OVERVIEW

Obesity experts Drs. Apovian and Kushner delve into the complex and undertreated disease of obesity, addressing the importance of weight loss and chronic weight management. They discuss obesity as a chronic disease with its pathophysiologic basis, associated cardiometabolic risks, treatment options including pharmacotherapy, focusing on incretin-based medications, optimizing weight loss and maintenance, and how to approach patients about obesity. Case studies are utilized in which the faculty share their experiences to individualize patient management so as to improve long-term weight-related health outcomes.

CONTENT AREAS

- Pathophysiology
- Cardiometabolic Risk
- Treatment Options
- Incretin-based Therapy
- Optimizing Outcomes

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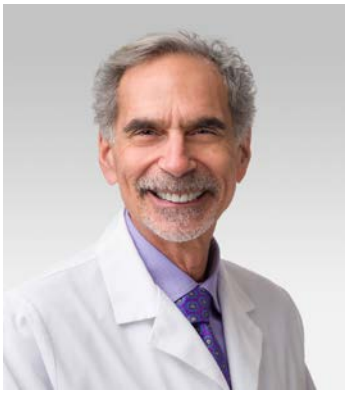

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TARGET AUDIENCE

This activity was developed for cardiologists, endocrinologists, primary care physicians, and other healthcare providers who treat patients' obesity and other commonly associated diseases.

Learning Objectives
At the conclusion of this activity, participants should be better able to:

- Recognize obesity as a chronic disease
- Describe the impact of obesity on cardiovascular comorbidities often associated with obesity
- Select patients for whom pharmacotherapy would be appropriate
- Individualize treatment based on patient's cardiovascular risk and other patient factors in order to promote long-term maintenance of weight loss

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The estimated time to complete the activity is 1.25 hours.

This activity was released on March 31, 2022 and is eligible for credit through March 31, 2023

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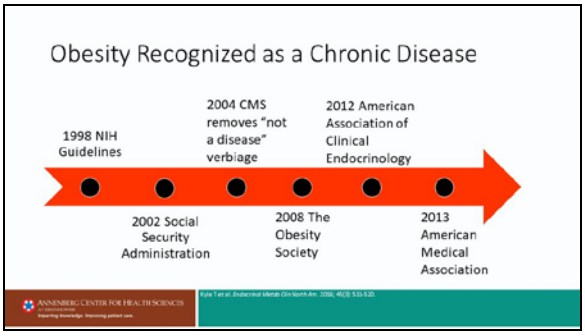
Editor's Note: This is a transcript of a webcast presented in February 2022. It has been edited and condensed for clarity.

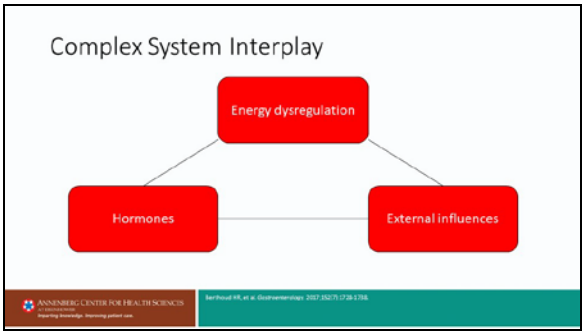
INTRODUCTION

OBESITY AS A CHRONIC DISEASE

Caroline Apovian, MD: When was obesity recognized as a chronic disease? That's a really good question. Many of us in the field—I've been in the field, along with Dr. Kushner, for over 30-35 years—and we recognized obesity to be a chronic disease. The 1998 NIH guidelines were written for the treatment of obesity and it was very clear, if you read those guidelines, that obesity is considered to be a disease.



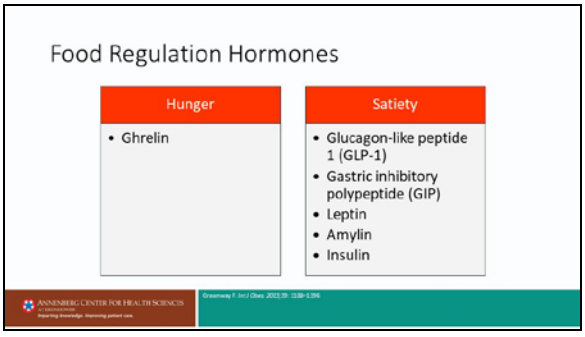
In 2002, the Social Security Administration recognized that obesity is a disability. Then, fast forward another 10 years, and the Obesity Society also recognized obesity to be a disease in a white paper. But it wasn't until 2013 that the American Medical Association mandated that obesity be treated as a disease by recognizing it. We now know that obesity is certainly not a matter of willpower, that there is a dysfunction in the energy regulation system in the brain, that I'll talk about in a moment, in obesity that promotes the maintenance of a higher body weight set point.



We talk about it as a set point, and in obesity there is an energy balance dysregulation. In everybody, lean or those with obesity, energy balance is tightly regulated so that you maintain a certain body set point in weight, in your weight, and that you maintain a certain body fat. And when you lose weight, even if you're lean and you try to lose weight, your body thinks it's starving and there are complex systems, hormones and external influences, that interplay with that so that you get hungry and you regain the weight. This is also true in obesity, but in obesity there's some kind of an energy imbalance such that those people who gain excess weight maintain that higher body weight set point.

GUT-BRAIN AXIS

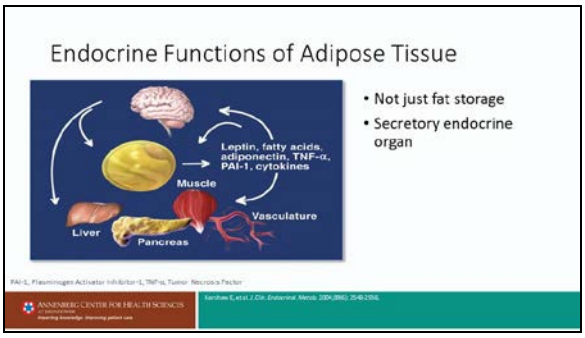
The hunger hormones that we're talking about, we really know of only one, called ghrelin.



It's secreted in the stomach right before you're about to eat, [that] causes you to be hungry to eat that food. There are many more satiety hormones that we've discovered. We know that there probably are many more hunger hormones; we just haven't discovered them yet. The satiety hormones are GLP-1 (glucagon-like peptide), GIP (gastric inhibitory peptide), leptin, amylin and insulin. These hormones come from the stomach, come from the small intestine, come from the pancreas and come from fat tissue or adipose tissue. And this adipose tissue, the hormones that come from adipose tissue regulate body fat stores.

ADIPOSE TISSUE

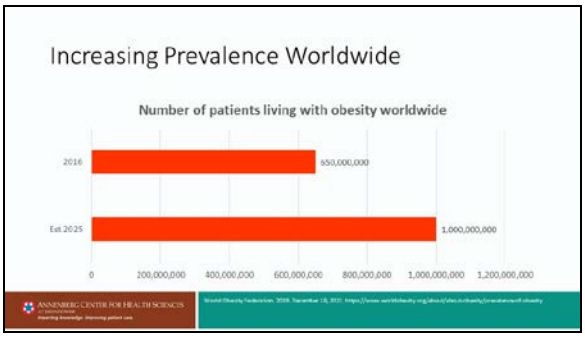
Adipose tissue is now recognized as an endocrine organ. It's not just a set of cells that sit there and store fat. It's a secretory endocrine organ. What does that mean? It means that it sends out signals to other organs, the main one is the brain. It sends out signals signifying to the brain and the energy regulation system whether or not there's enough fat so that the body can maintain its regular metabolic rate and it can maintain activities and the organs are well fed, basically. Again, when you lose weight, less leptin is secreted from fat tissue, and the brain sends signals throughout the body that eventually leads to regain of that body weight.



Fat tissue speaks to other organ systems based on paracrine and endocrine ways by secreting leptin, free fatty acids, adiponectin, TNF-alpha and other cytokines. And when there is excessive fat tissue, those cytokines increase, inflammation increases, and it leads to disease in other organ systems. The bottom line is there's a certain degree of body weight, body fat, that you need for survival, but in excess of that, that's when inflammation starts.

PREVALENCE

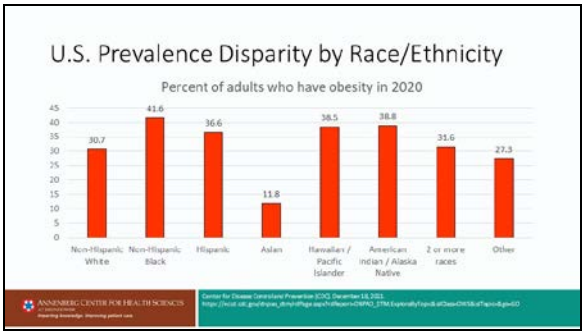
Now, something happened worldwide over the past 50 years that has allowed many more people in this environment to defend a higher body weight set point. The prevalence of obesity has increased. Even since 2016 or 2015, there was 650 million people who had obesity and now there's over a billion.



Something is going on that has affected us in this environment and there are many, many reasons thrown out there, but we think it's the advent of high-fat, high-sugar foods, highly-processed foods. There are other factors, temperature regulation, lack of physical activity, but the bottom line is there's an increasing prevalence worldwide of obesity and the question is why did this happen. This is still being debated today. What we need to know is how to treat it.

We also talk about disparities in obesity, racial disparity. It seems that certain races, African Americans and the Hispanic population in the United States, have a higher prevalence of obesity than non-Hispanic, White patients, and Asians. Many people feel that this is because of

socioeconomic conditions in some of the more minority races and some seem to feel that it must be a combination of genetics and socioeconomic status.



When you look at the data, it does point the finger to socioeconomic status with food availability, whole food availability vs highly-processed food. This is where we get some of the ideas that we have that it's really our toxic food environment that is causing much of the problem.

HEALTHCARE CHALLENGES

When dealing with obesity, whether you're high or low socioeconomic status, many patients with obesity fear seeking treatment because of the stigma that patients seem to feel on a community level and also on an MD/provider level and other providers, that there's still weight bias. There still is lack of provider knowledge about obesity being a disease and available treatments. What do I mean by that?

It's still true that some providers, when faced with patients with obesity will say, well, just lose weight, just lose weight by dieting and exercise not understanding that patients have tried and failed many, many times to do this and because it's a disease that they're dealing with, it's not a matter of willpower.

This breeds low trust and poor communication. There is also, for other reasons, an underutilization of treatment options. We have 6 medications that are FDA-approved for obesity treatment. Only 2% of patients eligible for one of these treatments in the United States receives a prescription per year. Of all the patients with BMIs over 30, only 2% in the United States get a prescription for an anti-obesity agent.

If you look at bariatric surgery, it is also true that about 1% to 2% of patients who are eligible for bariatric surgery receive an operation per year. We have millions of patients with a BMI over 40 in the United States and there's still only about 250,000 procedures done per year for bariatric surgery. This is a big problem that we still have to solve.

There are many complications associated with obesity. Certainly, obesity itself, the anatomic derangements caused by obesity are osteoarthritis, back pain, but there are also metabolic complications associated with obesity that, because of the inflammation primarily, cause type 2 diabetes, heart disease, stroke, hypertension, nonalcoholic fatty liver disease. Sleep apnea is caused by a combination of anatomic and metabolic complications of obesity and we also have reflux disease, GERD, that is associated with obesity.

For all these reasons, obesity needs to be treated. The cost of obesity is tremendous. Healthcare costs, if you just look per patient, there's an additional $1,800 per year associated with a person with obesity compared to someone with a BMI of 25 or less, and then life expectancy drops in patients with obesity. There are 2.6 million deaths annual from noncommunicable diseases with many, many ties to obesity. On average, it's estimated that for patients with BMIs over 30, they live about 12 years less than other, normal weight patients. The cost of obesity is high. The patient burden of disease is very high.

BURDEN OF DISEASE - PATIENT INTERVIEW

Do you feel like healthcare providers make assumptions about you because of your weight?

I think that sometimes there is an assumption that you're not physically active when you're overweight and, for me, that's not the case. I mean, and I don't know if it's the healthcare provider or if it's my own internal, but I feel like I have to defend those things sometimes to my healthcare providers that, you know, the normal person comes in and says, hey, they say how physically active are you and they're like, oh I exercise four days a week and they're like okay. For me, I feel like the look on their face says this guy's full of it. You know what I mean? And so I feel like I have to defend that to the point where I even have said to my wife, you tell them I go to tennis. You know what I mean? And my wife's a nurse, so then I assume they're going to, you know, they're going to believe her.

If you could tell your provider, how would you prefer to be treated instead?

You know, I think that, I think that sometimes it's very hard for people to fight their internal assumptions and I think that, especially medical providers, I think it's really important that they, that they really cultivate an environment where you feel that you're not being judged or that there's no preconceived perceptions of either how you got to a place in your life and where you're at. That just, they're there to help you and to understand you. And I think a lot of times you get more of a perspective, or I feel that you get more of a perspective of this is how we think you got there and this is what you need to do. You know? So, I think really cultivating a, not a perception, but an actual environment that really feels inclusive and not exclusive where you really feel that you are being included a part of the treatment plan, not being dictated the treatment plan.

What is one thing you wish all healthcare providers knew about living with obesity?

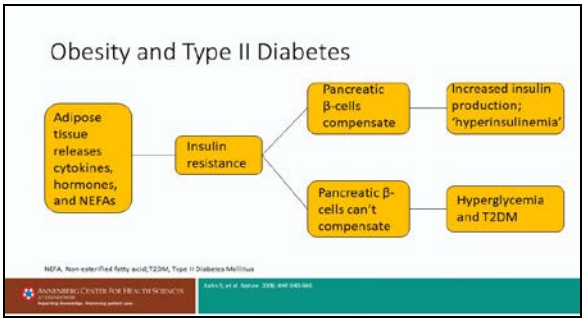
I think that sometimes it's, I think it's hard to explain failure. So, we get into these programs and we want to be doing a good job. You know, we want to be losing weight and we want to be following the treatment plan. But much like someone with addiction, it's very, because in many ways this is in some ways for some people, right, it's very difficult and I think that's one thing that I've really struggled with, that I've just kind of realized, I've done pretty well, I've lost weight doing this, but I haven't done everything perfectly and I think that sometimes they're, and I don't know how to fix this, right, it's something that I'd really have to think about, but creating an environment where it just feels a little bit easier to fail and bring that up to the healthcare provider, like I think that sometimes there's this sense that if we let you

down, we're going to be judged or whatever, right, this preconceived notion. So, I just think while we're, while people are going through this process, maybe proactively checking in with them a little bit more and letting them know whether you're doing, whether you're following the treatment plan exactly or not, the more proactive touches that can be made, I think the better.

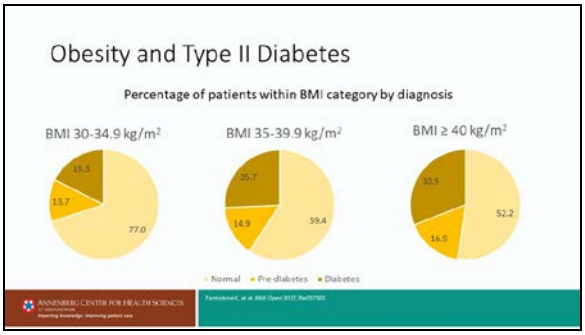
CARDIOMETABOLIC RISK

TYPE II DIABETES

Robert Kushner, MD: Let's first start with type 2 diabetes. This data's pretty well worked out, both in the lab and in clinical studies, and it seems to begin with adipose tissue itself as an endocrine organ that releases cytokines, hormones, as well as fatty acids, and those signals then go primarily skeletal to muscle, but other organs, as well, to cause insulin resistance.



Once you have insulin resistance, the beta cell is prompted to respond by secreting more insulin in order to compensate for the insulin resistance and, at first, you end up with hyperinsulinemia, but a normal blood sugar, as you try to compensate. But over time, the beta cells become exhausted. They can't keep up with the insulin resistance that's primarily driven by the increased adipose mass, as well as the cytokines and adipokines, and that's when you end up with not only hyperinsulinemia, but the blood sugar starts to rise and you end up with hyperglycemia and type 2 diabetes. So that's the sequence that we've been working on as far as the cascade of the problem that occurs with type 2 diabetes.



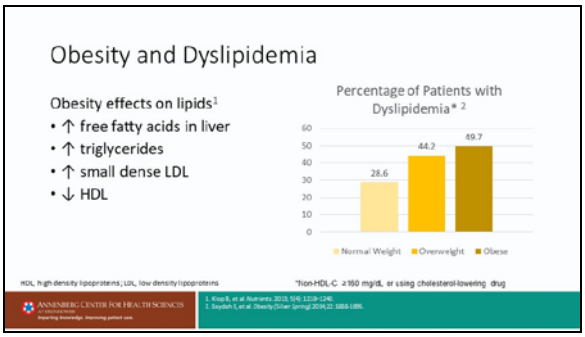
If you look at how common this problem is, Cleveland Clinic performed a cross-sectional observational study where they looked at their data set from their healthcare system and divided up the patients coming to Cleveland Clinic into the different BMI classifications that are classically used: class I, which is a BMI 30 to 34.9, class II obesity, a BMI 35 to 39.9 and then finally class III obesity which is 40 or more. Now we know BMI is probably a terrible way to describe the disease of obesity, but for the purposes of epidemiologic studies, it actually works pretty well. And a key finding from this Cleveland Clinic study is when you look at each of the BMI classifications and you look at how many of those had normal glucose control, how many had prediabetes and how many had diabetes, what you notice is that as BMI classes go up, so does the prevalence of prediabetes and diabetes.

For example, in the class I obesity group, diabetes was diagnosed in just under 20 percent, which is pretty darn high, but when you get to class III obesity, it goes up to over 31%. When you see a patient in your office, just having the BMI in the medical record already gives you a marker of what comorbidity,

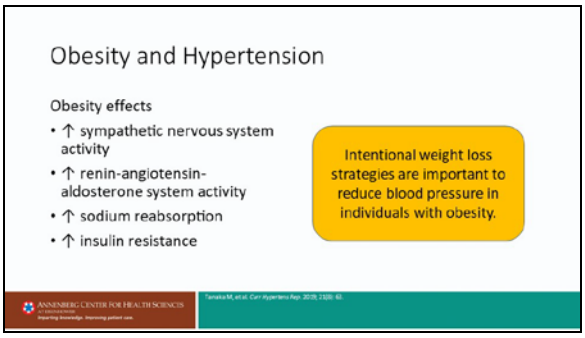
typically diabetes, that person's likely to present with.

DYSLIPIDEMIA AND HYPERTENSION

Now, if we look at also obesity and dyslipidemia, there's some very nice data from NHANES that shows that the higher the BMI classification, as you go from normal weight to overweight to obesity, the higher the dyslipidemia, going from 29% all the way up to nearly 50% in those who suffer from obesity.



We also know the underlying etiology, just like we did in diabetes. We know that, in obesity, there's increased free fatty acid release from the liver. We know there's increased triglycerides primarily coming from the liver. You have an increase in the small dense LDL, those are the atherogenic particles, and conversely HDL, the health lipoprotein, starts to go down. This is consistent with what we call metabolic syndrome dyslipidemia, not the classical high LDL cholesterol. That's not what you really see in diabetes.



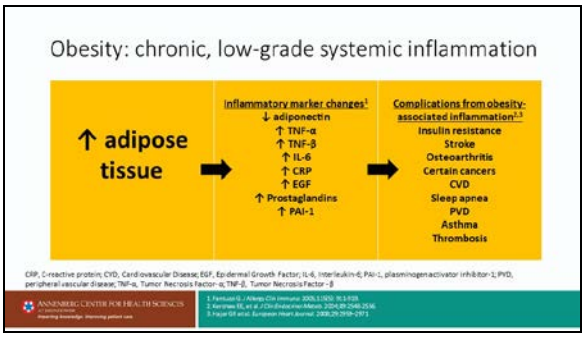
The third major cardiovascular risk factor that we all screen for and control, is hypertension. The pathophysiology of obesity and hypertension has also been pretty well characterized and studied. We know that with obesity, there's an increase in sympathetic tone. We know there's an increase in renin-angiotensin-aldosterone system activity, increased sodium reabsorption, increased insulin resistance which we just talked about, and the kidney tries to compensate. And you actually get a decrease in the GFR which is called obesity nephropathy from that alone.

So that cascade continues to occur, over time, as well as higher rates of hypertension with higher classes of obesity. And we now know that intentional weight loss strategies are important to reduce blood pressure in individuals with obesity. And the paradigm that Caroline and I are going to be talking about is shifting from just treating diabetes, dyslipidemia and hypertension alone, as the target, and thinking more of an obesity- or weight-centric approach to treat the underlying problem in order to improve all these cardiovascular risk factors.

CARDIOVASCULAR DISEASE

If we summarize obesity and cardiovascular disease together, which we all know that individuals with obesity suffer higher rates of myocardial infarction, stroke, atrial fibrillation, congestive heart failure, and we know now that underlying mechanisms that are often associated with that, such as increased cardiac workload, raised atherosclerotic lesions, increased systemic and vascular inflammation. We know there's an endothelial dysfunction in these individuals and they are often presenting with what we call the high-risk obesity phenotype which is this upper body fat obesity or increased waist circumference and also we know that the extent and duration of obesity increases cardiovascular risk. All of these

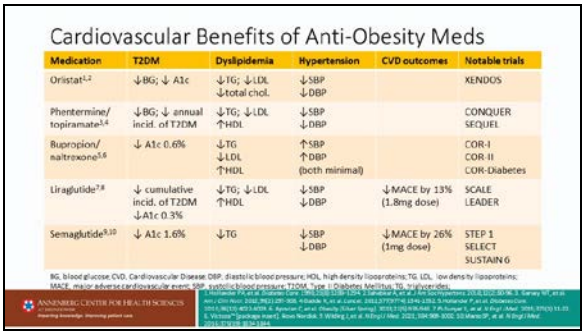
independent risk factors that are associated with obesity go on to cause these intermediate risk factors, like type 2 diabetes, dyslipidemia, hypertension, increased sleep apnea and obesity hypoventilation syndrome, and that then goes on and causes things like stroke, myocardial infarction, heart failure and so forth.



If we summarize this whole obesity-centric approach, this new paradigm, as we approach individuals at high phenotype risk, we start off with this increased adipose tissue, particularly in the visceral compartment or increased waist circumferences. That then leads to inflammatory response of increase in TNF-alpha, TNF-beta, interleukin-6, CRP which is a marker of inflammation, increased PAI-1 for endothelial dysfunction and thrombogenesis and so forth. And that inflammatory response, along with development of other intermediate risk factors, then goes on and causes these complications that we desperately want to avoid, as I've said before, like stroke, cardiovascular disease, peripheral vascular disease, thrombosis and others, like asthma and certain forms of cancer.

WEIGHT LOSS BENEFITS

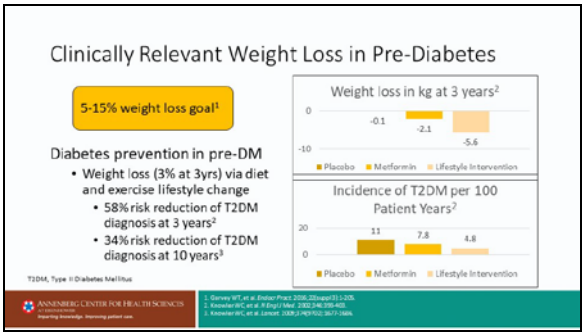
Now, we're going to talk a little bit later about the medications we use, but if we look at the medications that are currently approved by the FDA, all of them improve diabetes, not only the risk of developing diabetes, but also diabetes itself with a reduction in hemoglobin A1c.



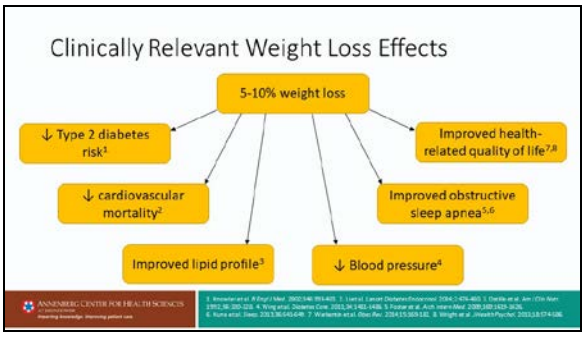
Two of them, which happen to be GLP-1 receptor agonists that are also approved for diabetes, they work as incretin hormones so they directly affect diabetes as well the benefit you get from weight loss. Dyslipidemia generally improves with the medications and with weight loss. Hypertension also generally improves with the use of these medications. All but one though, we need to single out, and that is the combination of bupropion and naltrexone, because mostly the bupropion component, you could end up with a slight increase in systolic and diastolic blood pressure.

Two of the drugs, the GLP-1 receptor agonists, have cardiovascular outcome trials so we know that not only do the intermediate risk factors improve, but heart endpoints improved, the major adverse cardiovascular events improved. And they all have been studied in trials that I would encourage everyone to actually look at.

What can we do about it? Well, there's pretty good data that weight loss will improve the cardiovascular risk factors and, as we've said, even heart endpoints with at least the GLP-1 receptor agonists.



There's a landmark study published 20 years ago now which is the Diabetes Prevention Program and this study looked at individuals with prediabetes and we learned a very important lesson from that study. And that is a small amount of weight loss in individuals with prediabetes will reduce or delay the development of developing diabetes over time. In the DPP trial, those individuals who were assigned or randomized to lifestyle management, the risk of developing type 2 diabetes over 3 years was reduced by 58% and those that were assigned to metformin was reduced about 34%. We know that small amounts of weight loss, 5, 6 kg or so, leads to reduction in type 2 diabetes, and in post hoc analysis of this very important study, the primary determinant that delayed the occurrence of diabetes was the weight loss itself.



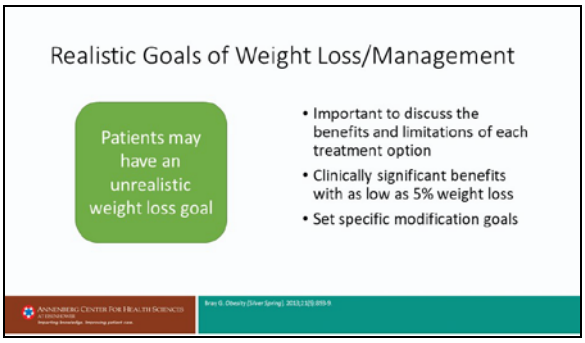
In summary, we know that a modest weight loss, 5% to 10%, you know, often the more the better, but as little as a 5% to 10% weight loss will reduce the risk of type 2 diabetes as well as improve diabetes itself, will improve lipid profiles, reduce blood pressure, will improve sleep apnea particularly in the higher amounts of weight loss, improve quality of life and, in some of the studies, actually reduced cardiovascular mortality.

TREATMENT OVERVIEW

TREATMENT GOALS

Caroline Apovian, MD: We are going to talk about treatment. How to do it with lifestyle and diet and exercise, but many patients with moderate-to-severe obesity also need medications, pharmacotherapy, antiobesity agents to help, to help change that body weight set point to a lower level to keep that weight off and then other patients do need surgery. We are going to talk about this.

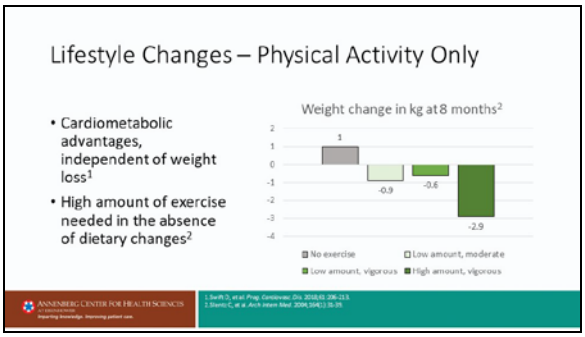
Patients may have an unrealistic weight loss goal. Unless they're candidates for surgery and are interested in surgery, it may not be possible for patients who let's say weigh 300 lb to really get down to 150 without surgery or even with surgery.



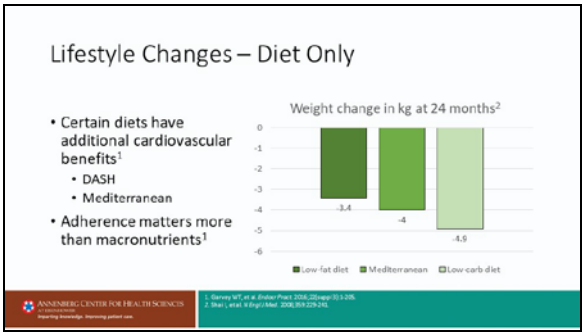
It's important to discuss realistic weight goals, and because of the DPP trial and other trials that show that with a 5% to 10% weight loss you can really reduce your risk of diabetes, of heart disease and other morbidity and mortality, that it is important to set realistic goals because that may be under the control of the patient, with or without medication. And there are clinically significant benefits with even as low as a 5% weight loss. It's very important to talk about that right up-front.

LIFESTYLE CHANGES

When we talk about lifestyle change, we're talking about diet, physical activity and the other behavioral changes that allow for patients to adhere to a specific diet or physical activity pattern.

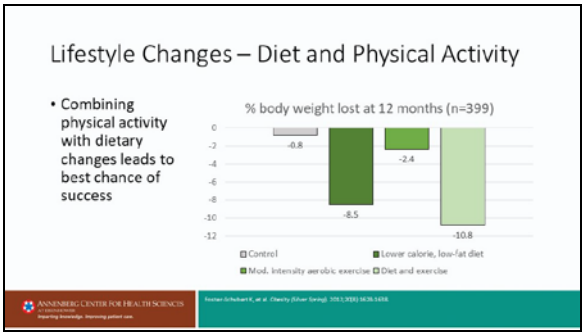


There are certainly many cardiometabolic advantages of doing physical activity independent of weight loss. So physical activity has been shown to improve longevity, to reduce blood glucose, blood pressure, lipids in and of itself, even without weight loss. Now, if you do use physical activity to reduce weight, you're going to have to be almost an elite athlete to be able to do that. So we're talking about high amounts, vigorous exercise, without changing your diet, to lose weight.



Exercise alone, really great for cardiometabolic health, but if you're looking to help your patients lose weight in addition to the cardiometabolic health, you really have to talk about dietary changes as well. What about diet only without exercise? Certainly you can help your patients lose weight with diet alone. We have learned, however, that without a regular physical activity program to offset that, that drop in resting metabolic rate, very hard for patients to keep weight off with diet alone.

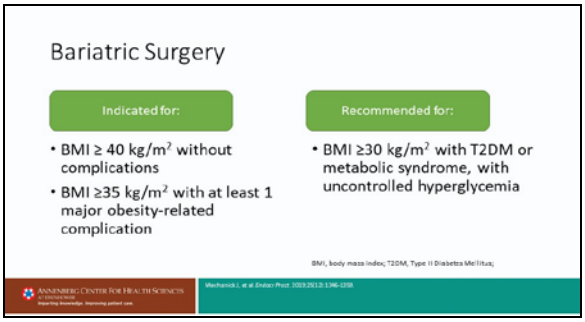
What kind of diet? There are certain diets that have additional cardiovascular benefits besides weight loss, including the DASH diet. The DASH diet has been shown in many studies to be able to lower blood pressure without weight loss and also to lower lipids and improve blood glucose. The Mediterranean diet, a style of eating with healthy fats, small amounts of protein, whole grains, has been shown to have cardiovascular benefits, with or without weight loss. When you're talking about diets to lose weight, however, it doesn't matter what diet you put the patient. It matters that the patient can stick to that diet. And then you can have good weight loss with a low-fat diet which is the DASH diet, similar diets are low-fat, the Mediterranean diet, which is a high-fat diet but healthy fats, and even a low-carb diet where carbohydrates are almost eliminated. It doesn't matter what diet the patient's on. There will be weight loss.



When you combine diet and physical activity, you definitely get the biggest bang for your buck, and why is that? Because the calorie deficit of the diet is going to drop that weight; the physical activity is going to add a little bit to that weight loss, but really the physical activity is going to help maintain that weight loss. Exercising muscle talks to fat tissue and it looks as if some of that fat tissue gets turned into beige or brown fat and brown fat burns more energy than white fat. That's why we think physical activity is so important. You can get a bigger weight loss in the end and better maintenance with diet and physical activity.

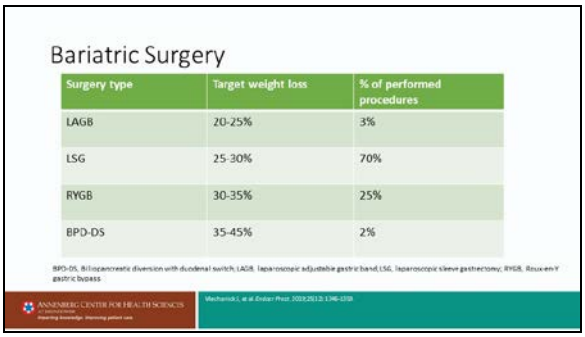
BARIATRIC SURGERY

We're going to talk about medications to enhance the weight loss that we get from diet and exercise. The other big treatment for certain patients that can help propel that weight loss further out to 20% and 30% and 35% weight loss is bariatric surgery.



Bariatric surgery is indicated for BMIs over 40 without complications or BMIs over 35 with at least 1 major obesity-related complication. Those complications are type 2 diabetes, sleep apnea, cardiac disease, severe osteoarthritis.

Now, sometimes bariatric surgery can be recommended for BMIs over 30 with type 2 diabetes or metabolic syndrome and for those with uncontrolled hyperglycemia.



The laparoscopic adjustable gastric band is simply a band that's placed around the stomach so you get a partial obstruction and a narrowing of the stomach. And in many studies, it has been reported to help patients lose 20% to 25% of their initial body weight. We really don't do that procedure in large numbers in the United States anymore because of the weight regain and complications, band slippage.

There are 3 other procedures which are done. The laparoscopic sleeve gastrectomy gives a target weight loss of roughly 25% to 30% weight loss. About 70% of the procedures done in the United States are the laparoscopic sleeve gastrectomy.

The Roux-Y gastric bypass used to be the gold standard, giving you 30% to 35% weight loss. Only about 25% of procedures in the States are currently the Roux-Y gastric bypass and that's because the sleeve gastrectomy, giving you similar weight loss, is considered to be

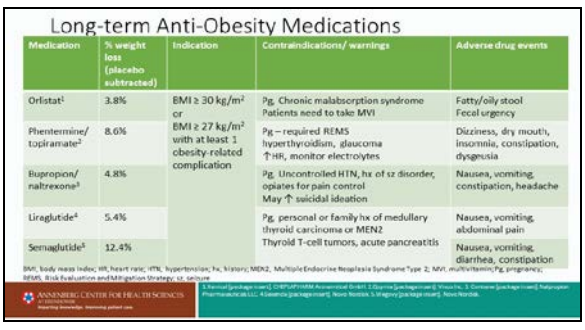
technically easier and doesn't bypass part of the small intestine. The weight loss is greater than sleeve gastrectomy, but there are a few more complications that occur and more often you'll see deficiencies in iron, B12 and folate.

Now the biliopancreatic diversion with duodenal switch is a very aggressive procedure, very similar to the other 2 procedures except for the fact that a bigger proportion of the small intestine is bypassed, you're getting 35%, 45% weight loss. Only 2% of the procedures in the United States are the BPD with DS.

Those are the procedures that we do. Again, for BMIs over 40 or over 35 with a condition.

ANTI-OBESITY MEDICATIONS

Typically, the medications that we have available are going to help the patient lose 5% to maybe now, with the new medications, 15% of their initial body weight. Is that less than the surgical procedures? Yes, it is. Is it significant weight loss? Yes, it is. The rationale for use of medications is, number 1, that obesity is a disease and so it's going to help, these medications are going to help patients adhere to a lifestyle change, lower calorie intake per day plus exercise, to overcome those hormonal changes that naturally occur to push the body to regain the weight.


Long-term Anti-Obesity Medications

Medication	% weight loss (placebo subtracted)	Indication	Contraindications/ warnings	Adverse drug events
Orlistat[1]	3.8%	BMI ≥ 30 kg/m² or BMI ≥ 27 kg/m² with at least 1 obesity-related complication	Pg, Chronic malabsorption syndrome Patients need to take MVI	Fatty/oily stool Fecel urgency
Phentermine/ topiramate[2]	8.6%		Pg – required REMS hyperthyroidism, glaucoma ↑HR, monitor electrolytes	Dizziness, dry mouth, insomnia, constipation, dysgeusia
Bupropion/ naltrexone[3]	4.8%		Pg, Uncontroled HTN, hx of sz disorder, opiates for pain control May ↑ suicidal ideation	Nausea, vomiting, constipation, headache
Liraglutide[4]	5.4%		Pg, personal or family hx of medullary thyroid carcinoma or MEN2 Thyroid T-cell tumors, acute pancreatitis	Nausea, vomiting, abdominal pain
Semaglutide[5]	12.4%			Nausea, vomiting, diarrhea, constipation

BMI, body mass index; HR, heart rate; HTN, hypertension; hx, history; MEN2, Multiple Endocrine Neoplasia Syndrome Type 2; MVI, multivitamin; Pg, pregnancy; REMS, Risk Evaluation and Mitigation Strategy; sz, seizure

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Orlistat is a medication that was approved in 1999. It is the only medication available that does not work centrally. It is a partial fat blocker. What does that mean? It blocks the absorption of about 25% to 30% of fat intake, so food intake, fat intake, to help patients lose about 2% to 4% of their body weight when taken for at least a year. There was a trial that showed that when taken over 4 years, you could still lose and maintain a 2% to 3% weight loss.

There are some adverse drug events, you know, GI side effects that make orlistat a little bit difficult to prescribe to patients, however it is considered a very, very safe drug and it's even over-the-counter it's so safe.

The other medications I'm going to talk about all work centrally. There is a drug combination, phentermine combined with topiramate. Phentermine is an epinephrine-releasing agent; topiramate, as you know, is an antiseizure medication but it has dopaminergic activity and the combination has been shown to help patients lose about 8% to 9% of their initial body weight. And all of these drugs are indicated for patients with a BMI over 30 or over 27 with at least 1 comorbidity.

There are side effects to the combination of phentermine and topiramate having to do with each individual moiety. Phentermine can cause dizziness, elevations in blood pressure, dry mouth, constipation and insomnia. Topiramate, in larger doses, can cause memory loss and paresthesias. The combination together has been shown to mitigate each other's side effects.

The combination of bupropion which, as you know, is an antidepressant and naltrexone which is an anti-addiction agent, gives you about a 4.8%, 5% weight loss. There are side effects to this medication, to this combo, having to do, again, to each individual moiety. Blood pressure elevations, nausea, vomiting, constipation, headache. Bupropion decreases

the seizure threshold. But the combination together has been shown to promote good weight loss.

There are 2 other medications to discuss and these are both GLP-1 analogs. These 2 medications have heralded new age in treatment of obesity to try and get weight loss in a safe manner and to try and, with combinations now of more GLP-1 agonists and other hormones, to inch toward the kind of weight loss that you can see with bariatric surgery.

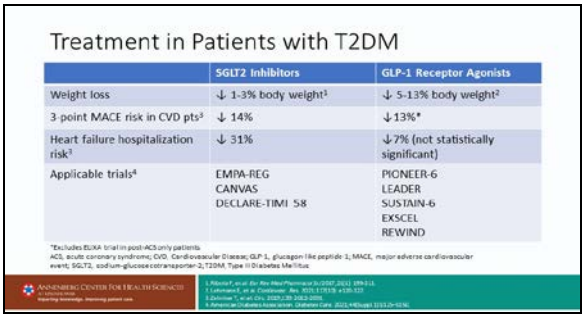
Liraglutide was the first to be approved GLP-1 analog. The weight loss is about 5% to 6%. Side effects of the GLP-1s really are pretty benign compared to the other medications I talked about. Nausea, really it's just nausea, but in higher doses, nausea, vomiting, abdominal pain. Weight loss with liraglutide is about 5.4%, 6%. Semaglutide was recently approved, about a year ago now. It's a GLP-1 analog but it has really pushed the envelope in these appetite suppressants now to get a weight loss of 12.4% and the fantastic thing about semaglutide is, in 1 of the trials in the intervention arm, if you look at the categorical weight loss, about a third of patients on semaglutide for a year lost over 20% of their initial body weight. This heralds the advent of other medications now that are going to inch toward the type of weight loss that you can see with bariatric surgery. Again, side effects similar to liraglutide, nausea, vomiting, diarrhea, constipation.

Those are the drugs available long-term. And I say long-term, we do have phentermine alone. Now if you use phentermine alone, it was approved in 1959 for short-term weight loss up to 3 months, and the combination phentermine and topiramate, because there are smaller doses of phentermine utilized and studied for 2 years, this combination is a long-term treatment and phentermine alone really is not. Even though many of us use it long-term, it's off-label for long-term treatment.

INCRETIN-BASED OPTIONS

GLP-1RAs vs SGLT-2Is

Robert Kushner, MD: We do want to turn to incretin-based pharmacologic options because this is an approach that is really driven by evidence-based cardiovascular outcomes and I want to start with type 2 diabetes in which the guidelines now have evolved to really highlight the use of 2 different drug classes because of the improvement in cardiovascular risk, as well as improvement in blood sugar and those outcomes. That's the SGLT2 inhibitors and the GLP-1 receptor agonists. Of course, we've been talking about the GLP-1 receptor agonists thus far. We haven't talked about the SGLT2 inhibitors which has equally great data for it. And if you look at the newest ADA guidelines, if you have type 2 diabetes, one of the additional targets is weight loss. The recommendations are to consider, with or without metformin, and certainly with lifestyle, 1 of these 2 drugs.


Treatment in Patients with T2DM

	SGLT2 Inhibitors	GLP-1 Receptor Agonists
Weight loss	↓ 1-3% body weight[1]	↓ 5-13% body weight[2]
3-point MACE risk in CVD pts[3]	↓ 14%	↓13%*
Heart failure hospitalization risk[3]	↓ 31%	↓7% (not statistically significant)
Applicable trials[4]	EMPA-REG CANVAS DECLARE-TIMI 58	PIONEER-6 LEADER SUSTAIN-6 EXSCEL REWIND

*Excludes ELIXA trial in post-ACS only patients

ACS, acute coronary syndrome; CVD, Cardiovascular Disease; GLP-1, glucagon like peptide 1; MACE, major adverse cardiovascular event; SGLT2, sodium-glucose cotransporter-2; T2DM, Type II Diabetes Mellitus

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I wanted to start with that as our paradigm shift and as a starting point. For weight loss itself, it's clear the GLP-1 receptor agonists are superior, 5% to 13% total body weight loss, where the SGLT2 inhibitors, it's more modest, about a 1% to 3% body weight loss. And if you look at the 3-point MACE risk in these individuals, again to remind you MACE stands

for major adverse cardiovascular event, and 3-point MACE, to remind you, is looking at the combination of nonfatal stroke, nonfatal MI and cardiovascular death, they're pretty similar, actually. The SGLT2 inhibitors, about a 14% reduction in 3-point MACE, and the GLP-1 receptor agonists, about 13% reduction. Both of them have excellent cardiovascular outcomes.

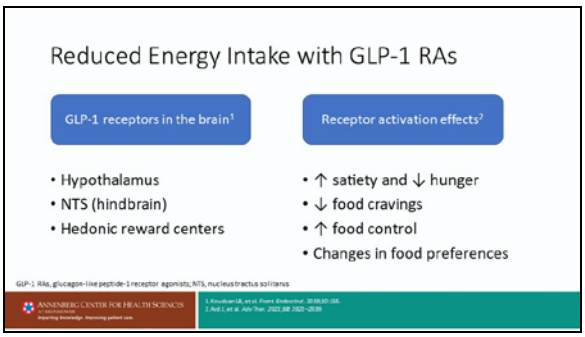
Where it differs, though, is if you have a patient with type 2 diabetes and heart failure and you want to reduce the ongoing occurrence of heart failure, there the SGLT2 inhibitors have shown to be beneficial, where the GLP-1 receptor agonists not quite so. That's where it differs a bit. And there's excellent trials that you could all look at on your own that look at the data more specifically, and I encourage you to go ahead and look those up, that are all published in prominent journals.

Both of them have great cardiovascular outcome improvements in patients with type 2

diabetes, but the GLP-1 receptor agonists are much more powerful in resulting in weight loss.

ENERGY INTAKE

There are GLP-1 receptors in the brain, in the hypothalamus, in the hindbrain as well as the reward centers of the brain.

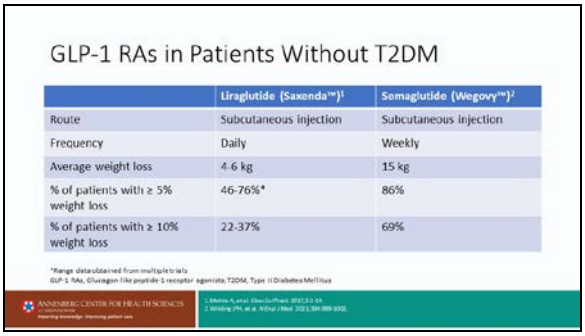


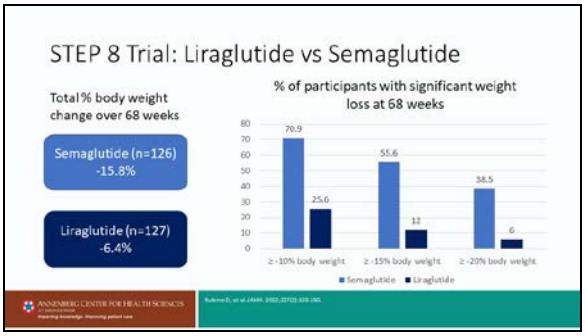
It hits multiple GLP-1 receptor agonists and GLP-1 receptor agonists mimic the naturally occurring gut hormone, which is GLP-1. By giving a naturally occurring hormone in pharmacologic doses, you can augment or accelerate those types of side effects. And interestingly, it's not the drug itself that causes weight loss, it's the effect on appetite, on hunger, fullness, satiety, cravings, thoughts of food, wanting a food, liking a food. By changing the signals of those sensations, individuals are then able to follow a calorie-controlled, portion-controlled diet more consistently. It brings up this very important interface between biologic actions in the brain that affect appetite that is then translated through eating behavior, and therefore they're consuming less calories.

That's why it's so important to counsel your patient on lifestyle counseling when you use a drug like this. It's really quite powerful, it's 1½ to 2 times more effective than other medications.

LIRAGLUTIDE & SEMAGLUTIDE

Now there's only 2 GLP-1 receptor agonists that have been approved specifically for obesity. There's certainly others that are approved for diabetes, but if you want to use ones FDA-approved for obesity, there are 2 drugs that currently are used for diabetes, but at higher doses, you now start to hit more of the receptors in the brain that have to do with appetite regulation beyond the incretin effect for glucose control.





Liraglutide, which we call kind of first generation GLP-1 receptor agonist, it's injected because it's a peptide. It's taken daily, average weight loss 4 kg to 6 kg, and if you look at 2 categorical weight losses thresholds of losing 5% or more, or 10% or more weight loss, it's about 50% and up to 30% respectively for that. It's actually a pretty good drug. But, if we now look at what we all call the second generation GLP-1 receptor agonist, that would be semaglutide, again at a higher dose for obesity care. Again, it's injected, self-administered subcutaneously but now it's longer-acting by modifying the compound, so it can be done weekly. The weight loss is now essentially 2 to 3 times the amount of weight loss you see with liraglutide. Eighty-six percent of individuals are losing 5% or more of their body weight and almost 70% are losing 10% or more of their body weight. And actually a third lose 20% or more of their body weight. It really is so much more effective than other drugs we've seen, thought, in part, due to deeper brain penetration of these receptors that affect multiple appetite regulating centers or signals in the brain.

LIRAGLUTIDE VS SEMAGLUTIDE

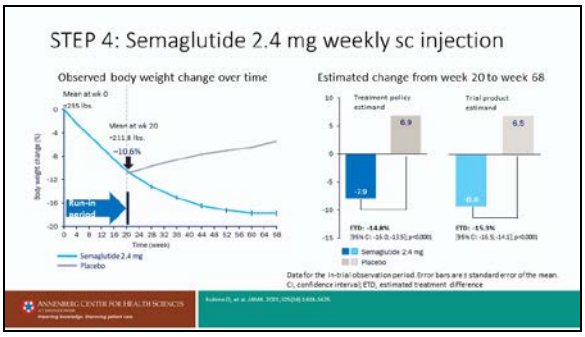
An interesting study just came out. It's actually the first head-to-head trial of 2 drugs approved for chronic weight management to really look within the same trial what the effectiveness, safety and tolerability is.

It's called the STEP 8 trial, that compares liraglutide, so-called first generation GLP-1 receptor agonist, and semaglutide, the second generation. And in summary, the average weight loss after 68 weeks with semaglutide was about 16%, really quite effective. Liraglutide was about 6% weight loss, so almost 3 times the effectiveness, and the categorical weight loss also quite significant.

If we take this incredible amount of weight loss, which is 20% or more, a third of individuals on semaglutide reached that threshold, where only 6% of individuals in this study on liraglutide reached that threshold. We expect other second-generation hormonal treatments that are emerging and are likely to be approved, we hope, over the coming years. Semaglutide is, I think, the first in a wave of more effective hormonal treatments for obesity.

SEMAGLUTIDE: STEP 4

There's 1 more study I wanted to highlight. It's called the STEP 4 trial because there's such important information that came out of it, clinically-useful information about not only the biology of obesity, but also with clinical impact about how we think about treating patients with drug therapy for obesity.



In this STEP 4 trial in which individuals were treated with semaglutide, again the 2.4 mg dose approved by the FDA, all individuals went through a run-in period, so they all received and they knew they were receiving semaglutide 2.4. And after 20 weeks, the average weight loss was about 10%. And at 20 weeks, individuals were then blindly randomized, without their knowing which one they were getting, half the group stayed on semaglutide out to 68 weeks. The other group was randomized in a trial to placebo. They continued to receive diet and physical activity guidance but only 1 group actually received the drug at that point. The other group received placebo.

So interesting. Those that remained on the drug continued to lose weight, losing upwards about almost 18% of their body weight by that point, but the group that were randomized to placebo, and they didn't know it, right, because they were just randomized, they started gaining weight despite being in the trial and, frankly, wanting to lose weight. But because of the forces, the biological forces that led to weight regain, they really could not compensate. They ended up gaining about 7% of their body weight back when they initially lost 10% of the weight.

The underscore, what we learned is that obesity is a biologically-driven disorder that, when you take the drug off, even if they're still in the program and thinking they're getting the medication, they started to gain the weight back because they were eating more and they were getting hungrier and less full. And the take-home message for the clinician, of course, is that if you're going to use a medication, medication only works while you take it. Obesity is a chronic, relapsing disease that requires long-term treatment just like diabetes, just like hypertension and dyslipidemia.

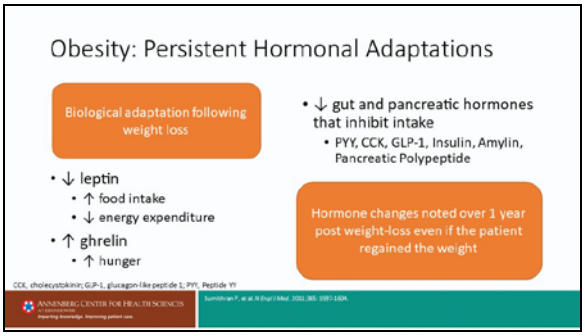
ORAL SEMAGLUTIDE

Now, before I end this section, I also want to mention to you drugs on the horizon. One is oral semaglutide. All the peptide agents that we know of have to be taken by injection because of gastrointestinal breakdown of peptides into amino acids. It's very hard to give a peptide orally, but there's new formulations now, this is a unique formulation called smack in which you can. You can combine it with a semaglutide and it starts to resist the peptidases within the gastrointestinal tract and you can then take it orally. This is already available for diabetes at doses of 3, 7 and 14 mg. You can order it for diabetes, but it's now in the OASIS trial at a much higher dose, 50 mg, they're going to test it for the specific treatment of obesity and that's not going to be due for several years and we'll see how that actually plays out.

TREATMENT STRATEGIES

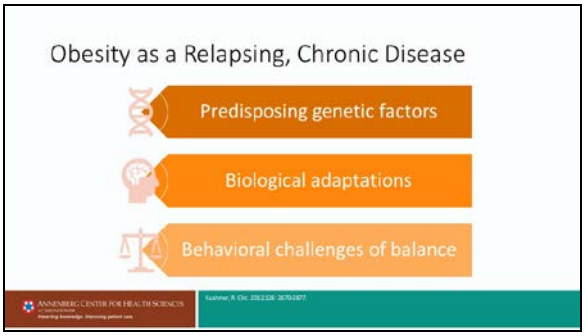
CHRONIC, RELAPSING OBESITY

Caroline Apovian, MD: Let's talk about strategies to optimize the weight loss, keep it off and move to maintenance. And this involves helping your patients with those very important lifestyle changes.



Again, what are the biological adaptations following weight loss? You have these hormone changes, a decrease in leptin. You have less fat tissue, so there's less leptin being made by less fat, less leptin goes to the brain, you get an increase in food intake, almost forced increase in food intake because of that hunger. There is a decrease in resting energy expenditure that is attributed to lower leptin levels. There's an increase in the hunger hormone, ghrelin. That promotes an increase in hunger.

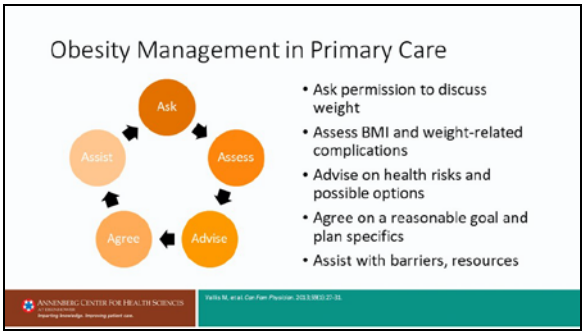
In addition, there's a decrease in the gut and pancreatic factors that inhibit food intake because, as you eat food, you get increases in these hormones: PYY, CCK, GLP-1, insulin, amylin, pancreatic polypeptide. This is where we're adding these new medications. We have GLP-1 analogs that can enhance and give you back those satiety hormones. And we know that those hormone changes that I've just talked about with weight loss, you still have them as a factor over a year post-weight loss, even if the patient regained the weight. Now you have a situation where patients are almost forced to regain that weight. This is where our medications can help.



Obesity is a relapsing, chronic disease. We have predisposing genetic factors. We have genes that help us gain weight in this environment and those are genetic, we can't do anything about that. We also have these biological adaptations in our environment that somehow, in this toxic food environment, many of us have begun to defend a higher body weight set point for whatever reason and then we have these behavioral challenges of balancing the genetic factors and trying to figure out how to maintain a lower body weight set point in our current environment.

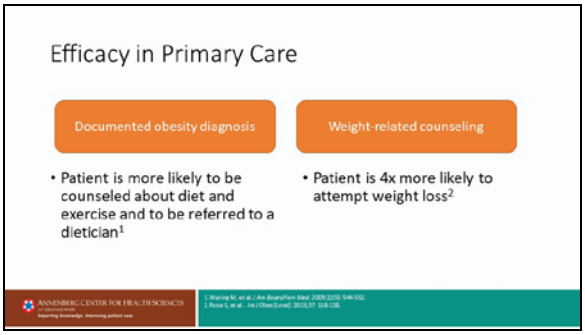
PRIMARY CARE

Obesity management in primary care. How do you approach the patient with obesity? It's very important because of the stigma and the bias that we have associated with many primary care providers in the past in dealing with a patient's obesity.



You want to ask permission to discuss a patient's weight. We talk about the 5 As, ask permission, assess the patient, assess BMI and weight-related complications. This is going to help the patient understand the relationship between weight and weight gain and the complications of diabetes, heart disease, hypertension. Next, advise the patient about their health risks and the possible options. So, ask, assess, advise. And then after you have this conversation with the patient, agreeing with the patient on a reasonable goal and plan specifics. A reasonable goal would be, you know, right off the bat to try and help the patient achieve a 5% to 10% weight loss, as we discussed, and plan specifics. How are we going to do that? And then, eventually, to assist. Ask, assess, advise, agree and assist with barriers and resources. Resources, meaning dietary strategies, exercise strategies, gyms in the area, Weight Watchers in the area for dietary strategies. Other resources, such as how to get our anti-obesity agents covered by that particular insurance. That can be a barrier. What are the other barriers? Socioeconomic barriers, what if the patient can't afford a gym? What if their housing is so small that they can't afford or don't have room for a treadmill or a bike? How to help the patient with their dietary and exercise goals.

These 5 As can help you treat a patient in your center for their obesity and definitely talking to the patient about how reduction in weight can help all of the other comorbidities that that patient may have, including blood glucose, prediabetes/diabetes. Getting patients off those antidiabetic agents with weight loss, off antihypertensives, anti-lipid agents, GERD medications, osteoarthritis medications. It can be so, so illuminating for you to have the discussion with that patient to help them realize that maybe 1 drug can avoid the need for all of these other drugs for all of these other comorbidities.



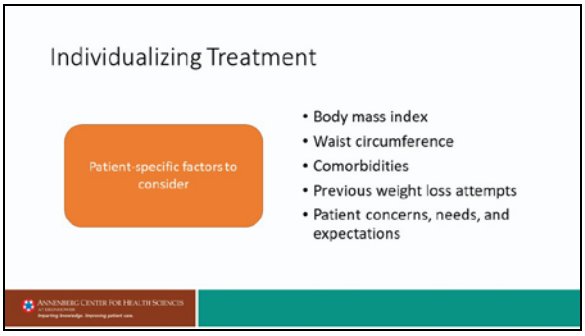
How to improve efficacy in primary care? You know, first of all, document the obesity diagnosis. We have found that many, many primary cares are not documenting that obesity. Primary care providers are documenting hypertension, type 2 diabetes, dyslipidemia, arthritis, but if obesity is documented, we have seen in studies that the patient is therefore more likely to be counseled about diet and exercise and to be referred to a dietician. It's just a matter if you're thinking about making that obesity diagnosis, you're also thinking about how to counsel for obesity.

If you do provide weight-related counseling, either you yourself or referring to a dietician, studies have shown that a patient is 4 times more likely to attempt weight loss. This is very important. How to improve efficacy in primary care.

INITIATING TREATMENT

Start with diet and exercise, behavior modification, and you can escalate the care from there. Diet and exercise, behavior modification is important for anyone with a BMI over 25. Do think about an anti-obesity medication for patients with a BMI over 30 or over 27 with 1 of the comorbidities, and the 2013 guidelines were the strongest in advising primary cares that if the patient has a BMI over 40 or over 35 with a serious condition and has

tried diet and exercise, that you really should advise that patient that bariatric surgery may be a viable option. It's very important to apprise the patient of their obesity treatment options.



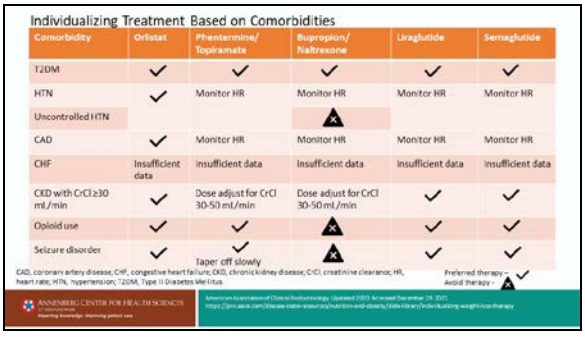
Individualizing treatment is also very important. There are many patient-specific factors to consider when counseling your patients for obesity. Certainly, the body mass index. What is the body mass index? Over 40, over 35, over 27, over 30, talk about medication. Over 40, talk about bariatric surgery. Between 25 and 30, you may want to focus on diet and exercise and behavior modification. It's important to measure the waist circumference because if your patient has a BMI between 25 and 30 and the waist circumference is high, meaning over 40 inches in men, over 35 inches in women, that signifies a high percentage of visceral body fat and that patient may be at higher risk for diabetes, hypertension, heart disease beyond the BMI.

Talk about comorbidities. Previous weight loss attempts. A patient may likely be ready for a medication or a discussion about surgery if they come in and tell you that they've been through every diet known to mankind, they've been through Weight Watchers, Jenny Craig and they're ready for something else. That's individual treatment.

Don't just start off with, "Okay, first we're going to talk about diet and exercise" for the next 6 months if the patient is telling you, "I've tried that." Talk about likely barriers, insurance barriers, socioeconomic barriers. Are patients able to afford good whole grains, healthy lean meats, low-fat dairy and healthy fats? Or are they eating fast food because it's the cheapest thing available to them or they just don't have time to cook? You've got to talk about likely barriers. And then talk about concerns, needs and expectations of the patient, as we discussed.

INDIVIDUALIZING TREATMENT

Let's talk about now the comorbidity the patient may or may not have and which drug is going to be better for which patient. We talked about the 6 FDA-approved drugs. Orlistat is very safe, very benign side effect profile, weight loss is going to be modest, 2% to 3%. It's really indicated for many, many patients, for those with diabetes, hypertension, heart disease, any kind of comorbidity. You may want to think about orlistat after apprising the patient of the GI side effects, of course.



The other medications, the combination of phentermine and topiramate, is if your patient has diabetes and obesity and they don't have the other blood pressure issues, hypertension, heart disease, congestive heart failure, then the combination of phen/top may be a viable option for that patient. In your patients who have hypertension, heart disease, any kind of cardiac issue, and it's not uncontrolled hypertension, you're going to want to monitor

the heart rate. You're going to monitor blood pressure, alright? These are issues that you're going to have to take with each patient individually. You can't just pick a drug that you like for the patient with obesity, without looking at all of the comorbidities.

The combination of bupropion/naltrexone, again bupropion can raise blood pressure so you're still going to have to be careful in those patients with hypertension and heart disease. You want to monitor heart rate and blood pressure. For type 2 diabetes, both the combo of phen/top and bupropion/naltrexone are probably safe options as long as we don't have a history of heart disease or hypertension.

Liraglutide and semaglutide, the beauty of these agents is that they don't have untoward cardiovascular effects. You are going to be able to use them in patients, not just with type 2 diabetes and obesity, but also in patients with hypertension, heart disease and other cardiac issues. The beauty of these agents, liraglutide and semaglutide and those coming down the pike, are their safety profile. We still use these other agents, phen/top, bupropion/naltrexone, but we have to be very careful with patients with cardiac and hypertension issues.

PUTTING IT ALL TOGETHER

CASE 1: JEANNE 55-YEAR-OLD WOMAN

Robert Kushner, MD: Jeanne who's a 55-year-old woman who was diagnosed with type 2 diabetes 12 years ago. She's currently on metformin and sitagliptin for her diabetes. She wants to lose weight, but has gradually noticed an increase in fatigue and shortness of breath impacting her physical activity level. She's concerned about what she can do.

On examination, her BMI's 34. She has an elevated waist circumference, you told us that a waist circumference of 38 inches is upper body segment, 35 is kind of threshold that we use in guidelines. Blood pressure 137/82, creatinine clearance GFR is 67, that's a little bit lower. Hemoglobin A1c is 7.8% on her medications and she's had no lipid panel since 2017. By taking a better weight history, you notice that she's had many unsuccessful attempts to lose weight. She tells you that she tried the Atkins diet which is a low carbohydrate diet and it was too difficult for her. She took HCG when she lost weight because of the 500 calorie diet, but regained it. And she tried over-the-counter Alli which is orlistat at a lower dose, but did not like the GI side effects at all.

The goal is to discuss an individualized weight loss plan for Jeanne based on her history, comorbidities and her current concerns. What are you thinking about when you think about Jeanne?

Caroline Apovian, MD: This is a great study because what we're looking at here is obesity and type 2 diabetes. And she also tells you she's on metformin and sitagliptin for her diabetes. Her BMI is 34, so she is certainly over 30. Waist circumference indicates visceral body fat. Blood pressure's slightly high. And her hemoglobin A1c is 7.8. Right off the bat, a patient on metformin and sitagliptin without a GLP-1, this is a great introduction for this patient to try a GLP-1 analog, both for her diabetes and for her obesity. This is perfect. She's a perfect candidate for a GLP-1. She's had no lipid panels since 2017, so you absolutely want to get that lipid panel to look for other cardiac risk factors in addition to that sightly high blood pressure. She's definitely got metabolic syndrome with that diabetes, waist

circumference and elevated blood pressure and you want to get a lipid level.

The other thing you want to talk to her about, really the cornerstone here, is diet and exercise. Now, she's already told you the Atkins diet, too difficult for her. The HCG diet is really not a diet, right, so HCG is an injection that, along with 500-calorie diet, helped patients lose weight. It was really the low-calorie diet and not the HCG. Alli, now you know orlistat, she hated the side effects so you're not going to go to orlistat.

But the Atkins diet, too difficult for her. So that's a clue that what you want for this patient is perhaps a more well-rounded, macronutrient content diet. I would think about either the DASH diet for her or even better, the Mediterranean style eating plan where, you know, it's really about eliminating ultra-processed food and Gardner and colleagues had this study a few years ago that showed that if you educate patients on healthy eating with whole grains, lean protein, low-fat dairy and some good fats, you don't really have to count calories. That naturally you're going to get full. But I definitely would add that to starting her on a GLP-1 agonist. And we really do need to talk to her about exercise as well. As I said before, it's going to help patients get in the right frame of mind to keep the weight off and it's actually going to help patients keep the weight off.

Robert Kushner, MD: Caroline, let me follow up with 1 question. That is, she comes to you on metformin and sitagliptin and you're thinking about a GLP-1 receptor agonist. Would you change any of those medications? Sitagliptin is a DPP-4 inhibitor. Would you continue that drug with a GLP-1 receptor agonist or would you stop that?

Caroline Apovian, MD: I've done both, but I think it's probably a good idea to stop that drug and add the GLP-1 agonist because, they're basically doing the same thing and you want the GLP-1 to be on board and help patients with weight loss. The DPP-4 inhibitors really don't promote weight loss.

Robert Kushner, MD: I probably would stop that because, of course, the GLP-1s are broken down by DPP-4, so you have a long-acting GLP-1, so probably would go ahead and stop that. Metformin, we would continue, right? You could just add that easily onto the metformin.

Caroline Apovian, MD: Especially, if she's been on it and she has no side effects from metformin. You know, a lot of patients will have some GI side effects with metformin. She's been on it for a while, she's probably tolerating the metformin very, very well and you can add liraglutide or semaglutide to metformin without an issue.

Robert Kushner, MD: I have 1 more point before we go to case 2. It is that she came in talking about shortness of breath impacting her physical activity we want to recognize that. We're not going to say, go climb 9 stories in your nine-story walk-up or start walking on a treadmill for 40 minutes every day. We want to recognize that, and I think it's important to, one, not overwhelm the patient; number 2, to really guide them that they can get control of their diabetes and can lose weight without becoming a marathon runner. You kind of do the physical activities she can, building up which is what you were talking about, up and perhaps going with what she has self-efficacy for and things that she can do, changes in diet, use medication and, as she loses weight, people often will be able to do more and more physical activity as they're losing weight.

Caroline Apovian, MD: She's 55 so she's probably just post-menopausal at this point or perimenopausal, but probably post, and so that waist circumference of 38 inches is signifying that perhaps she's redistributed her body fat to the visceral area and, you're right, she's at higher risk then of cardiovascular issues and so you want to go slowly on the exercise. But, you know, most patients can walk, for example. A walk for 30 minutes to an hour most days of the week is probably a safe way to begin to get her to incorporate more exercise in her program and then later on, when she's lost a little bit of weight, to start to incorporate resistance exercise training as well.

CASE 2: MICHAEL 40-YEAR-OLD MALE

Caroline Apovian, MD: We have a 40-year-old male, Michael, who was diagnosed with hypertension and dyslipidemia for which he is currently on medication. Michael's at the office for his annual physical and you note his BMI which is 38, his blood pressure 144/96, creatinine clearance is 87 mL/min, LDL 127, HDL 52 and triglycerides of 167. And he is on medication for his lipids. He's on rosuvastatin at 10 mg daily, taking atenolol 100 mg daily for hypertension. He's taking amitriptyline 25 mg at bedtime for sleep. He takes a men's multivitamin daily and he takes Tylenol as needed for body aches.

With Michael, who's 40 with this BMI of 38, elevated blood pressure, lipids and needing something for sleep. Bob, how would you approach the subject of weight loss and management with Michael?

Robert Kushner, MD: First thing I think about is, at least as far as a teaching point and of clinical importance is broaching the topic. Michael's not really coming in talking about, "I want to talk about my weight." It's up to us to be proactive as clinicians to make that link for him. It may not be apparent to him that his high blood pressure and his hyperlipidemia and sleep and so forth may be or probably is related to his weight. Broaching the topic, opening up the conversation, "Is it okay if we talk about your weight because I think you can get an improvement in your diabetes and your other medical problems if we focused a bit more on your weight." Ask for permission. If he's welcome to have that conversation, then you can take a more detailed weight history, what have you tried, has this been a long-term struggle, what are your challenges. You kind of have that whole conversation with him.

If he's game and he wants to get involved in more weight management, then you can go on and talk about different dietary approaches and so forth. We don't have a blood sugar or hemoglobin A1c with him. If we think of that triad that we've talked about today, hypertension, dysglycemia and hypertension, we need to have his blood glucose as well.

The other thing that's very important, Caroline, is to take a look at his medications. We don't want to use medications that could actually cause weight gain or impair weight loss. And we have data on use of beta blockers which can have an effect on weight gain and some of the TCAs, tricyclic antidepressants, can also have an effect on weight loss. We may want to revisit those particular drugs and maybe substitute them with others.

We know that SGLT2 inhibitors can be very effective for bringing blood pressure down as well as improvement in diabetes, if he happened to have that. The other medications

that you reviewed for us, anti-obesity medications used for chronic weight management, can also be options here as well. Again, we have to be careful to watch his blood pressure and get that under better control. And you mentioned GLP-1 receptor agonists which can have an effect as well.

In summary, it begins with broaching the topic, bringing his attention to his weight, talking about how his medical problems are linked to his weight, kind of get buy-in at that level and then start having a conversation about what can you do proactively using smart goals, right, specific and measurable and actionable, timely and so forth that you're not going to overwhelm him but actually get him marching towards improved health.

Caroline Apovian, MD: That's a great summary to how to approach this patient. With his medications, his BMI is 38, he's on atenolol at a pretty high dose, 100 mg, and also taking amitriptyline at night. I've had patients like this where, you know, you just switch that atenolol, right, slowly of course because it's a beta blocker so you don't want to get rebound elevated pulse and blood pressure, but if you slowly switch that off to maybe an ACE or an ARB, you know, lisinopril or losartan, and then, as he's losing weight, of course with diet and exercise, and get him to stop the amitriptyline at night and maybe start a little bit more exercise so he does get tired at night. I've seen patients, right off the bat, lose 20 lb just with that small change in medications. In addition, if you do start an anti-obesity agent such as an SGLT2 inhibitor or a GLP-1, you can even get better, you can even get, you know, 10%, 20% weight loss at that point.

Small changes for a patient like this can really go a long way. Your initial 5 As assessment will start the ball rolling because you need to figure out, well, is Michael there, does he want to lose weight, what has he tried, what has worked or failed and what is Michael's weight loss goal, right? You need to have that conversation with the patient as well. This is a great case to figure out weight loss goals, an individual approach to the patient and making small changes to induce weight loss.