CARDIOMETABOLIC HEALTH CONGRESS

Webinar #3: Balancing Glycemic Management with Need to Address Overweight and Obesity in Patients with Type 2 Diabetes

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DR. ECKEL: Hello, I'm Dr. Bob Eckel from the University of Colorado Anschutz Medical Campus, and I'm introducing one of six webinars entitled **'Balancing glycemic management, with the need to address overweight and obesity in patients who are living with type two diabetes and obesity**'.

I'm pleased to introduce to you today Sangeeta Kashyap from the Cleveland Clinic, Lerner College of Medicine. She's a Professor of Medicine there and she's also in the Department of Endocrinology Diabetes Metabolism. Sangeeta is going to address the emphasis on glycemic management in patients living with overweight, obesity, and type two diabetes. Sangeeta, you're on please.

DR. KASHYAP: Thank you Dr. Eckel. It's an honor to be here. And my goal is to share some insight about how we manage glycemic control in the patient who's overweight with type two diabetes. What I'm going to do is present aspects of a patient's case and go down the clinical guidelines of how we should formulate a plan to address their glycemic control, keeping in mind that they have obesity and not exacerbating their weight.

So, this is a patient, Maya. Her initial visit with us was at the age of 30 years. Her medical history was unremarkable, and she was on no medication. Her family history though did include obesity in her sister and her mother, and type two diabetes that later developed in her mother. Her review of systems showed that she had a depressed mood. And on exam she had a height of five foot four, weight 165 pounds, waist circumference 35 inches, a BMI of 28.3, blood pressure 134/82, and her fasting glucose was 104. Her total cholesterol was 189 and her triglyceride were 200 and her HDL levels were 36.

So, if we graph her weight based on her history, we see that she's had a steady weight gain since the age of 18 - college, some personal stressors. She reported being hungry at night, lack of exercise, and at that visit, she was manifesting signs of prediabetes with an elevated fasting glucose.

So now, at that time the approach for her that was formulated was to create a more personalized dietary plan that supports the DASH program, and that was culturally sensitive to include Mexican foods. The physical activity plan included walking her dog and sharing in meal planning with her family. So, she was also referred to a psychologist for depression and binge eating, and with this initial approach, she lost 8% of her body weight and had maintained it for some time, until she was lost to follow up.

So now she comes back to see us. She's 42 years old as she returns for a visit regarding new-onset type two diabetes. And now her medical history includes hypertension for five years. That's treated with enalapril 20 mg, atenolol 100 mg, hypercholesterolemia for five years, treated with atorvastatin 40 mg/daily. Depression treated with paroxetine 20 mg/daily.

She's a little short of breath, she has daytime lethargy, and some low back pain. Her height remains the same, but now her weight is 200 pounds. Waist 38 inches, BMI 34.3, and her blood pressure is 142/90. Now her fasting glucose is 146 and her A1C is 7.8%. And if we look at her lipid profile, her total cholesterol is 195, her HDL'S 42, LDL cholesterol of 110, triglycerides 196. Her ALT is slightly elevated at 90, and her AST is 24.

Her other laboratory tests, including an EKG, are fine. There's No ALC hematuria and she has a normal fundus exam, and her sensation of her feet are intact with the monofilament.

So, she's prescribed a Mediterranean diet, exercise at the YMCA, and after six months, her weight really didn't have a significant change, and her A1C was 7.6%. She was initially placed on metformin, but had a lot of GI side effects. So, she was subsequently placed on glyburide 2.5 mg/day, and sitagliptin 100 mg/day.

And in six months, her A1C dropped to 6.8%. But the patient had gained six pounds and was not comfortable with this outcome.

So, this is a case that describes to you how we need to consider harmonizing treatment goals. Again, this patient is unhappy. She has improved glycemic control, but she's very far from her ideal body weight. And obviously our treatment plan, we have to target glycemic control to prevent complications related to diabetes, which are often exacerbated by obesity because of the induction of insulin resistance and beta cell dysfunction.

So clearly she's got metabolic syndrome, hypertension, dyslipidemia, elevated ALT, which, you know, tells us that she might have some liver injury related to NAFLD and obviously ensuing hyperglycemia that can cause vascular disease.

So, we've known for some time that even modest weight loss in patients with type two diabetes can induce remission. In fact, a very elegant study that was published in *Cell Metabolism* showed that with diet and exercise, even moderate weight loss at 5% improved multi-organ insulin sensitivity and beta cell function. And that additional weight loss of about 11% to 16% further enhanced peripheral insulin sensitivity in the muscle and even greater weight loss causes caused a stepwise change in adipose tissue biology, reducing inflammation and signaling factors.

So, we know weight loss is very important and, there are two real areas of focus that have been advocated by our major societies. So, one approach is to understand a patient's BMI and try to target 5-10% of their body weight. And then the other aspect of metabolic control is to look at the complications related to adiposity and make sure that we're addressing all the complications. And so, you know, in both areas of focus, you'll see that typically, if we focus on complication centric approach that is related to obesity, that we can see high benefit, a lower risk, and it is generally higher cost effective.

And if we think about a patient with diabetes, how can we reduce glycemia, reduce their complications of diabetes, and yet minimize weight gain and promote weight loss. So, this is an approach that's advocated by the American Diabetes Association where initially what's recommended is to start with metformin as a baseline if a patient tolerates it, and then consider adding a GLP-1 receptor agonist, which is very effective for weight loss.

And if a patient is not at target, then consider adding an SGLT2 inhibitor, which can also promote glycosuria and caloric loss, so a modest weight loss. And if these approaches are not getting a patient to their target A1C, then consider adding basal insulin. But instead of adding short-acting insulin, consider adding basal insulin along with the GLP agonist and SGLT2. And this can minimize the need for adding more and more insulin.

Obviously patients have to also comply with a lower glycemic diet, and so having them see diabetic educators and nutritionist are also very important, especially if they require insulin. Obviously we have to consider cost and access, and we want to advocate for algorithms that minimize hypoglycemia when treating diabetes. So, there's a variety of approaches that are developed that not only target the physiology of diabetes, but also target obesity. And so, many of our treatments include to reduce hepatic glucose production, so with the use of metformin, bariatric surgery, thiazolidinediones, which are very potent insulin sensitizers. And we can consider using them in very low doses, although they are associated with fluid retention and weight gain.

But sometimes when a patient is not able to tolerate metformin, this could be considered an alternative in low doses. And then, interventions that target glucose uptake, as well as interventions that target insulin secretion with a GLP agonist, or DPP4 inhibitors. Obviously if there's advanced beta cell failure, then using a DPP4 inhibitor, insulin analogs as well as bariatric surgery. And then targeting satiety through agents such as metformin, GLP agonists, phentermine/topiramate or other anti-obesity agents such as naltrexone/bupropion. And then targeting glucose re-absorption in the kidney, including SGLT2 inhibitors.

When considering a patient's case, obviously they have other comorbidities, such as the case that was presented, and so we want to also consider iatrogenic medications that can contribute to weight gain. And so, in this case, there were actually three agents that were responsible for some weight gain. And so, including sulfonylurea, metoprolol, and paroxetine, which is very strongly associated with weight gain.

And in this table, what you can see is that there are agents in diabetes, hypertension, depression, psychosis, epilepsy, contraceptives, anti-inflammatory, and antihistamines. There are drugs in each of these classes that promote weight gain, and the goal of the clinician is to understand and substitute some of these agents for alternatives.

So rather than a sulfonylurea, we should consider a GLP agonist, a SGLT2 inhibitor, consider perhaps amylin analogs in a patient with type one diabetes, for instance, who's also dealing with weight issues. The other option for weight is to consider using ACE inhibitors and ARBs and for antidepressants, bupropion and SSRIs are considered more weight neutral or weight losing, and so those agents would be considered preferable.

So, if we look at data specifically related to diabetes medications, and this UKPDS study showed this very well, when patients were randomized, to sulfonylurea, insulin versus diet alone. What was see is that over the years of randomization, almost 12 years, that insulin was associated with almost 6kg of weight gain. Sulfonylurea was associated with about 3.5kg of weight gain. Metformin, and this was very similar to that of diet alone. And so, there was a modest to 0.5 kg of weight gain.

And if we look at head-to-head studies of GLP agonists that were seen in patients with, as well as patients without diabetes. What you can see is that some agents, some GLP agonists are far more effective in terms of inducing weight loss, and these results are more robust in patients without diabetes as compared to patients with diabetes. So, semaglutide, as well

as dulaglutide and exenatide, again, liraglutide when used in high doses, and it's a dose response that we see with liraglutide, can also produce significant weight loss.

So, what predicts long term efficacy when we use these agents? For instance, when we look at trials with liraglutide 3.0mg dose in the SCALE studies, what we see is that the early response really predicted long-term efficacy in terms of weight. And, when we look at patients with diabetes, they had a less robust response to weight loss at the same dose as patients without diabetes.

And similarly, if we look at what results, if we add a GLP agonist, in this case, liraglutide 3.0mg to basal insulin. What we see in the cohort is that there is greater weight loss of 6.5% versus 1.5%. There's a greater reduction in A1C of 1.2% versus in the placebo 0.7%.

And there's a reduction in the daily dose of insulin that's required minus three units per day versus addition of 18 units a day. So, adding a GLP agonist has multiple benefits.

And finally, if we look at the ACE guidelines, this is a far more intricate guideline. But what it states is that we really have to individualize goals and we individualize treatment goals based on various factors for the patient, their age, their comorbidities, etc.

But based on their baseline A1C, you can consider monotherapy with metformin, GLP agonists, SGLT2 inhibitors, and if their A1C is fairly high, 7.5 – 9%, then you can start with dual therapy using the combination of these agents. And then if the patient has an A1C that's poorly controlled, over 9% and is symptomatic, then you want to use these dual agents, but consider adding basal insulin from the get-go.

And so, this is the updated treatment algorithm proposed by the ACE Society. So, if we look at the revised treatment approach for this patient, what we did is we discontinued DPP4 inhibitor and glyburide for semaglutide starting at 0.25 mg/week. We titrated it to 2mg/week over the course of a few weeks, to achieve an A1C of less than 7%. And consider adding SGLT2 inhibitor and basal insulin to the GLP agonist as needed to maintain glycemic control if the A1C is rising.

And number two, discontinue atenolol and substitute amlodipine 10 milligrams per day. We also discontinued paroxetine and substituted that with venlafaxine 150mg daily. And with this approach she lost an additional 6% at three months on new medications. So, it was resulting in almost a 12% weight loss achieved at a year.

Her fasting glucose, blood pressure, triglycerides, ALT, and energy levels all improved. She moved to San Francisco for better employment and to be closer to her family for support. And so, I think this is a much better treatment plan for this patient. And so, with that, I will conclude my portion of the talk.

DR. ECKEL: Great. Well, you covered a lot of important points, and it kind of reminds me of the most recent meeting of the American Diabetes Association in New Orleans in June. There was a symposium where there was a debate, should weight be the primary focus of diabetes management, or in fact, should glucose be the primary focus of management for patients with living with diabetes and obesity?

Your thoughts on that very controversial topic. Should glucose be centric? Or ultimately weight loss be centric in terms of the approach to patients with obesity, living with obesity and type two diabetes?

DR. KASHYAP: Yeah, I think both approaches are so important, and I think when I see a patient with early onset diabetes and their BMI is in 34, they have class one or two obesity, I find that if you really target the obesity, the visceral adiposity specifically, you get improvements in the pathophysiology of diabetes.

So often with weight loss, we can induce remission of the disease. However, when you see a patient with a long-standing disease and they've got very poor beta cell function, you know, weight loss isn't going to cut it. I mean, of course it's going to improve their cardiometabolic risk, but you're going to have to consider adding things like insulin analogs. But we try to couple them to GLP agonists, SGLT2's to kind of minimize some of the weight gain that we see when someone goes from being poorly controlled to being well controlled with insulin.

So, I think overall we have to keep both things in mind. But I find that a more weight-centric approach is more beneficial, especially early in the onset of disease and perhaps less so as they have more advanced diabetes, they're requiring perhaps multiple insulin injections.

DR. ECKEL: Well, the benefit we see with GLP1 receptor agonists is problematic in terms of interpretation of mechanisms. So how much of the benefit in A1C lowering and overall glycemic burden is lowered by the weight reduction versus the other effects, pharmacological effects of this class of drugs? What are your thoughts there?

DR. KASHYAP: Yeah, I think that there's no doubt that GLP's activate satiety centers in the brain. And so, there is changes in cravings, eating patterns, and people generally eat less. I have seen a rapid improvement in glycemic control because they're changing their eating behaviors. But there's also insulin, production of glucagon.

And so, there's a lot of other things that we get benefits from these agents. So, I think they target multiple aspects of the pathophysiology of diabetes.

DR. ECKEL: Well, that's an excellent answer because I think we have mechanisms that relate to both. The weight loss itself is beneficial, particularly initially after appetite is reduced and weight is falling.

Glycemia can improve dramatically within days of effective GLP1 receptor agonist therapy, but the whole innovation of glucagon secretion, the paracrine effect within the islet to make the beta cell more sensitive to glucose, clearly is an important pharmacological mechanism too.

So, both are important, and I think the audience needs to appreciate both aspects of GLP1 receptor agonist action.

Now, Dr. Kashyap, you've worked a lot in the relationship between diabetes, other metabolic disorders, and excess body weight. And that relates to the option for metabolic surgery in patients who have modest degrees of obesity with other comorbidities, or in fact,

severe obesity as currently defined. So now we have high-dose semaglutide, and we have tirzepatide, which is a dual agonist, including GIP, in addition to the GLP1 receptor agonist.

So, in this current environment which we live, is the option between metabolic surgery and pharmacological management a dilemma that the clinician is in? Or what influences your choices of effective treatment of diabetes and excess weight that relate to one another, or alternatively the approach, the surgical approach you're so used to and coauthored in many publications.

DR. KASHYAP: Yeah, I don't think the two approaches are mutually exclusive. I think that we need to consider patients individually. I've seen patients with BMIs in the fifties, and I usually do both tirzepatide and also refer them for bariatric surgery. Because we know that, now we're seeing bariatric-range weight loss with very high doses of semaglutide and tirzepatide, but it still may not be enough for all the complications related to adiposity.

And so, I think it's absolutely fine to tell the patient, we'll certainly start out with this approach, but I think you may require surgery in the future. I also notify my bariatric surgeons that I work with and say, hey, I've put this patient on tirzepatide. I do expect an improvement in their weight, but I'm not sure where they're going to level out and still may need your services. So, I think a combination approach is absolutely indicated in patients based on the severity of their obesity and the severity of their diabetes. And so, using complimentary approaches are the way to go.

DR. ECKEL: Think it's important to remind our audience that ultimately tirzepatide is approved for the treatment of type two diabetes, but currently does not have an independent indication for the treatment of obesity in the absence of type two diabetes.

DR. KASHYAP: Correct, we use it off label, that's right.

DR. ECKEL: That's right. The standard practice in most clinics that are particularly those that are on top of the recent data that have been published.

So, I think it's very important that you reviewed the review of the medications that are used in patients with diabetes that can impact body weight either favorably or unfavorably. And I think the TZD's need some new attention because at low dose therapy, the benefit may still be there to some extent in insulin sensitivity without the weight gain that accompanies higher dose TZDs. But I'm going to think a little bit about insulin and sulfonylurea. Do they actually make people gain weight or are they associated with weight gain?

DR. KASHYAP: Well, they're both associated with weight gain. I think there's more data towards sulfonylureas causing weight gain and there's literature supporting that sulfonylureas may actually increase visceral adiposity. Whereas with insulin you're—well with both agents, you know, you're going from a catabolic—in a patient with poor controlled catabolic state to an anabolic state. And you're improving their glucose control. If we look at like the ORIGIN study, I think the weight gain with glargine was about three and a half to four kilos.

But you know, when we see patients who've had far more weight gain we have to also think about, well, what exactly are they eating? How much are they eating? And you know,

because if you look at most of the trials, the weight gain with insulin is three and a half to four and a half kilos. I mean, and now with the addition of GLP's we can minimize that quite substantially.

DR. ECKEL: Well, that's excellent. Well, then to conclude, we've had a very exciting presentation from Dr. Kashyap related to steps to modify glycemic control in patients living with both obesity and type two diabetes. And we've emphasized in some of the other webinars, the approach to obesity is the primary area of focus in the treatment of patients living with obesity and type two diabetes. And I think Dr. Kashyap kind of summarized her presentation, as I might opine, very well in saying that beta cell function is really modified substantially, much more with long standing diabetes. That would make weight reduction perhaps less successful than pharmacological management. But that's an individualized decision and that's one you clinicians out there have to make in each and every patient.

So, I want to thank Dr. Kashyap again for an outstanding presentation and an excellent response to the questions that were posed. And I hope this is worthwhile to our listening and viewing audience. Thank you very much.

DR. KASHYAP: Thank you Dr Eckel.