CARDIOMETABOLIC HEALTH CONGRESS

Webinar #2: The Foundations of Managing Obesity in Type 2 Diabetes

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DR. RYAN: Hello. I'm Donna Ryan, Professor Emerita at the Pennington Biomedical Research Center, and it is my great pleasure to welcome you to the second webinar in our series on Optimizing Long-Term Weight Loss in Patients with T2DM: Advances and Expert Perspectives. Today we are fortunate. We have Jennifer Green who is going to be talking to us about the foundations of managing obesity in T2DM. Dr. Green is Professor of Medicine in the Division of Endocrinology, Metabolism, and Nutrition at Duke University Medical Center. Jennifer, take it away.

DR. GREEN: Well, thank you so much for the kind introduction. And, really my job today is to focus on lifestyle modification as the foundation for the management of obesity. Obviously, it's not the whole story, but it is the foundation upon which all of our other efforts are built. And let's kick things off with a patient case.

So this is Jackie. She is a 40-year-old woman. She has a history of hypertension, obesity, and she also had gestational diabetes with her last pregnancy. Her height is 5'6", her weight is 230 lb., or 105 kg. so that translates into a BMI of 37. Now, she has been working on lifestyle changes for many years without successful sustained weight loss. I will say that she hasn't been adhering to any particular kind of weight loss or dietary program, and over time her hemoglobin A1C has recently risen. So, it's actually now in the frank pre-diabetes range, so it most recently was 6.3%.

So, what is the next best step for Jackie? Would you recommend to her

A. A low fat diet?

B. A low carb diet?

C. Intermittent fasting, limiting her food intake to only about 8 hours a day?

D. A structured diet of between 1200 to 1800 kcal/day which does allow use of meal replacements?

E. Would you use shared decision making to identify one of the above that she is most comfortable with?

I would recommend E. And the reasons for that are that there are many diets or dietary patterns that are considered nutritious. These are some examples. For example, we have the DASH Food Pyramid. An example of the Mediterranean diet, the USDA My Plate example. But you have many other choices, too. The Nordic diet, the lacto-ovo-vegetarian diet, or, of course, on the right-hand side, what can be recommended to someone with any degree of hyperglycemia is consideration of a low or restricted carbohydrate data where you see carbohydrates are present, but they are comprised of fruits and vegetables with a lower glycemic index.

Now, the reason I show all of those options is it actually doesn't seem to matter which diet, per se, a person is using for weight loss. It's actually adherence and not the dietary composition itself that predicts success in weight loss. And, so, I think what is most important for Jackie, and frankly, every person who is interested in losing weight, is that they really find a diet that will work with their lifestyle and that they can adhere to it over

time. Because it really turns that adherence and not the diet is what predicts success.

This slide shows that in meta-analyses, including four meta-analyses performed in 2012 which actually included between thirteen and twenty-four trials, and adherence was the feature most strongly associated with weight loss. So I think that's really a positive finding, and it allows us to engage in shared decision-making so that our patients may choose from among a variety of options that which may work best for them. And frankly, sometimes people have to try a couple of different approaches to dietary modification before they find one that really fits them best.

This is another example of analysis that have shown that adherence is the most important factor in predicting the degree of weight loss that will be experienced in a person who is on a particular diet. This is an older analysis that included the results of people who were assigned to different diets including Atkins, Zone, Weight-Watchers, and the Ornish diet. And I think most important is on the right-hand side the screen, you can see that irrespective, again, of the type of diet to which the person was assigned it is really the adherence over time that greater degrees of adherence were associated with greater degrees of weight loss over time. So, again, a simple message. Simple to convey, but maybe not simple to achieve and maintain over time. We do know that adherence can be best early on, but adherence over the long term can be challenging.

These are data, again, from individuals assigned to these four different diets. And these are their mean, self-recorded dietary adherence levels by month for these four diets that were popular at the time. And you can see adherence not bad to begin with on all of these diets. But this sort of steady and slow decline over time out to a year, where, in fact, there were very low levels of dietary adherence. So I think that reinforcement over time, and recommitment will be very important to having someone lose weight and successfully keep it off.

During the remainder of the presentation we are going to talk a little bit, just briefly, about three landmark studies that included lifestyle intervention as key treatment modalities. And the take-home messages are that lifestyle interventions can deliver modest weight loss, but they also deliver major health benefits. So, again, we don't necessarily need a dramatic amount of weight loss to derive a medical outcomes benefit.

And we will talk first about the Diabetes Prevention Program because that is really the one most applicable to Jackie at this time. So she has pre-diabetes now, based on her hemoglobin A1C. The Diabetes Prevention Program enrolled over 3000 people with impaired glucose tolerance, so essentially what we call prediabetes at this time. And, over time, with a great deal of support in implementing meaningful lifestyle intervention, they achieved a mean weight loss of 5.6%, and that translated into a very significant reduction in conversion from impaired glucose tolerance, or prediabetes to frank type 2 diabetes over time. So, in the Diabetes Prevention Program, people were randomized either to placebo with some standard care counseling, metformin, or, as you can see at the bottom, very intensive lifestyle modification. And this slide shows the change in weight, the reduction in weight and how that was maintained over time in the three treatment groups. And you see here, of course, the group in the lifestyle intervention group did the best. They lost the greatest degree of weight on average, so about 7 kg. of weight loss early on, within the first

year. And it does tend to tail up over time, so they do regain on average a little bit of weight. But, still, the weight loss was significantly different from the other two treatment groups, and that separation was maintained over time.

Now, as you might expect, people had individual sessions. They had sixteen in six months, and then monthly sessions thereafter. And they focused on a low-fat diet, in general.

Now, the really important slide and finding from this is that every kilogram lost by DPP participants reduced their risk of diabetes by 16%. So that is a really meaningful reduction in the primary outcome, which was progression to T2DM. Now, I would note on this slide, though, there is a little bit of a plateau in risk reduction noted at about 10 kg., or 10% of body weight lost. But, still, overall a really dramatic impact in benefit from loss of just a kilo of weight.

She is now 43 years old. Again, she has a history of hypertension, obesity, and prediabetes, and with primarily an approach including intermittent fasting. She was initially able to lose about 7 kg. or 7% of her body weight, but over time, she slowly regained, which we see is a fairly typical pattern. Importantly from the management perspective, she doesn't plan to have additional children. But, unfortunately, her hemoglobin A1C is now in the diabetes range, so it is 7.4%. Now, she has progressed to T2DM, but it is very likely that the weight loss that she successfully accomplished delayed that progression from pre-diabetes to T2DM.

Now, if we revisit these landmark studies of lifestyle intervention, let's talk about LOOK AHEAD, which is, again, the patient population most like Jackie now, who has T2DM. so this trial enrolled a little over 5000 people with T2DM, and it actually was a cardiovascular outcomes trial that looked at the effect of lifestyle modification on cardiovascular outcomes. And although the trial did not significantly reduce cardiovascular outcomes within the time from of the study itself, a mean weight loss of 8.7% at year one, and 4.7% at year four was associated with many other health and economic benefits, which we will cover shortly.

So, when we look at LOOK AHEAD again, these were people with T2DM who were randomized to standard diabetes support and education versus intensive lifestyle intervention being intensively managed group lost about 8.5% of their body weight at year one, and again, it tailed up a little bit, but they lost more weight, and were successful in maintaining some degree of that weight loss, to an extent greater than that derived in the diabetes support and education group. And, again, there were weekly group and individual sessions for six months, and then every other week. And they also received meal replacements as options, too. So they derived a great deal of support. But, the key take-aways from LOOK AHEAD were that modest weight loss is good, moderate weight loss is better, and major weight loss is the best. And, again, on average, this moderate weight loss of 8.7% was associated with improved glycemic control. People needed fewer diabetes medicines, lower doses of diabetes medicine. Blood pressure and lipids were easier to manage. They had less hepatic fat content on MRI imaging. They were able to get around better. They had less incontinence. They had better measures of sexual function. And there were cost savings from a hospitalization and medication perspective. So, these are

all really important outcomes that I would argue that many of these are very important to the person who was able to lose weight.

If we look at diabetes remission in the LOOK AHEAD study, which wasn't a primary outcome of this trial, but still, we like to look at the effects of intensive lifestyle intervention on the ability to manage glucose without use of medications in people with diabetes. What you see on the left-hand side is the slide that you have seen previously. On the right-hand side is looking at what we describe in diabetes remission in this trial, so the prevalence of continuous hemoglobin A1C of <6.5% on no diabetes medications. And in blue you can see the percentage of people who were able to achieve that with intensive lifestyle intervention. And in orange is the control group. And you do see, particularly at year one, almost 12% of people with T2DM had a hemoglobin A1c sustained in that range without any medications.

It does, of course, kind of drop off over time, maybe in concert with this rise and regain of weight over time. But, still, the intensive lifestyle intervention approach was far more successful than the results shown in orange, those experienced by the control group.

Finally, we do want to make sure that these lifestyle interventions that are recommended for weight loss are appropriate and successful in a very diverse array of people affected by obesity.

And, along those lines, I will briefly mention the PROPEL trial. This was a trial that enrolled patients at eighteen federally qualified health clinics in Louisiana. And, by applying some similar principles used in the other trials, they were successful in achieving a mean weight loss of 6.7% at a year, and 5% in two years. And notably, this was successful. These approaches were successful in a very underserved and under-resourced population. And, again, these interventions were delivered in the primary care population, so it is important to understand that these interventions should not need referral to a specialist. Sometimes, of course, that is necessary. But these interventions were successful in a primary care setting, and a primary care population.

Shown on this slide are just what you see are some interesting differences in success in weight loss achieved by different groups. It actually turns out that people who were older probably were more successful in losing weight than people who were younger. You see some minor differences according to weight and sex, but again, the intensive lifestyle modification consistently more successful than the control intervention in achieving weight loss in this under-resourced, diverse patient population.

How can we translate this to clinical care? Remember that the lifestyle interventions include specific goals for weight loss, and physical activity, and patients did receive quite a bit of, I would say, a high touch interaction, including counseling, reinforcement, review of how they were doing, and helping people get back on track if they fell of the wagon, so to speak. And there were many behavioral elements that were incorporated. I would highlight at the bottom left the Diabetes Prevention Program approach, which included a lot of self-monitoring, stimulus control, reinforcement, again, goal-setting, behavioral contracting, problem solving, and all of these approaches were really reproduced and mirrored, if not expanded upon, in the other two trials of Look Ahead and Propel. So we do need to think

about how we can reproduce the success of these studies by incorporating as many of these elements as we can.

So, self-monitoring, not listed here, yes, you could recommend wearables or smart phone apps. But, frankly, stepping on the scale consistently is an important monitoring. There are many handouts available that go through and provide the principles of some of these behavioral approaches that are available from the Diabetes Prevention Program study group. And, also, if your patient is a veteran, where they have successfully reproduced and implemented those general principles. New replacements can be very successful. And, of course, this is something that has been studied in people with established diabetes. So this is okay, and sometimes can make weight loss significantly easier and more convenient for the affected person. You may need to designate a coach on your staff or in your community who might be able to start a group and really tailor the intervention to your particular community and practice. And remember that monitoring and physical activity are the keys here. All of these other behavioral elements are really focused on the consistent and successful implementation of dietary and activity-related changes.

We do know that there are some predictors of long-term weight loss, and these are the thing that we communicate fairly readily to our patients. So, more activity and eating a low-calorie and low-fat diet. Eating breakfast and maintaining a consistent eating pattern. And, of course, self-monitoring weight on a regular basis and helping to correct course if a person has had a slip, like around the holidays or a period of high stress, to try to get people back on track as quickly as possible while understanding that these bumps in the road will occur. These are really the key strategies, and I think the average person can really understand this very, very readily.

So, let's return to Jackie. She is, again, 43 years old. She has hypertension, and obesity, and now she does have T2DM. She has engaged with a lifestyle modification program at her local Y where many Ys have programs where that translate the principles of the **Diabetes Prevention Program** into the community setting. She has been taking metformin 1000 mg. BID for about three months, and she is doing fine on it. But her hemoglobin A1C is now 8.2%, so not much improvement in her hemoglobin A1C.

What is the next best step for Jackie? Would it be

A. Continue to work on lifestyle modification?

B. Add glimepiride to metformin therapy?

C. Add pioglitazone to metformin therapy?

D. Add the GLP-1 receptor agonist semaglutide to metformin therapy?

E. Refer for bariatric surgery?

Well, I'll tell you. These are all things that could be done. And in diabetes care, there are many potentially correct answers. But I would recommend as the next step option D. And I will show you why. This was a very large, complex algorithm for pharmacologic treatment

of hyperglycemia in T2DM that is annually updated and published by the American Diabetes Association.

The left-hand side of the slide is really intended for people with or at high risk for diabetes related complications. So, that's not really the case for Jackie at this point, as far as we understand her overall health.

So, let's focus on the right-hand side, and you can see particular pathways here that include approaches to minimize hypoglycemia, importantly for Jackie to minimize weight gain, and promote weight loss, and on the right-hand side to consider cost and access. And, of course, we know that these are often overlapping concerns. So, it is unusual for a person to be in just one pathway, so we need to look for opportunities to really achieve multiple goals with as few medications as possible. But, again, with this minimization of weight gain or promotion of weight loss pathway, these are the recommendations for pharmacologic therapy after they had been started on metformin. If they need additional therapy, the recommendation now, and it's in very fine print and easy to miss, in my opinion, the ADA recommend says that the next step is use of GLP-1 receptor agonist with good efficacy for weight loss.

Now, if for some reason your patient cannot access, or cannot take a GLP-1, an SGLT2 inhibitor is offered as an alternative. But we do know that the degree of weight loss conveyed by an SGLT2 inhibitor is generally less than that than you would see with GLP-1 receptor agonist therapy. And note, too, that if your patient is on metformin, and, for example, an SGLT2 inhibitor, and their A1C remains above target despite that combination therapy, they recommend as the next step the addition of the other class listed here. So, a GLP-1 receptor agonist. And again, if these drugs cannot be used for any reason, at least try to choose medicine for diabetes control that are weight neutral, such as, for example, DPP-4 inhibitors.

You could, before I move away from Jackie, certainly you could consider bariatric surgery as an intervention for her. And her outcomes benefit may be very, very great from bariatric surgery to address her obesity. Because she is early on in her life span with T2DM, her likelihood of diabetes remission and reduction in long-term complications may be greater than someone who waits until later. However, I would, as the next step, introduce the GLP-1 receptor agonist because I don't want her hemoglobin A1C to stay at 8.2% or even go higher over time. It takes a while to get involved in a surgical program, and she may, or may not be interested. So, don't wait until someone is assessed. Don't wait until they decide whether or not they want to do that to take action to control their glucose level.

So, this actually is a slide from Dr. Ryan. And I think it is a really nice way to display how we all need to take a holistic approach to weight management interventions. And it is not just increased diet and physical activity. There are many factors that need to be assessed, and potentially included in a person's overall approach to weight management. So, how is your patient sleeping? What do we need to do with their medications to reduce the risk of hypoglycemia? Do we have depression or other mental health issues, or stress management. Or do they need stress management counseling in order for them to reduce the amount of stress in their daily life that may translate into unhealthy behaviors? Let's choose medicines that reduce the risk of medication induced weight gain.

And, finally, and maybe most importantly, people may need some financial management skills or counseling to help them figure out how they are going to afford somewhat healthier food, for example, or their medicine. So, often, a healthier approach to diet is a little more expensive than ways that people have already been eating. So, we do need to consistently advocate for a better built food and work environment and for social justice for equity in our approaches to obesity management. Thank you very much for your attention.

DR. RYAN: Jennifer, that was wonderful. Thank you so much. That was terrific. You know, I am so glad you reminded our listeners about financial management skills. I will tell you a little story. One time at Pennington we did a study, and we were looking for a community-based intervention, and we did one that was, of course, a weight management intervention, and we wanted a control condition. So, for the control condition, we had somebody who was adept at teaching good financial management. So that was our control condition. And our control condition lost just as much weight as the weight loss intervention. It is really a big stressor for people.

DR. GREEN: It really is, and I do think that we need to be very cognizant of our patients' financial restrictions or situation. It's okay, I think, to ask and feel that out. It is one thing to recommend that someone go to a farmer's market to choose healthy, organically grown vegetables. But, for many people, first of all they can't get there, and second of all, that can be a very, very expensive way to each fresh fruits and vegetables. And, so to really think about other ways of introducing healthier foods like, for example, frozen vegetables are a much more economical alternative and provide essentially the same health benefits. So, it is very, very important. Don't be afraid, I think, to have those discussions. We know how to talk about sort of sensitive subjects in a careful way. We do that with lots of other kinds of conditions, so let's think about how we can make weight loss successful for each individual person and their circumstances.

DR. RYAN: And you did a great job of the new ADA standards of medical care recommendation that we prefer the use of GLP-1 receptor agonist for weight management, ones that have a good weight loss profile. But what about the new GLP-1? Is it the same? That has a good weight loss profile.

DR. GREEN: Oh, yeah. So, that is not in the ADA guidelines yet because those are generally completed in the fall of the year before they are published. And, so tirzepatide, which is the dual GLP-1-GIP receptor agonist that is now approved, and can be prescribed for management of T2DM frankly does convey the greatest degree of glucose lowering and weight loss of, really, the importin-based therapies that we have available now. It may not be on everyone's formulary of their commercial insurance yet. It may not be accessible to everybody on Medicaid or Medicare. But it is newly available. And, you know, personally, I do like to manage diabetes with a minimal list of hypoglycemia, minimal risk of weight gain, and also just a minimal medication burden. That, I think, makes my patients lives easier, which is one of my primary goals. And it is an injection that is given once a week. So it is very unusual for me to have someone refuse to add an injection that will effectively lower their blood sugars, and can help with weight loss in a really meaningful way that they just have to take once a week. And I'd like to look for opportunities to introduce medicines like that, and maybe, not right away, but maybe over time, I can actually take away some

of the other medicines that they are taking. Certainly can reduce the need for them to add additional medications over time. So, it is a really exciting time in diabetes and weight management. I think we have many, many more very effective and well tolerated tools than we did in the past. So, I personally feel very positive about this when I go to clinic. And, you know, it's not always the case when we go to clinic.

DR. RYAN: We are lucky we have all these choices of GLP-1s and GIP now. But, how do these stack up in terms of relative weight loss and relative improvements in A1C? Which are the ones that produce the most, and which the less, and what about dosing? Does dosing make a difference?

DR. GREEN: Well, I'll take your last question first. So, yeah, so the degree of weight loss and glucose-lowering that is derived by the GLP-1 receptor agonist and the dual agonist now, tirzepatide, they do seem to be dose-dependent. And, so, if I put somebody on a medicine, now they do have primarily GI side effects, so why don't we start low and go slow? I start at the lowest dose, and then I make sure that my patient is really feeling good before I up titrate the dose because I want to have them tolerate it as best as possible. If they have GI side effects, usually they go away over time, even if they stay on the medication. So that's an important piece of counseling to tell the person who is starting a medicine. But, over time I like to make sure they are feeling okay, and then I will up titrate, and I do try to up titrate the dose as far as I can because, if they are on that drug, I want them to derive the maximum benefit.

Now, only in a few trials have the different GLP-1 receptor agonists or dual importin agonists been compared head-to-head. But, based on the information that we do have available, it looks like many of the once-weekly GLP-1 receptor agonists, and then, of course, tirzepatide. So, if you think about dulaglutide, for example, semaglutide, and tirzepatide, these seem to be very, very effective, and particularly in that order. So, you probably have liraglutide, dulaglutide, semaglutide, and tirzepatide -that's really the order of potency or efficacy that I generally consider. But, honestly, for the individual person sitting in front of you, the key is going to be which one of these can they actually get, right? So, which is covered. Right? So, I am an equal opportunity prescriber as a class, or sort of a class-plus. These are great medicines for diabetes management. They are some of the most effective, I mean, it has been unusual over the years for me to be able to prescribe many drugs for diabetes that are actually good for weight loss, too. So I will prescribe whatever they can access.

Now, we didn't go over the left-hand side of that ADA algorithm. That's really focused more on people with established cardiovascular or kidney disease. In that particular situation, if you are treating with a GLP-1 receptor agonist, you are going to want to choose from among the ones with proven cardiovascular outcomes benefit, which at present would be liraglutide, dulaglutide, and injected once-weekly semaglutide. So, I do preferentially go for those in the higher risk person with T2DM. But, again, if you are treating a "lower risk" person with T2DM, I think any of the GLP-1 receptor agonists that they can access is going to be a fantastic option for glucose management and weight management.

DR. RYAN: So, when you are prescribing these medications, how do you use the medication with lifestyle instructions? Give us a tutorial on that.

DR. GREEN: You know, that's a good question. Most of the time, hopefully the person I am managing, because I am a specialist, hopefully they have received some type of nutritional counseling, they've received diabetes self-management education, but we often need to reinforce that. By the time a person comes to see an endocrinologist, that counseling may have been many, many years ago. So, what I do for new patients, I like to assess their literacy when it comes to appropriate lifestyle modification, and I often need people to have a bit of a refresher. And I have them meet with a nutritionist, or dietician, or certified diabetes educator affiliated with my practice, frankly, much of which can be delivered remotely now, so it can be often delivered in the convenience of a person's own home. But I do emphasize that the medicines and the lifestyle modifications work together. And I show them kind of a see-saw image. So, if you are doing less from the lifestyle perspective, then you are going to need more of the medicines to achieve your personal target. So, we really want this balance. And I think, again, that is something that is easy for people to understand, and they need the skills. They need to kind of sit down, maybe with the rest of their family, and talk with a nutritionist or dietician and talk about ways that they might be able to make some relatively simple changes to their meal plans. It is often something that affects the entire family, so we need to take that into consideration. But to really reinforce these lifestyle principles. And then to talk about and think about ways for people to safely exercise within their personal limitations. And, again, many of my patients do have a lot of restrictions, and they may not be able to walk very far. But sometimes people can do a little bit of upper body exercises with cans of beans, you know. It's an inexpensive home gym. But, just ways to think about sliding in a little bit of increased physical activity on a regular basis.

DR. RYAN: Yeah. I think it's very important for patients to understand that the medications do not work at their best on their own. We have to help them by an intention to diet.

Jennifer, this has been wonderful. I have so enjoyed your presentation. I learned from you. Thank you. Thanks very much. And thanks to all our viewers and listeners to this, our second webinar in our series.