**Speaker 1:** The *BioWorld Insider* podcast.

**Lynn Yoffee:** This is the *BioWorld Insider* podcast. I'm Lynn Yoffee, BioWorld's publisher. After many years of research and development, drug-induced weight loss has matured into a viable therapeutic option for patients. At the same time, there are longstanding concerns that the health effects of weight might be overrated. Can a person still be considered fit and healthy despite being over what is considered a normal weight? And how will future medical science consider what's called the obesity epidemic? Here to unravel all of this is Anette Breindl. She's the managing editor of BioWorld Science.

Anette has been analyzing studies related to weight loss and metabolic health for quite some time. Anette, what you wrote in Monday's edition of BioWorld seems almost revolutionary and goes against the mainstream healthcare state of mind about obesity. Lee Landenberger, a staff writer for BioWorld, is here to help us understand and to have this discussion with Anette. Over to you Lee.

**Lee Landenberger:** Thanks, Lynn. Anette wrote about this subject recently in BioWorld and we found the subject fascinating. She's talking to us today from her home in Hanover, Germany. Anette, help me understand these conflicting ideas. Obesity is nearly universally considered to be a bad thing, and now we have these new GLP-1 receptor agonists that appear to promote weight loss. Yet there is a question if they are a blessing or a blind alley?

You liken the modern views of weight loss to phlogiston, which is a discarded theory of science that people look back on now and say, "Well, we used to think that, but we don't anymore." Could you tell me about why the comparison to phlogiston may be comparable to these new drugs?

**Anette Breindl:** Sure. I have long been fascinated with the relationship between weight and health for many reasons. Weight is really one of those things where as a science writer, that's one of the things where the public is really interested in, I'm not necessarily going to say in the science, but in weight loss itself. It's very unquestioned, just like phlogiston was in its time. It was something that you don't really look at whether that is there because that is your bedrock assumption.

Weight in some ways is the same way. It has become this bedrock assumption that higher weight is an indicator of poor health and that the thing to do about that is to lose weight. When you look at studies that go back and say, "Okay, let's actually check these assumptions," there's really not that much there. The evidence is thin, and that's not a good thing. That is where my comparison came from with weight and phlogiston.

**Lee:** The new receptor agonists, can you give me an idea of how they work, what they do in the body, and if you think they're step in the right direction? You want to lose weight, right? That's okay. Tell me I'm wrong.

**Anette:** [laughs] You're wrong. Certainly, it seems like the GLP-1 agonists, which are these new weight loss drugs, are going to be a very useful drug class for metabolic health. It is also true that they seem to cause weight loss. The question is whether those two things are related, and we could talk a little bit about whether the reason they work is important as long as they do. I would argue that they do, and I can give you examples of that.

Let's talk about these weight loss drugs themselves first. This new class of drugs, they're not that new by now, actually. The first one was approved in 2005. That was Byetta. They are GLP-1 agonists and they seem to lead to significant weight loss. The gold standard treatment for weight loss has long been bariatric surgery. Now you can get equivalent weight loss, apparently, with these GLP-1 agonists. There are two that are approved for that, Wegovy and Saxenda.

I'll say the long-term data on whether this weight loss is sustained is not in yet, but the drugs do seem to stay effective for as long as they're taken. That's a big difference to weight loss and response to dietary changes, which initially works for most people. 90% of individuals, if you restrict your calories, you will lose weigh, but also 90% of individuals then gain that weight back. That seems to be different with these drugs although they are new enough in the weight loss space that I would wait for longer-term data there.

The other important thing about these GLP-1 agonists is that they appear to have other health benefits as well. Earlier generations of weight loss drugs typically had cardiovascular risks. Some of the worst like the fen-phen drugs are now off the market because they increase the risk for heart attacks, and others, certainly, that is one of their problematic side effects.

That does not appear to be the case for GLP-1 agonists. The FDA started requiring cardiovascular outcome trials for metabolic drugs because of these past experiences with drugs that maybe did what they were supposed to do in terms of weight or insulin sensitivity, but then increased your risk of heart attacks, and that's not the case here. Wegovy and Saxenda have cardiovascular benefits, and other drugs that have been in trials. The data is not as clear, but they do not seem to pose big cardiovascular risks, and there may be benefits there as well.

Those drugs, they are good for you, it appears, but the question is whether they are good for you because you're losing weight. There have been increasing questions of how strongly weight is really linked to health, and certainly, the body mass index or BMI has come under massive criticism there.

**Lee:** You're leading me exactly to the questions I was curious about, so the idea about the relationship between weight and good health is changing. Can you tell me a little bit about the latest research and what people think?

**Anette:** Yes. Again, as far as weight is concerned, if you actually do studies where you separate out the effects of exercise, where you look at increasing fitness levels, then you very often see that increased fitness leads to better health outcomes, and then there's really no added benefit of losing weight. There seems to be something about fitness that is improving metabolic health that may be unrelated to weight. Weight and the way to measure weight, which is the BMI, is really, I don't know whether the whole idea that weight is important for health will go the way of phlogiston, but the BMI, the sooner we get rid of it the better.

It was really never meant to be an indicator of health on an individual level. That may sound strange. Of course, on some level, the population level link comes from individual data, but in individuals, that link is so weak that using weight as a proxy for health ends up medicalizing a lot of healthy people and missing a lot of people with metabolic problems. That goes back to what I was saying earlier, if they work, it doesn't matter why. Here's the reason why. If you look at weight and you say, "Okay, high weight, metabolic problems, good candidate for a prescription," that does not work if you're using a population level indicator to assess health, and that is easiest to understand when you compare it to height.

In height, there's an undisputable population level linked to sex. On the average, men are taller than women, but now let's say I am trying to use just height to determine whether someone needs a medical procedure. Let's say I'm looking at height and that's how I'm going to decide whether someone should get a pap smear. I use a cutoff, if you're shorter than 5'8", you should get a pap smear that would be good for you. Well, there it's very easy to see the issue.

Personally, I would not be able to get a pap smear if we were using a height cutoff of of 5'8", and Michelle Obama wouldn't, and Melania Trump wouldn't, and certainly, Brittney Griner, who is 6'9" wouldn't. You know who would be eligible for a pap smear? That would be Tony Fauci, that would be Martin Luther King Jr, that would be Pablo Picasso and many others, I'm sure, they could all get pap smears there. If you use height as a proxy for who needs a pap smear, that would lead to literally millions of people being identified as needing a pap smear who in fact have no need for a pap smear at all and where you couldn't get one. At the same time, it would miss all these people who could benefit from getting a pap smear.

The bottom line is, you're just much better off looking for another marker, a better marker to look for who needs a pap smear. For a pap smear, obviously, that's 2X chromosomes, and that is how it works with weight and health, especially near the middle, if you're trying to say heavier is worse or heavier is unhealthy and lighter is healthy, you are wrong almost as many times as you are right when you're using that, and even at the extremes, you can be wrong. Like I said, Brittney Griner is 6'9", so even if you are very heavy, you can still be healthy, even though at those extremes, it is a better predictor, weight is a better predictor of health than in the middle.

There are a lot of other issues with BMI as well. It's based exclusively on data from males, and we know perfectly well that collecting data on one's sex and claiming that applies equally to both is very often just a bad idea. There's some CDC data that shows that even at the population level, what's classified as overweight is healthier than what's classified as normal weight, and what's classified class one obesity is the same as normal weight, but the main issue is that the BMI was just never meant to predict an individual's health and it does a poor job at it and we need better measures.

**Lee:** Some of those other better measures, what might they be?

**Anette:** There are a lot of them. You can check for actual metabolic markers. For example, insulin resistance is a precursor to diabetes and a strong predictor of future health problems. In that context, let me get back to this, the fact that by Byetta was the first GLP-1 receptor agonist to be approved by the FDA, and that was for the treatment of type 2 diabetes. Insulin resistance or sensitivity, how well you can control your blood sugar levels, that is one excellent marker.

There are some very simple tests, for example, grip strength or walking speed, and people over the age of 65, just watching them walk and see how fast they do is very good at predicting remaining lifespan, which is fascinating. Of course, both walking speed and grip strength are correlated with overall fitness, and that links back to what I was saying earlier that fitness is much more directly linked to health than weight is, and there's been some interesting research to find metabolites that are related to exercise or fitness in general.

One of my favorite papers of last year was from the Stanford group, where they took blood samples from lab animals that were forced to exercise and from human volunteers that were exercising, and from racehorses. There was a racecourse near Stanford University, and these horses get tested for doping all the time, so they have all these blood samples sitting around. They identified this peptide, it's called lacfi, whose levels go up whenever a mouse, or a horse, or a person are exercising.

Then there was recently a paper, just earlier this month, by researchers from the Dana-Farber Cancer Institute, and they have found a way to look at secreted proteins that change when-- For now, animals are exercising, and what they did is they essentially do this version of low-speed centrifugation. They centrifuge the muscles and they can get the extracellular fluid. That is much better for looking at proteins where the changes are somewhat subtle.

What happens if you take a blood sample is that your blood is just full of antibodies, of course, because that's its main job, immunoglobulins everywhere. It's hard when you're trying to measure everything that's going on in there to see these smaller changes that are happening that are flooded out, that signal is flooded out by the immunoglobulins, and muscles are, of course, full of myosin and actin, which are the two proteins that are responsible for muscle contraction.

If you look at the muscle itself, you will, again, have a hard time finding things that change in response to exercise, but like I said, they did this little low-frequency centrifugation and they were able to get the interstitial fluid, the extracellular fluid, and they were able to really look at things and they identified what's to date known as a neurotrophic factor. It's called prosaposin. It's known as a nerve growth factor, but it apparently also comes out of muscles when you exercise.

The main point of the paper was not just that they identified this prosaposin as an exercise protein, but that they have this method to find all these proteins. I suspect that there will be lots of interesting things that you can find using that method to look for exercise-induced changes.

Treatment-wise, there's also attempts to distinguish different fat types. I think it has made its way into the public consciousness that there are better and worse types of fat, but when you lose weight, you lose all these types of fat to the same extent. There are now new nanotechnology approaches that allow you to specifically target some of the fat that you most want to be rid of because it is metabolically detrimental.

**Lee:** With these weight loss drugs, in order to become healthier, are they worth taking?

**Anette:** [laughs] Talk to your doctor. Like I said, Byetta is approved as a diabetes drug. These drugs, they do seem to have health benefits. I talked to a researcher from the Lunenfeld-Tanenbaum Institute in Canada last year. He's been studying GLP agonists for decades. He was saying that his hypothesis by now is that they seem to be good for diseases with an inflammatory component. GLP-1 agonists are being tested in clinical trials in Alzheimer's disease, for example. Again, there are the cardiovascular benefits.

Again, I am not a doctor and certainly not a futurologist, but my best guess is that these drugs do have health benefits and that they will find a useful market. A lot of people want to lose weight for aesthetic reasons because they think that is more attractive. Certainly, they may have a market there that may be a non-prescription, that may be a gray market block. There was just a story in *The New York Times* about how people are taking Wegovy for weight loss and then they're getting fillers in their face because they're also losing weight in their face. Then they don't like that because then your body looks younger and your face looks older. That's not our remit.

Again, I would not want to predict there, but I do think that these drugs are likely beneficial for health? The question is whether they are that way because they lead to weight loss. Interestingly enough, bariatric surgery, which is the gold standard for weight loss, if you do bariatric surgery, the patient's insulin sensitivity increases long before there is time to lose a significant amount of weight. Even with the bariatric surgery, it's not really clear or there is an argument to be made that weight loss is at the very least not the whole story of why bariatric surgery works.

**Lee:** Your big takeaway on this, sounds like a lot of it's individual, but also, the science changes just enough that you have to keep your eye on it.

**Anette:** Yes. I think it's a fascinating area right now. I'm very much looking forward to this molecular exercise science because exercise, it's a very squishy concept, especially at the level where most people would do it. It's molecular underpinnings are really not that clear yet, but there is a lot to be discovered there. It is possible that some of these findings will form the basis of therapeutics that target the same pathways that right now you turn on by going for a run or hopping in the pool or whatever it is that you do for exercise.

**Lee:** Great. Thank you. This is fascinating and incredibly complex. I look forward to reading more about it in BioWorld. Thanks for your insight and thanks for your time, Anette.

**Anette:** Thank you. Always a pleasure.

**Lee:** Lynn?

**Lynn:** Anette, you've taken some big ideas and thrown them into the controversy pool here that it's no longer about the number on your scale, that maybe it's more about your fitness, is what my takeaway is from your discussion. Everyone, if you're interested, you can read more about what Anette has asserted here via her article on BioWorld, where she drew from a number of studies from a variety of angles to come up with these latest analyses about obesity, the use of weight loss drugs and how it all correlates with fitness and health as the human being. It's very, very complex.

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