OK. The time is now. Why wait?

These are my disclosures.

So let me ask you a question.

Whether you’re a scientist, a physician, a provider, a trainee, we’re all here with one common goal and that is to help our patients lead healthier lives.

And within the context of obesity, that’s why we’re here today.

And let’s think about the fact that if we can effectively treat obesity,
we can treat, mitigate and potentially prevent hundreds of other diseases. And so here we are in this transformative time, a time that is transformational because of the introduction of these new highly effective anti obesity medications. And I would argue that this is a moment in medical history akin to discoveries such as the discovery of insulin or the discovery of penicillin. Honestly treating this one disease can change the face of medicine and all of you here in this room and online are part of that history. So to illustrate this transformation,
I’m going to show you two patients, one treated with the older anti-obesity medications and one with the new. This is an 18 year old who saw her BMI was 57. She already had obesity-related diseases and had considered bariatric surgery but encountered some barriers. So what did I do over the next three to four years? Well, I used four different medications and her response was remarkable. She lost nearly 140 lbs over those three to four years.
00:01:56.760 --> 00:01:58.960 with her BMI decreasing to
NOTE Confidence: 0.80521114
00:01:58.960 --> 00:02:01.160 31 and her A1C normalizing.
NOTE Confidence: 0.80521114
00:02:01.160 --> 00:02:03.035 And so with these previous
NOTE Confidence: 0.80521114
00:02:03.035 --> 00:02:04.160 medications for agents,
NOTE Confidence: 0.80521114
00:02:04.160 --> 00:02:05.840 45% total body weight loss.
NOTE Confidence: 0.80521114
00:02:05.840 --> 00:02:07.268 This was possible.
NOTE Confidence: 0.80521114
00:02:07.268 --> 00:02:10.600 Now let’s look at our next patient,
NOTE Confidence: 0.80521114
00:02:10.600 --> 00:02:12.826 a 49 year old who came to
NOTE Confidence: 0.80521114
00:02:12.826 --> 00:02:15.157 see me when her BMI was 34.
NOTE Confidence: 0.80521114
00:02:15.160 --> 00:02:18.016 She had successfully lost weight multiple
NOTE Confidence: 0.80521114
00:02:18.016 --> 00:02:21.052 times in her life and had regained it,
NOTE Confidence: 0.80521114
00:02:21.052 --> 00:02:23.160 so losing weight was not the issue,
NOTE Confidence: 0.80521114
00:02:23.160 --> 00:02:25.240 It’s maintaining that weight reduction.
NOTE Confidence: 0.80521114
00:02:25.240 --> 00:02:28.194 She also had some obesity related diseases.
NOTE Confidence: 0.80521114
00:02:28.200 --> 00:02:29.760 So what did she do?
NOTE Confidence: 0.80521114
00:02:29.760 --> 00:02:30.166 Well,
We enrolled her in our surmount one trial with tirzepatide and this is what happened over the course of the year. She lost over 90 lbs, nearly £100 in the course of this trial and completely transformed her health and her life. So next generation medications, one agent maybe 45%. Of course she was a super responder but this is what we’re talking about when we talk about these new agents. So we’re clearly at this watershed brought on by the introduction of these highly effective anti obesity medications.
The older medications it was possible to achieve this type of obesity treatment but now with Somagletite and Tirzepatite really bringing forward the development of all of these new anti obesity medications. Now the ones that we’re focusing in on right now are nutrient stimulated hormone based therapies or Nushes. But please know this is only one class of medications for obesity treatment. There’s active and receptor inhibitors that can potentially increase lean mass while decreasing fat mass. There’s an MC4 agonist for monogenic obesity and there are many
other mechanisms being explored.

So this is just one class.

So in terms of these nutrients,

Well,

they're hormones that are stimulated

when we eat food and they signal

to various tissues in our body and

our brain about energy homeostasis,

about satiety and potentially

about energy expenditure.

Now,

the one that we're the most

familiar with is GLP one,

because GLP one receptor agonists
have been used for the treatment of diabetes for nearly two decades.

But there are so many others, ***Oxintomodulin,***

***Amylin*** and right now what’s being explored are dual and triple agonists.

But please know that there are monotherapies in development as well,

And this is just the beginning for this class of medications.

So this is a slide that I update almost daily because of the frenetic pace of development of these new anti obesity medications.

And I’m just highly highlighting
for you here those in phase two and three of development. And so we have all these new medications. We need to study them, and that was the impetus for Huawei, the Yale Obesity Research Center really at its inception to focus on investigation of these anti-obesity medications, looking at clinical obesity research in three areas. So clinical Physiology, So not just looking at whether or how these medications work, but also using the medications as
probes to better understand obesity,

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pathophysiology,

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clinical trials to understand if these

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medications are safe and effective and if so,

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for whom.

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And of course,

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patient outcomes,

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because we need to know how these

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medications work in the real world.

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Now additionally,

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there are 4 themes within Y Wait

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collaboration with translational and

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basic science, because of course,

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we’d have none of these medications

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if it wasn’t for our basic colleagues,

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mentorship of investigators and physicians,
scientists again, to take this forward, This is going to take many generations to figure out education of academic leaders in obesity medicine, really educating in terms of the biology of obesity and understanding obesity is a disease. And then integration with clinical care, which we're going to hear about today. And for all this we really need to build community which is a really important facet for all of this and there's amazing research already ongoing at Yale and how do we help bring this together. So there's many researchers looking
Sonia Caprio has been leading the charge in terms of pediatric obesity research for decades now and now she’s embarking on looking at some magnetite specifically for youth with obesity and pre-diabetes as well as type 2 and Maffold and she just started enrolling this summer for this study. So we anxiously await those results. There are many other physician investigators in pediatric obesity and you’ll hear from Michelle Van name today.
What about bariatric surgery and using these medications before and after surgical interventions? Willpower at Yale, led by Carlos Grillo has been looking at binge eating and more recently looking at naltrexone bupropion after bariatric surgery to look at whether it can impact loss of control eating as well as weight regain. And it’s great because the power at Yale partners with clinician educators to involve them in this type of research. The adolescent bariatric surgery program incredibly robust and now prospectively.
00:07:10.492 --> 00:07:12.952 looking at mitigating weight regain with

00:07:12.952 --> 00:07:15.192 somagletite in their young patients.

00:07:15.200 --> 00:07:17.300 And then John Morton partnering

00:07:17.300 --> 00:07:19.400 with the Yale Specialty Pharmacy,

00:07:19.400 --> 00:07:22.555 looking at implementing medication pathways

00:07:22.555 --> 00:07:26.253 before and after surgery at the Yale

00:07:26.253 --> 00:07:28.599 Stress Center directed by Rigita Sinha,

00:07:28.600 --> 00:07:30.532 who I’ve just had the incredible pleasure

00:07:30.532 --> 00:07:32.280 of working with for so many years,

00:07:32.280 --> 00:07:34.560 first as a mentor, now as a collaborator.

00:07:34.560 --> 00:07:37.240 We have an RO one looking at somagletite,

00:07:37.240 --> 00:07:39.180 basically the impact of Somagletite

00:07:39.180 --> 00:07:41.120 on metabolic and stress responses,

00:07:41.120 --> 00:07:42.419 predicting weight outcomes,

00:07:42.419 --> 00:07:44.139 looking at craving, hunger,

00:07:44.139 --> 00:07:46.234 food consumption and of course
we're doing an observed eating task. And this type of study that is so involved really requires A-Team. And at the Yale Stress Center, we're doing this study as well as several others looking at obesity treatment. Now obesity is a neuro metabolic disease and this is actually where I started my research. And now the question is how can we begin to look at this in terms of the impact of these medications and how they are working in the brain? There's some pilot studies and smaller studies, some of which we did.
but there's an incredible powerhouse of investigators at the Yale MRC and the Pet Center where we can really utilize these tools to better understand this. And you're going to hear from one of these investigators today, Murray Cirilli. Now what about cancer? So cancer is another area that we are fast moving into looking at the primary and secondary prevention with anti obesity medications. There are thirteen types of obesity related cancers and one of them endometrial cancer, there’s a sevenfold increase if
somebody has severe obesity.
And Claire Flannery has been looking
at this since fellowship when she
had a patient with endometrial
hyperplasia who is very young.
And now she’s moving forward with
her research looking at obesity
driven endometrial hyperplasia to
potentially use these medications and
look at outcomes in those patients.
She’s partnering with Sonia Caprio with
the patients that Sonia so eloquently
or elegantly phenotyped when they
were children looking at the Yale
longitudinal reproductive and obesity cohort.
There are many, many other avenues to take with these obesity related cancers and we look forward to that as well. Now what about health outcomes and anti obesity medication. So you’re going to hear an entire talk about this from Harlan Krumholtz. Today. It’s so important to look at different populations, for example, outcomes in older individuals, cardiovascular outcomes and beyond. Now moving into the clinical space, so you’re going to hear a talk about this not particular to obesity,
but the overall system. But how can we begin to engage patients to be partners in studies with us and invite them to engage in our protocols. This of course, will take all of us, the whole team of us, clinicians, scientists, everyone within our programs that are existing such as the pediatric program and newer programs like the Center for Weight management. I’d also like to highlight that at 8 Devine, we do have research space and that is
being led by Boo Boo Benini and Diana Rivera.
And and again, there’s so many other opportunities within the clinical space. And so here we are. Why wait? These are our goals and now into our workshop. So we really intend today to take you from the bench to bedside and beyond. And so we should do this in order. But since I’m standing here right now, I’m going to address briefly some of the clinical trials that we’ve done. Then you’re going to hear two talks that focus on Physiology,
00:10:44.856 --> 00:10:46.976 basic Physiology of obesity and
00:10:46.976 --> 00:10:49.520 then two clinical Physiology talks.
00:10:49.520 --> 00:10:51.644 Then you’ll hear a talk about
00:10:51.644 --> 00:10:53.572 patient outcomes or health outcomes
00:10:53.572 --> 00:10:55.787 and then integration with clinical
00:10:55.787 --> 00:10:57.559 care from Doctor McGovern.
00:11:01.368 --> 00:11:03.237 section by giving a big thank you,
00:11:03.240 --> 00:11:05.025 a huge thank you to YCCI because
00:11:05.025 --> 00:11:06.872 all of our clinical trials have
00:11:06.758 --> 00:11:08.872 been done at the CSRU with the
00:11:08.938 --> 00:11:10.688 staff who’s sitting right here
00:11:10.688 --> 00:11:12.845 supporting us through all of these
trials and especially Margo and Kim, who are the research coordinators that I work with that truly make all of this possible. So thank you so much.

So Samaglatide was FDA approved initially for diabetes and then for obesity in 2021 and it was really the first agent that demonstrated
double digit weight reduction.

Now we were part of the select cardiovascular outcomes trial which was the first trial that really looked at patients with obesity without type 2 diabetes over 17,000 participants and what was demonstrated was a 20% reduction in three-point MACE.

So we’ve been waiting to see does treating obesity with these medications improve health outcomes and the answer is clearly yes.

And now we’re seeing these outcomes with HEF, PEF just released yesterday evidence of in terms of kidney benefit.
So this is all coming full force Now we're also part of the step young trial looking at children aged 6 and above for treatment with somagotite now before you think well six years old, six years old and weighing 160 lbs or 70 kilograms. So this is severe obesity and we have to develop options for these young patients. And so we look forward to that trial. We're almost fully enrolled at our site now in terms of tirzepatide, this was originally FDA approved for diabetes and then FDA approved for obesity in 2023 and we were so honored to be a part of that process.
00:12:53.440 --> 00:12:56.968 So I was the lead Pi on the surmount tirzepatide trial.

00:12:56.968 --> 00:12:59.319 And in this trial,

00:12:59.320 --> 00:13:00.472 we demonstrated that with the highest dose of tirzepatide,

00:13:00.472 --> 00:13:01.912 participants on average lost 22.5% of their body weight,

00:13:01.912 --> 00:13:03.280 which translated to 52 lbs in just 72 weeks and 40% of individuals lost over 1/4 of their body weight.

00:13:03.280 --> 00:13:05.960 So this is really, truly amazing.

00:13:05.960 --> 00:13:07.160 We’re moving forward with additional studies.

00:13:07.160 --> 00:13:10.457 Now a cohort here about 40% had pre diabetes.

00:13:10.457 --> 00:13:12.990 So look out for those outcomes in the months to come.
And we’re also moving forward with the surmount MMO, the cardiovascular outcomes trial and I’m on the steering committee for that as well. Now what about CAGRI SEMA, So this is an Amylin analog with a GL, P1 receptor agonist also showing impressive weight reduction. And I’m on the steering committee for this cardiovascular outcomes trial as well. The one that’s farthest along is cerutatide. Again, impressive weight reduction results
with this agent and we’re also part of this phase three trial here now. Next we have a triple hormone receptor agonist and I’m going to spend a few slides speaking about retitrutide. So I was also the lead Pi on this trial and retitrutide is a GIPGL P1 Glucagon receptor agonist. And we were incredibly impressed to see that the weight reduction with this agent was 24.2% at just eleven months and that translated to an average weight reduction of £58 in the short time frame. And Please note that all the
participants were still actively losing weight at the time that the trial product was discontinued. So this will have to wait for the phase three to see the full efficacy, but eleven months this was very impressive. Now with this agent and with all agents we look at the the threshold that the percentage of people reaching the weight reduction threshold. So we often use 5% as that threshold because the FDA uses this in terms of its decision making of approval for these medications. And so with redditrutide,
this triple hormone receptor agonist, what we saw was that 100% of individuals taking this medication lost at least 5% of their body weight. I don’t think I’ll probably ever be able to say that again in clinical research of any kind, 100% of anything, but this was a phase two trial and now we’re doing phase three. Five well with the highest dose. Many individuals also reach this target. 1/4 of participants lost more than 30% of their body weight,
which has never been seen before. And again, this is just in 11 months. This is not the full efficacy of this agent. Now if we look at Redruitite a little bit more closely, as with any treatment for obesity, there's great variability in terms of response. So whether it's bariatric surgery, medications or anything, you'll have this variability. And if I can draw your attention just to the 8 milligram dose, you can see that some participants lost 10%, other participants lost more than 45%. And the question is why do we see
this type of variability and we have to understand this better. We genetics is really important to look at. We also look at clinical factors. And one of the things that we saw here was that sex actually made a difference. So women lost more weight than men, 28.5% at 11 months. So even looking at those type of factors and we need to understand why this is, is it the distribution of the adipose, the percent of adipose tissue, What’s different about women and men? And so now we’re in phase three and we’re almost fully enrolled here at Yale.
There’s oral agents in development. For the sake of time, I’m not going to speak about those. There’s also a monthly agent in development in case your patients are not able to take a daily oral or a weekly injectable. And so with all these medications, we know now that we can achieve fifteen 2025% weight reduction, but we’re really moving beyond weight reduction. We’re treating obesity and what we want to do is improve health outcomes. We’re treating obesity and what we want to do is improve health outcomes.
we’re treating obesity.

And in order to do that, we really need to understand the biology of obesity and how to target that pathophysiology to really maximize those health benefits for our patients. And so with this, I’m going to come back to our patient and tell you what happened with her after the trial. So as you remember from the beginning of my talk, she had lost over 90 lbs during the course of the trial.
a safety period.

It's about a month And she came to see me in clinic at 5 weeks and at that time she had already began to rapidly regain that weight.

And So what did we do?

Well, I started her on some Maglatite to try and temper that weight regain, which was successful.

She did slow down in terms of her weight regain as we escalated the dose. We then added naltrexone bupropion to try and bring her back down to around a BMI of 2425, which again we successfully did and she’s done so well with this now,
right now, just as of a few days ago.

Tirzepatide is available to her now.

So we're switching the Samaglatite for tirzepatide and we'll see if we'll be able to stop the naltrexone bupropion as well and switch her back to what was effective for her.

And what I'd like to highlight here right now is this is a patient case on a slide, but these are our patients and this patient is here sitting in the room with you today.

And she has graciously agreed to stand up when we give her a big round of applause.
So thank you so much, Lena.
And I don’t hear people were asking me if I was so. So I’m happy.
Yes. So thank you so much, Lena.
And thank you to all of you for your attention in this first talk.
And and we welcome you to check out our website at Y Wait,
which Lena made for us.
So thank you so much.
And we have a couple of minutes for questions before we move on
for questions before we move on
to the the stars of our show,
our speakers. Any questions?
Oh yes.
So what is the goal of these seven trees?
It’s like maybe it’s a lot of late time, but those like mall or is it going to like? Yeah. So that’s a really great question and we’re actually trying to figure that out. Obesity is a chronic disease. So what we believe is that chronic treatment is needed. Now whether it’s with that agent, whether it’s with a lower dose or a different medication, we don’t know. As you can see from the, there is variability and we can add in different medications over time, in different medications over time.
but we don’t know.

We do think that just as there’s variability in terms of response to these medications,

there’s also variability in terms of weight regain.

Some people very quickly gain back all the weight and others gain back less of the weight.

But on average,

most people regain the weight.

And again,

it’s because we’re trying to reset a defended fat mass or set point,

and that’s what we’re doing when we’re treating obesity rather than treating for weight loss per SE.
That’s a byproduct of what we’re trying to do. And I think you’re going to hear more about that today.