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Revolutionizing Care for Patients With T2D and Obesity: From Pathophysiology to Personalized Treatments

Announcer:
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[CHAPTER 1]

Dr. Kahan:
Treating obesity is a cornerstone for the prevention of management of type 2 diabetes, in some cases, even causing disease remission.

This CME is on ReachMD, and today we’re going to discuss some important questions surrounding diabetes and obesity, including emerging therapies for weight loss in patients with type 2 diabetes.

I’m Dr. Scott Kahan.

Dr. Wysham:
I’m Dr. Carol Wysham.

Dr. Fujioka:

And I’m Dr. Ken Fujioka.

Dr. Kahan:
In our first chapter we’ll focus on the pathophysiological nexus between obesity and type 2 diabetes, illuminating the pathways through which one condition intricately influences the other.

Carol, can you elaborate on the specific molecular mechanisms linking adiposity to type 2 diabetes?

Dr. Wysham:
It’s no secret to anybody listening that there’s been an increase in diabetes related in large part to the increases in average weight and obesity in our population. What we understand is that the presence of central adiposity, or upper body adiposity, is associated with much higher risk than lower body. And this is primarily because it’s a marker for ectopic fat deposition, not only in the viscera but also in the liver, in the skeletal muscle. And this all leads together to cause increase in insulin resistance. Furthermore, there are changes that happen in obesity that affect beta cell function and may very well be related to decrease in beta cell mass. So increase insulin resistance, decrease beta cell mass together results in hyperglycemia that leads to diabetes.

So, Ken, can you tell us why incretins are such good therapies for patients with diabetes?

Dr. Fujioka:

So let's define what are incretins. And incretins are hormones. There's 2 main ones, GLP-1 and GIP, and they come from the small intestines, and they go up to the brain, and they tell the brain, "I'm full. It's okay, you don't need to eat any more." The other very important thing they do, which is what we really first all got excited about, was they go to the pancreas and tell the pancreas, "Hey, make insulin because there's food in the intestines and you're going to start getting a lot of glucose or carbohydrates." So they are just such a key part.

Again, incretins have been, to me, the biggest boon in diabetes because you're not treating one thing. You're treating the blood sugar, but also the weight.

Dr. Wysham
So it's clear that the GIP is playing a role, and we're particularly interested in the fact that GIP has a specific impact on the adipose tissue.

Dr. Fujioka

Scott, I got a question for you. What's the biggest obstacle to sustaining weight loss in a patient with type 2 diabetes? And as we know, diet and exercise is not always all that successful.

Dr. Kahan:
When you're carrying a lot of weight and you lose a good amount of weight, there's a metabolic adaptation that tends to occur. A range of hunger hormones and satiety hormones tend to react to the weight loss such that people get physiologically hungrier and get less full with the same amount of food intake after losing a modest amount of weight. That's one of the reasons that it's so difficult not just to lose weight, but especially to keep off a good amount of weight after it's lost.

Dr. Wysham:
In most of our patients, obesity is a chronic and progressive disease. They have difficulties losing weight; they put their weight back on. Oftentimes, they gain more weight than they lost.

We've been telling our patients forever to lose weight. And we don't really, until recently, understand what appetite regulation is. And in addition to the incretins, there are multiple other redundant pathways associated with appetite. So if a person loses weight in the presence of or even in the absence of incretins, they'll get to the point that their leptin levels are lower; their amylin levels may be lower. There may be other transmission changes in the hypothalamus that result in not only an increased appetite, but also a decrease in energy expenditure, and the sum total of that is going to result in difficulty attaining and especially maintaining weight loss.

Dr. Kahan:
And so, Ken, what are the common pitfalls in diagnosing obesity in patients with diabetes, and might you have any practical tips for avoiding underdiagnosis and ensuring an accurate assessment?

Dr. Fujioka:
To me, it's not surprising that we don't code for obesity just because, as you all know, it actually just became a diagnosis.

The BMI is still kind of the cornerstone in the sense of diagnosing obesity because obviously if the BMI is over 30 and the patient is Caucasian, African American, yeah, they have obesity, and go ahead and code it. At least it's addressed, it's there, it's out in the open, and again, it's kind of like the elephant in the room.

If you do have an Asian patient though, you got to knock everything down from 30 to 25. Overweight is actually 23 to 24. If you happen to notice, though, that the weight is central, it's visceral, you might need to take a waist measurement.

Dr. Kahan:
I wonder, Ken, you just gave a good answer for how to minimize underdiagnosis. What about the opposite? What about overdiagnosis, which is to say there's been a lot of talk of the so-called metabolically healthy patient with obesity.

Dr. Fujioka:
These folks that think they're metabolically healthy, actually, many are not. And we used to say, oh, yeah, 20%-30% of the population is metabolically healthy even though they're obese. Well, that number is probably much lower than that.

Dr. Wysham:
Not only weight causes diabetes, but as was pointed out, it's associated with many other comorbidities, of which our patients with diabetes have: high blood pressure, dyslipidemia, fatty liver, as well as sleep apnea.

The other point, which I would think was well-discussed is that being overweight is not the patient's fault, that it's an interplay between

genetics, epigenetics, early lifestyle experiences, and that the long and the short of it is that the hypothalamus becomes resistant to the appetite-regulating hormones and the patients often are hungry all the time.

Dr. Kahan:
In our second chapter, we'll discuss the emerging weight management therapies for patients with type 2 diabetes and obesity. Stay tuned.

[CHAPTER 2]

Dr. Kahan:
Welcome back. In the first chapter we discussed links between obesity and type 2 diabetes. Now we're going to move on to emerging treatment options for our patients with type 2 diabetes and obesity.

Ken, what evidence supports weight loss as the primary treatment goal for our patients with type 2 diabetes and obesity?

Dr. Fujioka:
The data is just overwhelming that when you bring down the weight, everything gets better. The blood pressure – even the protein in the urine gets better. The dyslipidemia gets better, and obviously their A1c gets better. So again, you're seeing the shift and it's already starting. When you look at the guidelines, they're all saying, "Hey look, you've got to think about the weight."

I hear you have a case for us that highlights maybe some of these benefits that we can see with the emerging treatments.

Dr. Kahan:
This is a 48-year-old man with a history of hypertension and type 2 diabetes for 6 years. He has a number of other conditions in his medical history including sleep apnea degenerative joint disease of both knees, and esophageal reflux. And he is on a number of medications. For the diabetes, he's on glyburide and metformin. For the blood pressure, he is on losartan, diltiazem, and chlorthalidone. And as well, he's on atorvastatin, a baby aspirin, and a reflux medication. He has been overweight since childhood, with progressive weight gain throughout his adult life, particularly since he was diagnosed with diabetes 6 years ago.

He previously worked with a dietician when he was diagnosed with type 2 diabetes, but after making some progress, he hasn't continued that. He describes having excessive appetite and cravings, which has made dieting and weight loss attempts extremely difficult for him. Recently he saw his primary care doctor who told him he'd have to start insulin treatment if his glucose continues to increase.

On physical examination, his weight is 325 pounds; he has a BMI of nearly 45. His blood pressure is 128/62, heart rate 92. He has a small systolic ejection murmur at the apex, some dystrophic skin changes, and some small pitting edema in his legs. On the lab tests, his fasting sugar is 95, A1c 8.4, BUN 19, GFR 73, and his total cholesterol 152, LDL 70, triglycerides 181, and HDL 46.

Carol, can you elaborate more on the efficacy and safety of potential receptor agonist options based on recent clinical trial findings?

Dr. Wysham:
I think it's really important for us to understand what we have on the table for using the incretins for our patients with diabetes. So first of all, we have really good data to suggest that the GLP-1 as well as the dual agonist GLP-1/GIP are highly effective.

Now, if we look at the data that we have up to this point where we have a head-to-head comparison between semaglutide and tirzepatide, the dual GIP/GLP-1 receptor agonist, we can see that the dual agonist is associated with additional, not only A1c reduction, but also weight reduction. And what we're looking at from the standpoint of A1c is a difference between a reduction of 1.86 with semaglutide, 2.2% with tirzepatide. And the weight reduction with tirzepatide in the patient studies designed to treat diabetes, we see a doubling of the weight with tirzepatide compared to semaglutide.

The SURMOUNT-2 study, that has been done to look at the weight effects. If you put a patient with diabetes into a study where they're having a coordinated weight-reducing program, you see greater weight reduction. And so at the maximum dose, we saw 15.7% reduction with tirzepatide compared to about 3% with placebo. So clearly, our patients with diabetes are benefiting from the A1c reduction, but that the weight reduction that's accompanying that is what's been most exciting to me in terms of the use of these agents.

Dr. Kahan:
Yeah. Thank you, Carol. It really is impressive, what we're seeing with the newer agents for diabetes and obesity. And I think that gets back to the case that I just presented. You know, this is a patient who, again, I think a lot of us will see patients like this in the clinic, and unfortunately, often these patients are being treated in this manner, where he has severe obesity; he has significant diabetes. The diabetes, in my strong opinion, is not being treated in a way that would be optimal. He's on glyburide (sulfonylurea) that tends to increase weight. He's on metformin, which typically, at best, is weight neutral. It's not likely to lead to weight loss or certainly not much

weight loss. And meanwhile, we now have these newer medications that likely would lead to a better improvement in glycemic control while also likely leading to a substantial decrease in weight and, over time, likely further being able to better improve the diabetes. As the case was stated, this patient is someone who very well may even have to go on insulin sometime soon, which then likely contributes to further weight gain and potentially other risks of the insulin treatment.

So I think those are some of the really important reasons backing up the utility of this type of receptor agonist treatment that you point out, Carol.

Dr. Wysham:
The studies that are going on with these incretin therapies are now including triple agonists that have even greater reduction. But the most important thing that you pointed out, the idea that this guy goes from metformin/glyburide to insulin, goes against what the current recommendations, and those for many years of the ADA, and that is that the GLP-1s, or now the dual agents, should be considered the first injectables, not insulin.

Dr. Kahan:
If we treat the obesity primarily, we improve the diabetes, we likely improve quality of life, we very well may improve cardiovascular disease risk, we very well may improve renal outcomes, but it emanates from addressing the obesity.

So in our third chapter we'll focus on individualizing care to optimize the management of our patients who have type 2 diabetes and obesity. So again, stay tuned.

[CHAPTER 3]

Dr. Kahan:
For those just tuning in, you're listening to CME on ReachMD. I'm Dr. Scott Kahan, and here with me today are Dr. Carol Wysham and Dr. Ken Fujioka. Together we're exploring the rationale and importance of making weight loss a primary target of therapy in patients with type 2 diabetes. We're also looking at the emerging therapies that can help our patients achieve sustained weight loss and improve their diabetes management and other health outcomes.

In this chapter, our focus is on individualizing patient care to improve the health outcomes of our patients.

Ken, how can we move beyond a strict focus on glycemic control in type 2 diabetes treatment to a more obesity-centric personalized approach?

Dr. Fujioka:
Many, many patients that have type 2 diabetes that are obese, which is the vast majority, are going to tell you, I want my weight down. They could care less about their blood sugar or their blood pressure. They just want to get their weight down. So in that sense, you want to work with the patient in the sense that, yeah, we're going to help your weight, and we're going to help your diabetes. So let's say you have a patient who has a BMI of over 35. So this is somebody who qualifies for bariatric surgery right off the bat. As you know, there've been some changes and they'll even consider a BMI of 30 or higher with diabetes as someone who might want to consider bariatric surgery. I consider it overkill because there are risks with the surgery.

With these newer incretins, you can get weight loss that's approaching bariatric surgical numbers now. So again, now I'm saying, okay, good, I'm going to be more aggressive, I'm going to jump in and use my big guns right off the bat because I don't want to go down that road to surgery.

Dr. Kahan:
Let's think about this case in just a slightly different way. Let's say this patient was already on a GLP-1 medication. Let's say the patient was on semaglutide, got some benefit from it, but still, weight is very elevated, still his A1c is higher than we'd like.

Carol, how do you think about treatment intensification beyond GLP-1s to dual agonists?

Dr. Wysham:
Well, first of all, I think there's a lot of benefit to intensifying from a GLP-1, even if that GLP-1 is semaglutide, to tirzepatide based upon the clinical trials showing much greater A1c reduction and even a more impressive improvement in weight. Those patients who fail to achieve their glycemic targets, and especially if they have additional weight to lose, which most of them do, I honestly think that that's a natural next step.

I typically give patients a guidance for how to titrate their medications up, which oftentimes involves a message for us to send in the next dose as long as they're tolerating it. And as I indicated earlier, I do try to get patients up to, you know, a maximum dose or at least the step below the maximum dose so that they can get maximum benefit from the medication. But we do monitor their weight, we

monitor their liver function test, their kidney function test, their albumin levels. I do a FIB-4 index on all of my patients at least once a year when we do their routine annual labs. So if it's elevated in one visit, then we'd redo it and see if it's coming down with their weight loss. There are a very tiny amount of patients who won't lose weight with these agents and won't necessarily even have an improvement in glycemic control. And if that happens, you have to recognize that we need to move on and we need to do something else. But again, as you saw from the clinical trials, you know, 90% of patients with the tirzepatide 15 mg lost at least 5% of their body weight. So the vast majority of people are going to get clinically important weight loss from tirzepatide.

Dr. Kahan:
I worked on the ADA guideline, Standards of Care, there's a very good ACE [American College of Endocrinology] guideline, and they all say the same things. We should be utilizing these newer medications that lead to improved glycemic control, lead to improved weight loss, and typically also lead to other benefits, whether cardiovascular disease benefits, renal benefits, or otherwise.

And so I think there's an important call to action both for primary care doctors and endocrinologists and anyone who is treating patients who have obesity and type 2 diabetes to be aware of the guidelines to optimize the care of these patients utilizing the best up-to-date data and the best up-to-date medications that we have available.

Dr. Wysham:
You know what I would like to see is just a little bit more specificity for the primary care doctors to recommend the stronger agents in the face of an A1c that is more than a percent above target. And yes, I do think, just like the guidelines evolve some every year or 2, there will be more guidance in terms of when that weight becomes the most important thing that we should be treating over and beyond the A1c.

Both the GLP-1 receptor agonist and the dual agonist, the major side effects are gastrointestinal. They're nausea, they're vomiting, diarrhea, and believe it or not, even constipation, increased incidence of reflux. Those are described in about 15% to 20% of patients. I like to flip that around when I'm talking to patients. That means, you know, 80% to 85% of patients don't ever have any of those side effects. But you need to counsel patients about what they are and the fact that they generally are worse at the beginning of therapy and will get better over time.

There are some warnings that have come out about the GLP-1 receptor agonists. The FDA has obviously has talked about pancreatitis; they've talked about issues related to renal insufficiency. There's clear effects on development of gallstones. I just recently became aware that there are some issues that have been reported regarding hair loss – that's probably from weight loss; I'll be honest with you – as well as suicidal ideation, which, again, our clinical experience does not support that as a risk.

Dr. Kahan:
Well, this has certainly been a fascinating conversation. But before we wrap up, Carol and Ken, any take-home messages you'd like to share with our audience?

Dr. Wysham:
We have told our patients for the last umpteen years that they need to lose weight, and yet it is only recently that we have the tools that allow us to help not only improve their glycemic control, but help them with our mutual goal of helping them lose weight. And if you can identify those patients with central obesity, those are the folks that we really need to focus on metabolic health.

Dr. Fujioka:
At times, I might even be overwhelmed by these hormones. And so my take-home message to you is: Don't worry, you'll get it. They'll begin to make sense as time goes on and you use them more often and get comfortable with them.

Dr. Kahan:
We have good diabetes treatments that can improve glycemic control alone, but when we can do both in one fell swoop, that often works better. So treating obesity hopefully will significantly improve the diabetes and very likely, as we've discussed here, will improve other factors in the patient's health and wellness, including quality of life.

And so that's all the time we have today. I want to thank our audience for listening in. And especially, I want to thank Dr. Carol Wysham and Dr. Ken Fujioka for sharing all of your valuable insights and expertise. It was great exploring this topic with you.

Dr. Wysham:
Yeah, it was very enjoyable and a very important topic to explore. Thank you.

Dr. Fujioka:
My pleasure.

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