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GLP-1 Agonists: Are They Revolutionizing Obesity Treatment in Women's Health?

Announcer:
Welcome to CME on ReachMD. This activity, entitled "Medical Management of Obesity in Women's Health" is provided by Omnia Education and is supported by an independent educational grant from Novo Nordisk.

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Dr. Singer:
So we're going to start, and we'll get right to it, but we hear consistently that obesity is a worsening epidemic in the U.S. Let's start by talking a little bit about the impact of obesity, what's driving this epidemic, and what we should be considering in terms of women's health.

And there, as you can see from the slide, there are a number of factors that drive weight gain. We'll talk about some of them as we move through the first few slides. With that said, I think it's important to have the discussion focus on the concept of obesity as a disease; not either a lifestyle choice or a personal failure, which is what we've often described it as in the past. So what are some of the metabolic and endocrine changes that occur that make somebody more at risk or places someone more at risk?

Dr. Ryan:
You know, so the way we really think about risk for obesity is we have genetic factors that predispose us to risk for developing obesity within an environment and aspects of the environment that drive – that drive that weight gain risk. But there's a lot of pathobiology behind obesity, and we really need to understand that if we want to understand why our patients are struggling to lose weight and keep it off. But that biology is really the driver. I think the way we used to think about it is the way we were taught in medical school. We were taught this energy balance equation. They usually threw up a picture of a balance beam. And if you consume more calories from food intake, then you expend an energy expenditure. I think a more advanced and appropriate understanding of obesity as a disease is that there are many biologic forces that resist weight loss. And we enter a negative energy balance, that really drives weight gain. So it's not so much weak willpower that's the cause of our patients not losing weight as much as it is they're in a tug-of-war with these very powerful biologic forces. So if you look at average body weight for men on the top and women on the bottom, over that age 20 to 40 period, that young adulthood period, you see this slow, steady weight gain at about 1 pound a year on average in our population. Susceptible people are gaining more, resistant people are gaining less, but let me tell you, 95% of the population gains at least 1 BMI unit from age 20 to age 40, so there's this enormous environmental pressure that drives weight gain. And once that weight is gained, the body defends its highest fat mass. And that's the key for you to walk out of here today; that what happens is you gain some weight and your body settles at that. This is normal physiology that supports and defends your highest body weight. And a lot of that is driven by leptin. Leptin is a signal of how much fat mass you have. We'll talk a little bit more about that. So for women, and this is important for women, so women are at risk for weight gain by virtue of the difference of men and women and our hormones.

Dr. Singer:
We know that obesity can lead to many problems, many things down the line. We often focus on the cardiometabolic consequences that are linked to obesity. So let's talk about that for a few moments.

Dr. Ryan:
Yeah, I mean, obesity is a risk factor for – you all know this, for diabetes, for cardiovascular disease, for the 13 different types of cancer, for obstructive sleep apnea. It's the big driver of NAFLD and NASH, and cirrhosis. And the biggest cause of liver transplant today is fatty liver disease with NASH. But the good news is, is that we can get a lot of benefits if we can achieve and sustain some modest weight loss. We do not need to get every patient back to a so-called normal BMI. They don't need to be under 25, they may not even need to be under 30 or even 35, but we can get enormous benefits if we can achieve and sustain 5-10% weight loss because this will reduce the risk for progression to type 2 diabetes, it improves glycemia in patients with established diabetes. It reduces – it improves all the cardiovascular disease risk factors; blood pressure, lipids. But it takes a little bit more weight loss. It's going to take 10% or more weight loss to really get some significant improvements in symptoms of obstructive sleep apnea. And it's probably going to take about 15% or more weight loss to really have an impact on cardiovascular disease endpoints.

And here, I'm showing you different categories of weight gain and increased risk for diabetes, cardiovascular disease, cancer, and non-traumatic mortality. And as you can see for our never-smoking women on the left, and never-smoking men on the right, there is this direct and linear relationship between the amount of weight gain and the risk for these morbidities and mortality. And I want you to notice, it's worse with women. It is worse for the women.

Dr. Singer:
That's a nice segway into the next question, and that has to do with consequences beyond the cardiometabolic risk, which is clearly important, and on which we should all focus. But you mentioned how people look, and often obese people have been stigmatized, and there are many misperceptions when it comes both to the patient, as well as the clinician. Let's talk a little bit about the social impact and what we need to do to change that.

Dr. Ryan:
You know, women with obesity are less likely to have education – higher levels of education. They are less likely to be married. It's been proven they make less money. I mean, so our society really judges people by how they look, and stigmatizes this condition. So you need to understand where your patients are coming from in this. They're coming from a space where they feel judged. And so you need to communicate with them in a non-judgmental way.

Dr. Singer:
Let's talk about what we have available in the armamentarium today, and perhaps how you choose some nuances that might go along with each one, because in recent years, we've had a number of new options come out.

Dr. Ryan:
So you need to recognize that not everybody can do it with lifestyle alone; some people need help. So the medications that we have available to us, most of them work through appetite. One of them works in a different way, and that's orlistat. So, orlistat blocks the absorption of about 30% of the fat that you're eating, so it tends to reinforce this healthier, low-fat diet. And appetite is – it's not something that we control. This is our body's biology telling us when to start eating, when to stop eating, and when to start eating again. There's also a biology around food intake called the rewards system, and even if we're not hungry, sometimes we'll have – we'll ingest a high-fat or high-savory or high-sweet food because we know it's going to be delicious and rewarding to us, and we're going to enjoy it. So the way these medications, the other medications work is in the brain through these appetite mechanisms. And a new drug, liraglutide, is really based on our advanced understanding of this appetite regulation in the body. It's GLP-1 receptor agonist. You have familiarity with it because you've used all those GLP-1 receptor agonists for diabetes.

Dr. Singer:
GLP-1 receptor agonists, as you started to mention before, have emerged as both treatment for diabetes, as well as treatment for obesity. Can you explain for us exactly what the GLP-1 axis is in terms of effects on insulin, glucagon, gastric emptying, and satiety?

Dr. Ryan:
You know, we have this thing called gut-brain axis. So you know, as I said, we don't have to remind ourselves to eat; our body is sending us signals. And so the stomach puts out a hormone called ghrelin that tells us we're hungry. And after we eat, that ghrelin starts falling. It will fall for about three to four hours and go back up again, and we want to eat again. But once food is ingested and it enters the small intestine, a whole number of signals are released that go to the brain and tell the brain that food is on the way. GLP-1 is one of them, also CCK, PYY. And then when food is absorbed, signals are sent from the pancreas, amylin and insulin go to the pancreas, and they also help promote satiety. The body fat status is really important in body weight regulation. So we have a signal that tells the brain what our fat stores are. So leptin really corresponds to the total amount of body fat. And patients with obesity have very high levels of leptin. So what's going on there is that when leptin falls, it's very good about telling the brain that fat is going away, and the brain interprets this as starvation, and it puts into play signals that affect these hormones that make you hungrier, that make you less satisfied

with the food that you're eating. And it also reduces your metabolic rate, so you've got a double whammy to overcome when you're in that reduced weight state. So I think understanding this physiology is driving discovery, and we have a number of agents down that are in the pipeline for this, so we're in phase 3 with some second-generation GLP-1 receptor agonists. We have combinations of GLP-1 and GIP, another intestinal peptide, that's in phase 3 now. We also have amylin. Amylin is being investigated as a potential treatment. So understanding this is really driving discovery, and it's going to give us some great tools to help our patients.

Dr. Singer:
In order to sort of drive this home, I think we have a short video.

Narrator:
The hormone glucagon-like peptide-1, or GLP-1, is released in response to food and acts as a satiety signal leading to good feeding behavior and body weight. GLP-1 increases insulin and decreases glucagon section, delays gastric emptying, and helps regulate glycemia.

GLP-1 impairment in obesity diminishes satiety leading to a poor feeding behavior, with diminished impact on gastric emptying and insulin and glucagon secretion.

GLP-1 agonist therapy helps overcome obesity-associated GLP-1 impairment, supporting a more normal homeostatic state of improved satiety, good feeding behavior, and body weight, and reducing the risk for T2DM-associated morbidity.

Dr. Singer:
Now that we understand the role of GLP-1 agonists, let's take a look at the clinical data that supports a role for GLP-1 analogs; both in the setting of obesity, that's primarily what we're talking about, but also in diabetes, as well.

Dr. Ryan:
So there are a number of drugs in this class that have been approved for type 2 diabetes. And shortly, we'll have an oral one coming out. So these have typically been given by injection. And you all know them. But we're going to have an oral GLP-1 agonist coming on the market very soon. But I think – and they all are associated with weight loss. Liraglutide is approved in type 2 diabetes, and at a dose of 3 mg, it's approved for weight management. And so what is being illustrated here is the affect on hunger and satiety and gastric emptying with those two doses. And as you can see, the top panel on the left is satiety. And you can see there's an increase in satiety, the feeling of satiety after a test meal when liraglutide is given at either dose, and then a reduction in hunger around that test meal. So I think this is the very first one that we've been able to exploit. So this comes from our understanding of physiology and converting that physiology into pharmacology. So native GLP-1, it has a half-life of two minutes. Liraglutide has a half-life of about 15 hours. We've created – we've changed the physiology to pharmacology, and that's a good thing. So here's some evidence about using it over the long-term. So in this study, patients were randomized to either placebo in blue or liraglutide in purple. And here they're followed for a total of 160 weeks; that's three years. This requires a dose adjustment, so it takes about five weeks to get up to that 3-mg dose, and then weight loss occurs over about the first seven months. So we see this initial rapid weight loss, and then we see this plateau. This plateau does not mean the drug is not working. It means the body has reached a new settling point in harmony with the environment. Look at the very end, in that green shaded area, the patients were taken off of treatment; both the placebo and the liraglutide, and you see this dramatic increase in body weight over just 12 weeks. So medications work when they're used, and this is one that does that. So this, you know, the whole purpose of achieving weight loss is to get health benefit. And this shows you the health benefit in terms of prevention of type 2 diabetes. So in this scale obesity and pre-diabetes trial, this is the data on pre-diabetes, and you can see the progression from pre-diabetes to overt diabetes in the top line. Those are patients on placebo, and the bottom line those are patients on liraglutide. So that amount of weight loss is really pretty good for the prevention of type 2 diabetes.

Dr. Singer:
Let's try to pull all of this together. How does a clinician decide to utilize and in what combinations do we utilize lifestyle changes, behavioral changes, surgery, pharmacological approaches when we're managing a patient who is obese?

Dr. Ryan:
We don't treat it all at once, and we don't treat it with some standard formula. It's very much adapted to the person who is sitting in front of you. So it's hard to sum this up, you know, in just a few words, Andrea, but the key to success is shared decision-making. Everybody needs a personalized approach, and it's got to be something that they really buy into. Your job is to be the authoritative source about what's a good way to do it.

Dr. Singer:
Thank you, Donna, so much for joining us today.

Dr. Ryan:

I have enjoyed it so much. Thank you. Thanks everybody.

Announcer:
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