

Patient Perspectives for PCPs: Tackling the Treatment Paradigms of Obesity, T2D, and Other Metabolic Disorders

DIABESITY DIALOGUES

DIABESITY DIALOGUE 2

TWIN EPIDEMICS: PRIORITIZATION OF OBESITY AS A TREATMENT TARGET IN T2D

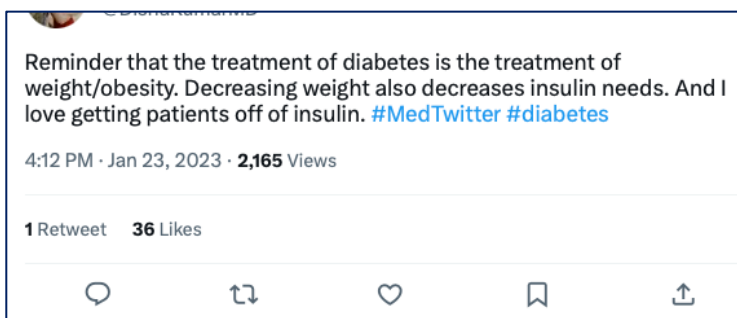
Jamy Ard, MD: Welcome to the Diabesity Dialogs. I'm Jamy Ard, Professor at Wake Forest School of Medicine, and I am joined by my hero and esteemed colleague, Dr. Bob Kushner. Dr. Kushner, would you like to introduce yourself please?

Robert Kushner MD: Oh, Jamy, please, please. I don't know about hero, but I'm pleased to be with you. I'm Bob Kushner. I'm a Professor of Medicine in Medical Education, Northwestern University, Feinberg School of Medicine, Chicago, and I'm absolutely pleased to be here with you, Jamy.

Dr. Ard: Great, well, thanks for joining me. Over the course of four episodes, Bob and I are exploring this discussion about Type 2 diabetes and obesity, trying to just be candid and honest about it, doing a deep dive into the latest clinical data. And we really want to highlight some of the new information about GLP-1 receptor agonist GIP/GLP-1 receptor dual agonist treatment.

we know it's gaining a lot of attention in the media for treatment of diabetes and obesity. So we want to have a deep discussion on that, and we're going to really sort of make sure we hear patient voices, and we'll discuss how we can ensure that their needs are met. This is Episode 2 of our series, and we're glad to have you here.

So, Bob, let's, let's kick off this episode and discuss what we're going to call the twin epidemics, Obesity and Type 2 diabetes. So let's start with this Tweet...



"Reminder that the treatment of diabetes is a treatment of weight/obesity. Decreasing weight also decreases insulin needs, and I love getting patients off of insulin."

That sounds like something I would say.

So, Bob, what are your thoughts about this Tweet? Should we prioritize weight as a treatment target for Type 2 diabetes?

Dr. Kushner: A lightning round question, yes, absolutely. We, we really are shifting very rapidly, I think, with the, with the development of the, all these new medications. A shift from a gluco-centric approach, which is really all through the 20th century and going into the century. It makes sense that we would focus on blood sugar early on as the key targets because we know that elevated blood sugar is associated with increased microvascular and macrovascular complications like retinopathy and cardiovascular disease. But we've learned so much more now that it's really, in large part, the obesity, insulin resistance, and all the other problems that are occurring that we want to focus on.

Dr. Ard: Um-hmm.

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Dr. Kushner: You know, regarding this twin epidemic, there are really good data from NHANES and, and so forth from around 1999 up to 2018; and over this period of time, the prevalence of di-, of diabetes has risen from about 10% up to about 14%. That's almost, what, 18 or 20-year period of time.

Obesity has also gone up. Currently the prevalence of obesity in the United States is over 40%, but here's, here's the key message is if you take individuals with diabetes specifically, over 60 to 90% of them have coexisting obesity, so that's where this dual epidemic comes from. Some people call it a syndemic, right? Coexistence, two chronic diseases, common fertile soil, so it makes sense. And I think as clinicians, when you see someone with Type 2 diabetes, you can almost be assured 9 out of 10 times they also are overweight or have obesity.

Okay. The syndemic, the twin epidemic here that you described really then positions us to think about, okay, well if we're going to treat obesity to treat Type 2 diabetes, then we're kind of in a really interesting time because now we have a lot of these newer Type 2 diabetes agents that are really getting traction from patients. You can see these posts that are here on the screen now.

The collage features several elements: a social media post from 'Mindset for Prosperity Mental Health & Weight Loss' dated April 20, 2022, with text about weight loss injections and hashtags like #semaglutide and #tirzepatide; a photo of a bakery counter with various pastries; a woman standing outdoors in a grey t-shirt that says 'WOMAN'; a social media post from 'MoreBitterness' dated Oct 13, 2022, asking 'Do they gain it back when they stop?'; a social media post from 'Dr. Spencer Nadolsky' dated Oct 13, 2022, stating 'Most will unfortunately.'; and a large advertisement for TIRZEPATIDE: WEIGHT LOSS MADE EASY. The ad includes text such as 'Ready to lose weight? Supercharge your weight loss efforts with our new Weight Loss Program featuring Tirzepatide home injection kits and start looking and feeling better now.' and 'Finally, lose weight and keep it off. A once-weekly GLP-1 RA for chronic weight management with significant, sustained weight loss.' It also lists benefits like 'Higher doses have been shown to increase weight reduction, improve cholesterol levels, decrease waist circumference, improve blood pressure and improve body composition.' and provides contact information for Dr. Rudy Best Life at 9655 S. Dixie Hwy, Suite 310, Pinecrest, FL 33156.

Patients are coming in with a lot of information, whether it's well-informed or mis-informed, or partially informed, but they've got a lot of information.

Dr. Ard: So, Bob, how do you talk to your patients who come in and say, "Hey, you know, I've heard about this new drug, and I saw this post, and I'm really interested in, you know, understanding if this type of drug would make sense for me because I also have Type 2 diabetes, and I'm thinking, you know, maybe this is the treatment I should be on."

Dr. Kushner: That's, that's a question, and you're seeing it too, how people are, indeed, coming in in Chicago where I, where I see patients.

Dr. Ard: Absolutely.

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Dr. Kushner: Saying, "I heard so much about it, and am I a candidate for it?"

Dr. Kushner: So the way that I, the way that I talk about it with them is that this medication has kind of two different purposes or it has two different mechanisms of action and why it's so well-purposed for treatment of diabetes.

Historically, we know that both a GLP-1 and GIP, these are called incretin hormones. They're pushed by the gastrointestinal tract, and what incretin means is that is a glucose-dependent increase in insulin, depending upon the glucose level when you take it in by mouth. So if you, if you infuse glucose in the blood stream, you get a rise in insulin to handle the blood sugar. But if you take that same amount of carbohydrate and glucose and ingest it, you get a more robust increase in insulin, and it's dependent on glucose. So that's #1. They're incretin hormones so it helps improve diabetes because it revs up or increases the amount of insulin required to clear the blood of, of sugar. That's where that insulin incretin effect comes from.

Dr. Ard: Just to ask a quick question, so then that means it won't make you hypoglycemic, right, because it's, if it's only acting once you take in the, the nutrient, so to speak, then the risk of hypoglycemia goes down. Is that, is that part of what happens there?

Dr. Kushner: That is exactly right. Thank you for cuing me up on that because actually there is a big difference from insulin and sulfonylureas, as the comparator, which it doesn't matter what your blood sugar is. It's going to pump out insulin, which makes you potentially hypoglycemic. You're absolutely right. This is glucose-dependent. If your blood sugar's normal, it doesn't have much action. As the blood sugar goes up, there's more action. And people with Type 2 diabetes, there's a blunted effect. That's why they're giving more of it. The other mechanism of action, I just want to mention, Jamy, where, where really it's the secret sauce, if you will, is that it needs drug to also have an effect on appetite regulation as the GLP-1 and GIP hormones and others from the gastrointestinal tract and pancreas have an effect on appetite regulation. So when they are given to the individual, not only help diabetes, which we just talked about, but also helps to suppress appetite, reduce hunger, increase fullness, affect changes on cravings and preference of food and thoughts of food. So it's this dual mechanism of action that is so exciting for individuals with diabetes, get diabetes under control, and at the same time help them with appetite so that they're able to lose weight at the same time.

Dr. Ard: So, let me ask you this, Bob. What would you say in your experience with your patients, and you've done these trials. You've been participating in these studies and this research that's been so informative. What would you say is the, the largest sort of consistent clinical effect that your patients will report to you once they are taking these drugs?

Dr. Kushner: Well, they're certainly very happy that their blood sugar is getting under better control, which is perhaps one of the things that they're looking at. But the other thing that they're voicing is, you know what, these medications are reducing my appetite, reducing the noise in my head thinking about food, which allows me for the first time in my life sometimes to really pay attention to my diet and not struggle with feeling restrained or feeling deprived. So that allows them to lose weight. So it's like a double hit, a win for them. Blood sugar goes down, diabetes improves, their weight goes down, and they feel more content.

Dr. Ard: Wow, that's great news for a lot of patients.

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Let's shift gears a little bit and talk about safety because something that's really effective but not safe doesn't really do much for us. And so, this is one of the number one questions I get from my colleagues here. I'm sure you get that. Is this safe?

Let's take a look at some of the trials. So, if we think about semaglutide and the diabetes program that was performed with the semaglutide compound, you have the SUSTAIN trials. And in those trials, you had comparisons between say placebo or between TZDs or between metformin and sulfonylureas, or between semaglutide and insulin, semaglutide versus other GLP-1 agonists like dulaglutide. And in all of those instances, you see really consistent performance of semaglutide in terms of a greater reduction in body weight compared to a lot of these other treatment, all, all of these other treatments. And this effect is generally sustained over a period of time that ranges in these trials, the SUSTAIN trials from 30 weeks all the way out to 104 weeks.

When we look at tirzepatide, again, dual agonist activity here, GIP and GLP-1, in the tirzepatide studies, those studies are called the SURPASS studies; and so in those studies you're comparing tirzepatide to either placebo or metformin plus alone or with a SGLT2 inhibitor or in multi-therapy, one to three drugs or with insulin and basal metformin. And again, what you see in a fairly dose-dependent manner, as the amount of tirzepatide being prescribed or used goes up from the 5 milligram, 10 milligram, 15 milligram doses, really consistent, greater amount of weight loss, and these are trials again that go from 40 to 52 weeks in people with diabetes. So, two new compounds that really sort of show a greater effect for GLP-1, GLP-1/GIP dual agonism in terms of what you just talked about, reducing blood glucose but also seeing weight reduction.

So we're all waiting for the SURMOUNT-2 trial, which is going to report out in another month or so at the American Diabetes Association meeting that's looking at tirzepatide in adults with overweight or obesity and Type 2 diabetes. So we're all really excited about where those data will land.

So, Bob, after going through all that information, you know all of that data very well, what's been your impression for the potential benefit of these drug classes, this drug class, the incretins, mimetics on treating diabetes and obesity when we see that there's a significant overlap between those two diseases in the same patient?

Dr. Kushner: Yeah, incredibly impressive. Yeah, we are truly treating a dual epidemic we call diabetes because this drug hits both of that, obesity and diabetes.

And one thing I want to emphasize is that these agents have shown reduction in cardiovascular risk, and that is in MACE events, and they are now preferred agents by the American Diabetes Association as kind of the top line when you have someone who has Type 2 diabetes and one of the goals is weight loss, which is probably true in about 90 or 85% of individuals.

So, and you're seeing significant reductions in hemoglobin A1C, 2% or so, and reductions in body weight of, you know, 15, average 15, 20% body weight using these agents. So, it is truly a, a, a paradigm shift in how we are treating this combination of obesity and diabetes.

Dr. Kushner: Yup. Jamy, let me, let me flip this on you. I'm going to ask you a question-

Dr. Ard: Okay.

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Dr. Kushner: -in Episode 2. So you covered a lot of data, which is, which is difficult to do, but I think you did a great job; and I'm sur-, I'm hoping it clears up a lot of misconceptions surrounding these new agents. But in the end, most patients are used to only hearing about insulin and metformin when they think about Type 2 diabetes. Only recently are they hearing more about the other types of Type 2 diabetes treatments that address weight loss as well.

So how do you, I kind of did a little bit when I explained the action of it, but how do you explain to a patient how these drugs work differently than other Type 2 diabetes medications such as metformin or insulin? What type of patient do you see these new agents or, single or dual agents, work, work best for?

Dr. Ard: So, when I talk to patients with diabetes and obesity about the potential for these drugs, I like to talk about it from both an intake and a utilization endpoint, perspective.

So what do I mean by that? Well, it's a, part of the challenge with what has led to Type 2 diabetes for you might be the fact that you've been gaining weight over time. And we know that if we treat that weight gain and help you get to a lower reduced body fat state, then you will actually see an improvement in your blood glucose; and we also know that we can help your body in the meantime work a little bit more efficiently by using this particular type of drug because it's going to help you get insulin when you need it, exactly the amount that you need to kind of help you get over the hump and clear that blood glucose effectively.

And by, by way of slowing down the emptying in the stomach, that's also going to help decrease how quickly your blood sugar goes up, right, because in a lot of people, they get that first dump of glucose into the blood stream, and they can tell you when they put that CGM on. "Man, I ate that," you name the bowl of cereal, "and, you know, my blood sugar shot up, you know, within minutes. And it stayed high fairly long. And then when it dropped, it dropped fairly precipitously; and I felt hungry again right after, and then I had to eat again." So they start to see that pattern, and I say, you know, "This drug is going to help smooth that out, and you're going to, you're going to get the benefit of, one, eating less because you just fill up faster and you fill full earlier. And that that you eat will go a little bit further and be a little bit more smooth in terms of its release of the blood glucose into the blood stream. And all those things are going to help you in terms of diabetes control.

Dr. Kushner: Good one. It works for me.

Dr. Ard: It works for you? All right.

Dr. Kushner: Yup.

All right, so this wraps up Episode 2. We hope you got some valuable information about the current treatment landscape, and we hope that you feel better positioned to talk to your patients about this idea of, you know, treating diabetes by treating obesity. And I think we can make a lot more progress in that twin epidemic if we're really sort of moving from, like you said, Bob, that gluco-centric point of view to more of a body fat-centric point of view and really, you know, sort of addressing those issues.

So we'll see you next episode where we're going to discuss the need for effective management of diabetes and complications, comorbidities. So stay tuned.