

Yale Talk: Conversations with Peter Salovey

Episode 35: Transforming Obesity Treatment

Guest: Dr. Ania Jastreboff, an associate professor in medicine and pediatrics (endocrinology) at Yale School of Medicine, co-director of the Yale Center for Weight Management, and medical director of the Yale Stress Center

Description: Dr. Ania Jastreboff and President Peter Salovey discuss breakthrough medical interventions for obesity and diabetes.

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FULL TRANSCRIPT

Peter: Hello, everyone. I'm Peter Salovey and welcome to Yale Talk. Ten years ago, the American Medical Association formally declared obesity a disease. At the time, there were two states with adult obesity rates above 35%. But less than a decade later, this figure surged to nineteen states nationwide: nineteen states with obesity rates above 35%. Obesity now affects 40% of all adults in this country. Although the prevalence of this disease has grown considerably, so too has the promise of breakthrough medications to treat it. My guest today, Dr. Ania Jastreboff has gained international regard for her translational research at the fore of anti-obesity pharmacotherapy. Most recently, for leading what has been heralded as the most important study of obesity in generations. Ania is an associate professor in medicine and pediatrics endocrinology at Yale School of Medicine and co-director of the Yale Center for Weight Management. She also serves as medical director of the Yale Stress Center and on the board of directors of the American Board of Obesity Medicine. And her many contributions to this field include developing clinical practice guidelines for the comprehensive care of patients with obesity. Ania, thank you so much for joining me today on Yale Talk.

Ania: Thank you so much. It's my pleasure to be here.

Peter: So before we delve into the breakthrough tirzepatide study, let's begin with how our understanding of obesity has deepened in recent decades. You often discuss the need to recognize obesity as a chronic metabolic disease rather than a behavioral disorder. So tell us more about the biology of obesity and the importance of approaching it as a chronic disease.

Ania: So as you said, obesity is a chronic neuro-metabolic disease. So what does that mean? And how did we get here? Basically, our body has this concerted interest in carrying an appropriate amount of energy, and it carries that energy by carrying fat. Now, how is this regulated? Well, there are hormones in our body that signal to our brain how much fat or how much energy were storing. And we don't want to carry not enough fat or not enough energy. And we also don't want to carry too much. So there's this beautiful system that has been developed whereby our brain regulates this and we call that the defended fat mass set point because our body defends a certain amount of fat. Now, what's happened in our current obesogenic environment that is filled with all of these highly palatable foods, with lack of sleep, lack of physical activity, increased stress; this obesogenic environment has pushed up that defended fat mass set point and has dysregulated it. And so what we need to do is re-regulate that defended fat mass set point. And as we'll discuss today, these novel anti-obesity medications do just that.

Peter: So this is a kind of interaction between biology and environment and the way the human psyche interacts in that situation.

Ania: Yes. And again, our body adapts. So this is how it has adapted to the current environment increasing that defended fat mass set point. And the issue for us now is that we're carrying this extra weight. We're carrying, specifically, this extra fat. And that extra fat has detrimental effects on our health. So obesity either contributes or causes over two hundred other obesity- or weight-related diseases. So by treating obesity, we're in effect treating so many other diseases in that process, whether it's type 2 diabetes, hypertension, heart disease, all of these other things. So it's critical to really treat the root cause, to treat the obesity.

Peter: So I'm guessing that part of the problem here, part of the challenge here, is bias and stigma. Individuals with obesity endure bias or stigma that translates into social inequities, including the way the health care system interacts with them. Is all that true and how does it play out?

Ania: It's very true. So tragically, our patients with obesity have faced shame and blame and stigma their entire lives, and that is from society as well as from the health care system. And having obesity is not our patients' choice. Two-thirds of Americans did not wake up one morning and decide to be overweight or have obesity. This is not a behavioral choice. So the example that I often give is our patients with diabetes, we would not say, 'Well, please will your blood sugars to be normal. Please control your blood sugars by thinking about it, by concentrating really hard on every morsel of food that you eat.' And yet, for patients with obesity, that's exactly what we've done for years. And we cannot ask our patients to use their prefrontal cortex to basically control every morsel of food that they eat for the rest of their lives. We need to treat the underlying cause and we need to treat the biology of obesity.

Peter: We know that obesity increases the risk of heart disease, diabetes, some cancers. But also there are additional hazards of obesity: depression, low levels of physical activity, maybe avoiding healthcare. What's cause and what's effect here? And are these the psychological consequences of obesity or are these causing obesity?

Ania: Well, I think that there's an interplay. So we can't necessarily say that one causes the other, but we know that they occur together. They may be co-morbid. But again, the stigma, blame and shame that our patients so unfairly face certainly contribute to all that. Perhaps a patient is reluctant to see their health care provider because they don't want to be told again, 'Well, eat less and move more.' That is not helpful. What we need to do is what we do for our patients who have any other chronic complex disease, which is to say, here are available treatments, here are medications or surgery. And I'm going to help you through this process. I'm going to guide you to the treatment that is most effective for you. And within that context, when we say, for example, for a patient with diabetes, here are several medications. Let's talk about them. And as you start this medication, I'd like you to speak with our dietitian. And also let's think about what types of things you like to do to move. What types of things are things that you would enjoy in terms of increasing physical activity and really focusing on those aspects for health. Whereas let us treat the underlying cause of obesity with medications, with surgery, with interventions that target the disease pathophysiology, that neuro-metabolic pathophysiology.

Peter: So the strategy is we can treat your metabolism medically. And it's not that we don't want to help you learn to eat healthier foods, help you learn to become more physically active. We want you to do that, too, but you're more likely to be willing to do those things or feel comfortable doing things or be motivated to do those things, if we're also treating you medically, if you see change happening.

Ania: We're targeting the mechanisms with medications, surgery, things that literally impact hormones that then signal the brain. There needs to be a reframing in terms of other interventions that are for health. We need to exercise for health and make healthy food choices. So, for example, these medications--and we're going to talk about this more--but in general, they help people feel more full, more sated. And so they help people eat less, especially during the weight reduction phase and even when they reach weight plateau. But there's no medicine, there's no pill or injection that helps you to eat more healthfully or move more. And so, again, there's this reframing of the things that we've been doing for years that is for health rather than the number on the scale, which is potentially the least important part. But let us take care of that with medications and surgery.

Peter: How can we remove the stigma that surrounds obesity? Get people to think about it. I know you can think of it as a chronic disease, but the idea here is so it receives the same standard of care as other conditions and so that patients aren't reluctant to come in and be treated because they feel they're being judged. How do we get rid of this?

Ania: Well, I think we're starting to and we're in the midst of this movement. But basically, we've said for years, as you pointed out, when speaking about the AMA, that obesity is a disease. But just because we say obesity is a disease does not mean that we're treating it like a disease. And that, I think, will be, and is, a critical frame shift. We need to use therapies that target disease mechanisms rather than blaming the patient for something that is not their fault. It is no more their fault that they have obesity, that it would be the fault of a patient who has diabetes, hypertension, or high cholesterol. So I think reframing the conversation around treating the disease of obesity as we treat any other disease will help move that along rather than putting the blame on our patients for something that they cannot control. Once you develop obesity, we have to treat the disease mechanisms.

Peter: And yet there's a whole industry around treating it as a moral failing or treating it as only a behavioral problem. So the messages that people get are quite conflicting.

Ania: And that will take time. That will be a shift. But I'm very optimistic--potentially biased--but very optimistic that that will happen. And we need to be part of that change. We need to advocate for our patients and we need to keep on advocating for appropriate treatment for obesity.

Peter: Now, let's get to the main event. You have just completed a study where you were the site principal investigator and lead author that was reported in The New York Times, published in the New England Journal of Medicine. The Times called it a study that amazed medical experts and it found that this drug, tirzepatide, which is a medication used to treat type 2 diabetes, provides a substantial and sustained reduction in body weight. Nine out of ten individuals with obesity who took this medication lost weight, and those treated with the highest dose lost twenty-two and a half percent of their body weight, which for this group was an average of about fifty pounds. This is a medical intervention that looks as effective as bariatric surgery. And so I would love to hear you tell us a little bit more about this trial, it's called the SURMOUNT trial. And one of the participants said it was just as easy to lose weight on the medication as it ever was to gain weight. Tell us more about the SURMOUNT trial and the attention that it has received.

Ania: So the SURMOUNT-1 trial was a phase three trial looking at a novel agent called tirzepatide. And tirzepatide is a GLP-1 GIP receptor agonist. So it mimics two hormones in our body, GIP and GLP-1, and it targets various tissues in our body as well as our brain. And we think that the way that it works is that

by targeting receptors in the brain, it may increase satiety as well as do other things to our metabolism. What we found is that on the highest dose of tirzepatide once weekly, the 15-milligram dose, the average weight reduction was 22.5% of total body weight. And on average in that group, individuals lost fifty-two pounds. Now, there's great variability in terms of how participants and patients respond. So some patients may have lost 15-20 pounds, and other patients may have lost 80, 90 or in excess of one hundred pounds. And the reason for this variability, and we see this with any treatment for obesity, is there's not one type of obesity. There are many different types of obesity. We just don't have the biomarkers yet to differentiate the different types of obesity. Another thing that was striking in this study was that on treatment with the highest dose of tirzepatide, nearly 40% of individuals lost a quarter of their body weight. So that would be a participant who started this study weighing two hundred pounds, losing down to 150 pounds. And that kind of weight reduction has not been seen in any phase three obesity trial. So that was really something striking. And just as you mentioned, in terms of the participant who relayed that this was easy in terms of the experience, that there's not the struggle, there's not the constant thinking about every morsel of food that you eat during the day. It opens up the mind to think about so many other things, and it's just normal. It's just normal to eat the way that you eat. And yet your weight, your body fat mass is reduced. It is incredibly freeing for patients and participants. There's nothing else like caring for patients with obesity. And certainly that's what we saw in this trial.

Peter: So this class of drugs are called nutrient-stimulated hormone therapies. Can you tell us how does this drug work?

Ania: Yeah. So these medications--tirzepatide, semaglutide--they are nutrient-stimulated hormone- based medications. So as we started our conversation, hormones in our body signal to our brain the amount of energy or fat mass we're carrying, the defended fat mass. And so what these medications do is they mimic those hormones in our body and they signal to various tissues in our body and our brain. And the way that they signal this to our brain is that we feel more full or more sated. So what our participants and our patients report is that they finish eating sooner. They may not go back for seconds. They don't crave the same types of foods that they may have wanted to eat before. And so they end up eating differently. They take in less food and potentially, these medications, we think that not only do they impact food intake, but also energy expenditure. And we do need more studies to investigate that in humans.

Peter: So there's an awful lot of attention to these drugs on social media. Not surprisingly, people are very excited about the potential here, the large weight losses that are reported. Celebrities are using them or at least expressing an interest in them. My understanding is one of the brand names is Ozempic, and you see the advertising for it on television. And the hashtag #Ozempic, for instance, has hundreds of millions of views on TikTok. This is creating a kind of global shortage. There's a strong demand. But are you in any way concerned about this massive popular appeal and popular embrace, while we're still doing the trials?

Ania: So by 2030, half of Americans will have obesity. So half of Americans would qualify for treatment with these medications potentially. And in fact, it's more because the criteria that the FDA has set is a BMI greater than or equal to 27 with a weight related disease such as type 2 diabetes or hypertension or a body mass index greater than thirty. Now, body mass index, we can have an entire conversation about. It doesn't actually tell us anything about fat. It's a screening tool, not a diagnostic tool. But regardless, if we think about this, a majority of Americans could potentially benefit for treatment with medications like this. Semaglutide is already FDA-approved for obesity treatment. Semaglutide is a GLP-1 receptor agonist, so GLP-1 is one of these hormones that we've just been speaking about in our body that is

released when we eat food. That's why it's nutrient-stimulated. Tirzepatide is the combination of GLP-1 and GIP. It's one single molecule that targets both of those receptors in our brain. So what I would say is that the societal response to these medications is one where, again, a lot of patients could benefit from this. So I don't think it's surprising given that we haven't had highly effective well-tolerated therapies, that this is the response that we're seeing. And over time there will be more therapy. So semaglutide and tirzepatide are the beginning of this transformation. They're the beginning of all these new, highly effective and well tolerated agents for the treatment of obesity.

Peter: And what do you say to the people who sort of view these drugs in an old-fashioned way and say that these are just vanity drugs, these are drugs for wealthy people who want to lose weight and don't want to get on the treadmill?

Ania: Again, we have to come back to what are we treating when we treat the disease of obesity and that we're targeting the pathophysiology. If we think about what's in the media right now, how many of those people maybe actually have the disease of obesity, maybe they are overweight and have weight related diseases? We don't know that. Just as we shouldn't blame and shame and stigmatize people who have obesity, we should also not blame and shame them for seeking treatment they may need and that they do need. And we also should not blame and shame the providers who give them that treatment. So I think, again, a complex interplay. There will be a shift, I believe, in society in how we view this in the same way that there was a shift in terms of caring for patients with cancer, with diabetes, with HIV. There will be this shift and the stigma, blame, and shame will subside as we grow to understand the disease of obesity.

Peter: You know, it's interesting that people would have those stigmatizing attitudes given that the obesity can be a causal agent in other more conventional diseases. Wouldn't we want people to treat their obesity in order to prevent lots of suffering, lots of challenges for their families when they have those diseases and costs to the health care system that could be prevented, that could be mitigated if we treat the obesity?

Ania: I absolutely agree. And again, that underscores the fact that if we treat obesity, we can effectively treat over two hundred other weight-related diseases and really transform patients' lives. And I can say without hesitation, I feel so grateful that I can care for patients with obesity, that they entrust me with their health, and that now we have these highly effective and well-tolerated therapies that we can use. We have these tools that we can use to effectively treat our patients with obesity.

Peter: I was looking recently at data from the National Health and Nutrition Examination Survey. Back in my day as being a psychologist in the health psychology area, we would focus on those kinds of data because they also reveal structural and social determinants of health outcomes that we might not always be thinking about. So in fact, what we learn is that obesity disproportionately affects communities of color and disproportionately affects those living in rural parts of this country. Black adults have the highest level of adult obesity in our country at about 50%, Hispanic adults at about 46%. There are drastic racial and ethnic disparities in food security. Black children are nearly three times likelier to live in a food insecure household than white children. How do we address these socioeconomic inequities in obesity and how do they interact with the kinds of metabolic issues that you have been focusing on?

Ania: So this is a very significant problem and one that we have to address head-on to decrease disparities in care by treating the disease of obesity. Obesity may be categorized as a cosmetic disease, which is just abysmal. Many insurance companies do not cover treatment for obesity, especially treatment

for anti-obesity medications. Many of us are lobbying to change that. Locally, I testified in front of our state Senate to try and get coverage for these medications for a Senate bill that has been tried to be passed several times now, both for covering treatment for bariatric surgery as well as anti-obesity medications. So there are state by state differences in terms of Medicaid coverage. Medicare generally has not been covering these medications. So really, that adds to that inequality and lack of access. And these tools are amazing. But what good are all of these tools that we're creating if they are not affordable and accessible to the patients who need them the most? So I think a lot of work to be done in terms of advocacy. I do think that this will change over time, and I think all patients who need these medications should have access to them.

Peter: So changes to Medicaid coverage, changes to Medicare coverage, would help. Are there other interventions or public policy changes that could help ensure that a breakthrough drug is readily available to everyone, not just people who can afford to pay the sticker price?

Ania: Well, I think one thing that we have to address is scalability, because again, these interventions are being created. There's almost a frenetic pace in terms of the various agents that are being developed, and there's such a great need. And so I think we really have to think about how do we scale interventions to a majority of our population, not just in the United States but all over the world. Mexico has now surpassed us in terms of rates of obesity. So I think that, within the field, we have to think very creatively about how we can deliver health care in a much more scalable way, specifically to treat this disease that affects so many people.

Peter: I want to make sure we have a moment for you to talk about some of the resources that are available to people who might be listening, particularly those living in the greater New Haven area.

Ania: Sure. So I encourage all patients with obesity to speak with their primary care provider or whoever they see regularly to see what are the available treatments for them for obesity, whether that's medications or surgery. If additional intervention is needed. I'm the co-director of the Yale Center for Weight Management. And we are opening a clinic in North Haven. And patients who are seen there will have the opportunity to access both medical weight management as well as surgical weight management. And additionally, if patients are interested in the newer agents that we have in development, I lead many trials at Yale of these new novel agents for obesity treatment, these anti-obesity medications, and we are currently expanding resources to create an obesity research center at the School of Medicine.

Peter: So let's make sure we also cover another role that you play, and that is you're the medical director of the Yale Stress Center. Rajita Sinha, my colleague in psychology, is the director of that clinic. It's been around since 2007. It develops new prevention and treatment strategies to decrease the harmful impact of stress on health. But tell us a little bit more about your work at the Yale Stress Center and also how stress and obesity relate to each other.

Ania: So Rajita was one of my mentors, actually, when I was doing my Ph.D. ten years after my M.D. here at Yale. So Rajita and I have worked together for years. And currently we have an R-1.

Peter: Yeah, and an R-1, for our listeners, is an individual research investigator award from the NIH. That's the way they code them.

Ania: Yes. So we have this grant from the NIH, specifically looking at semaglutide and looking at how stress may impact our response to semaglutide and also how semaglutide impacts various things in eating behavior. So how much we eat, what we eat, our food preference, and we're looking at responders and non-responders. So not everybody responds to these medications. And so we're really trying to parse out what are the hormonal responses when these medications are taken, and how does that affect our response to the medicine in terms of weight reduction, in terms of re-regulating that defended fat mass set point, as well as in terms of our changes in food preference and how much we eat? What are the factors that may impact patients who respond to this medication and patients who don't respond to this medication? And that includes hormonal assessment, eating behavior assessment, and really looking at those outcomes. So those are the types of studies that we conduct at the stress center.

Peter: Very good. And is there any advice you could give to listeners on how to manage their stress, maybe as a result, also manage their weight?

Ania: So I think a key message, and one of the most important things, is to underscore that obesity is a chronic, treatable disease and we need to treat obesity like we treat any other chronic, treatable disease. So this means that therapies have to be continued just as we continue blood pressure medications for patients with high blood pressure. We need to continue therapies for our patients with obesity. We need to deliver compassionate care. Our patients have so unfairly faced stigma, bias, and shame throughout their entire lives. And it's really our job to help guide them to their appropriate treatments, the treatments that are right for them, the individualized kind of care that we need to provide for this chronic disease as we provide for any other chronic disease.

Peter: Well, that is a hopeful and direct note on which to end it. I want to thank you, Ania, for speaking with me today.

Ania: Thank you so much for having me. And again, I'm so grateful to be caring for our patients with obesity.

Peter: You know, it's remarkable to reflect on your commitment to them, and to improving the lives of those battling with this disease, and to your field-changing contributions. Ania, your work brings much honor to Yale. It is equally a measure of hope to millions of individuals living with obesity.

And to our friends and members of the community, thank you all for joining me today for Yale Talk. Until our next conversation, best wishes and take care.

The theme music, Butterflies and Bees, is composed by Yale professor of music and director of university bands Thomas C. Duffy and is performed by the Yale Concert Band.