then an intermediate group, people whose prediabetes was diagnosed three to five years before they made their first visit to the lifestyle counseling session, and then a third group, the longest duration that had prediabetes diagnosed five years or longer before they arrived at the lifestyle intervention clinic for their first session.

For as long as individuals who are referred for lifestyle intervention, 50 percent of them the prediabetes they don't get worse, 44 percent it went away, and in only about seven percent or so did it worsen to diabetes. So our study confirms and extends the previously reported landmark studies regarding the highly effective nature of modest lifestyle modifications, specifically increased caloric expenditure from physical activity and decreased caloric intake from saturated fat and carbohydrates, the impact of these modest changes in locking in substantial metabolic benefits among those who have prediabetes either by preventing them from sliding further to diabetes or, even better, erasing the prediabetes and resetting their metabolic clock, if you will, to back in the days when they had pristine normal glucose regulation.

Dr. Buse:
It's really exciting. You know, 93 percent non-progression is extremely impressive when we compare to other interventions, and doing this in the African-American community really important for a community that's suffered such disparities in outcomes, in diabetes. I'm sure you have aspirations for how this gets translated into clinical practice. Could you tell us about that briefly? What do you think we should be doing tomorrow, next week, in our clinics?

Dr. Dagogo-Jack:
John, that is the point, and I'm glad you brought it up. There are more than 19 million Americans with prediabetes right now. The vast majority are unaware of their status, and their caregivers are also largely unaware because they are either not screening or not digesting this screened data. So the opportunity here is to increase and amplify the U.S. Preventive Task Force recommendations, the ADA guidelines and the numerous other authoritative associations' guidelines by raising the volume of the drumbeat in primary care environments.

The current something that needs to be done does not necessarily involve chemicals, medications or molecules. It involves a heart-to-heart talk with the patient to apprise them of the clear and present danger of future harm that can be averted by present action and to expose them to the DPP type protocol, which is now on the Centers for Disease Control website and quite widely known now, of modest reductions in calorie consumption and modest increases in physical activity maintained and repeated three to five times a week as a habit, and that these nonpharmacological approaches, when prescribed by meaningful and well-informed clinicians, can yield dividends beyond measure.

We need to expand our consciousness that the correct expectation is that any individual's blood glucose result or A1c result can give information of one of three natures: normal, prediabetic, or diabetic. We have been operating in a binary mode. We need to go into a ternary mode and then insert the prediabetic intermediary halfway house in our thinking consciousness so as to trigger appropriate clinical behavior.

Dr. Buse:
Well, thank you so much. That's so well said. And with those insights in mind, I want to thank you, Dr. Sam Dagogo-Jack, for sharing your insights on prediabetes and lifestyle interventions, and I really appreciate you joining us.

Dr. Dagogo-Jack:
Thank you, Dr. Buse, for the opportunity to talk about our work.

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.