Researchers call for makers of new anti-obesity drugs to study results of body composition in addition to weight loss

March 19 2024, by Alvin Powell

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Some health care professionals are growing concerned that amid the recent rush for the new highly effective, anti-obesity medications,

patients are losing muscle as well as fat, which carries the risk that frailty will accompany leanness.

The Gazette spoke with Fatima Cody Stanford, associate professor of medicine and pediatrics at Harvard Medical School and Massachusetts General Hospital's Division of Endocrinology. Stanford, an obesity medicine specialist, said she believes the drugs are both necessary and safe. But by focusing just on weight loss in their testing, big pharma companies are failing to produce all the data clinicians need to craft treatment plans to optimize overall health.

Stanford, who has consulted for anti-obesity medication manufacturer Novo Nordisk, said that the company, as well as competitor Eli Lilly and others with such drugs in the pipeline, have the resources to add body composition measurements to their studies and called on the U.S. Food and Drug Administration to pay attention to the issue.

Together with colleagues from Stanford University, Stanford penned a recent opinion piece on the topic in the journal *JAMA Internal Medicine*.

Your article hit on something I haven't heard a lot about: the importance of body composition in weight loss and making sure we're losing fat, not muscle. My sense is that this has been missing from the conversation about obesity and weight loss drugs. Is that the case?

We've known that BMI is a flawed health metric for a long time, but the criteria for prescribing the GLP-1s—any of the anti-obesity medications—focus on BMI, on weight, not on fat mass or muscle mass.

These medications can be prescribed if you have a BMI of 30 or higher or a BMI of 27, plus obesity-related diseases. However, the health status of those with a BMI of 30 can vary. This can be problematic when patients are hyper-focused on BMI instead of their overall health, such as cholesterol, liver function tests, blood pressure, etc.

I don't often have body composition data on a patient, but we know that when these drugs are utilized, patients lose fat and muscle. This becomes particularly important for older adults susceptible to losing muscle needed to get out of chairs, stand up, and perform other movements critical to maintaining independence.

The extensive studies, done by Novo Nordisk, Eli Lilly, or other companies—with 17,000, 20,000 people—don't look at the key metrics about body composition even though we've known for some time that with metabolic and bariatric surgery we need to pay attention to muscle loss in patients.

That hasn't translated to GLP-1s, even though we're starting to see numbers mirroring what we see in metabolic and bariatric surgery. These big companies have the money to do this consistently.

They're also doing trials in pediatrics and young adults, middle adults, and older adults. So what are they seeing across the age spectrum regarding fat loss, muscle loss, andlean mass loss, and what do the clinicians at the point of care need to look out for in these different populations?

Who's the boss with these trials? The FDA?

The FDA should be thinking about this. We wrote this Viewpoint so the FDA will see it and be thoughtful about what we're looking at with GLP-1 trials.

Several new drugs are in development, and a slew will come down the pike. The FDA should be thinking not just about total weight loss because we are not just one blob of clay.

They should consider the composition of the weight loss: fat and muscle. These are different parts of us and we need to know the components we're losing. This is particularly germane to older adults.

It seems the public has adopted "weight loss" as shorthand for "healthier." But you point out if you lose too much muscle weight, you can actually be unhealthier at a lower weight. Can you could expand on that?

This is key. When I talk to patients about losing weight, I tell them I want them to lose weight and gain health. But weight loss doesn't mean gaining health if you're unable to get up out of your seat and chase after your grandkids.

When I ask my patients, "What are the things you can do that you couldn't do when you carried extra weight?," if you say, "I'm starting to struggle to do something," maybe the weight loss is too much. We don't want to get to a point of frailty even though this desire for thinness and leanness is celebrated.

Last week, a patient of mine, an 81-year-old woman who happens to be on GLP-1s, said, "I'm getting too skinny," and I agreed with her. We adjusted her medications so that she wouldn't get too low.

Were you keeping track of her body composition through tests or was the standard purely functional?

There isn't a specific standard test for body composition. A DEXA scan is the gold standard. But that is several thousand dollars and is usually used for bone loss. It can tell a person's fat mass, but that's not in the standard read.

You can also do bioimpedance, which tells you your water and fat composition. That's around 85 percent accurate, not horrible but not amazing.

Is there an ideal number we should be shooting for, with regard to fat versus muscle?

That will vary from person to person and health state to health state. Suppose I have an 80-year-old white woman with a history of osteoporosis. In that case, I'm going to want her to retain more lean muscle and fat mass than an 80- or 81-year-old woman with a higher level of obesity but no evidence of osteoporosis. You need to tailor it based on their disease risk instead of saying, "We want everyone to lose 25 percent of total body weight."

A concern when these drugs became popular is that people naturally look for a magic bullet and might not bother adjusting their lifestyles. How are these actually being used?

By the time people make it to us in obesity medicine, they can usually write a book on lifestyle modification. It's not that they haven't tried. I've had triathletes and ultramarathoners as patients whose bodies are minimal to nonresponsive to those interventions. They're not just bumps on a log. A robust cohort is motivated to get back into exercise.

They want to maintain what they've been able to achieve; they don't want to go back to where they've been for 20, 30, 40 years. So I don't think

people see this as, "I'm taking the easy way out."

These drugs are relatively new. Are we, as a society, still learning to deploy them or have we pretty much figured that out?

I don't think we're necessarily learning how to deploy them, but I also don't think our workforce understands how to use them. That's a significant issue. A lot of the negative stories we're hearing reflect people not understanding how to use these medications. We read negative stories about stomach paralysis, about people going to the hospital. Still, I've prescribed these medications to over 3,000 people and I've never had a patient for whom this happened.

I think people are inappropriately using these medications for aesthetic reasons, and people are inappropriately titrating these medications due to a lack of supply. We've had shortages of the most commonly used medicines, manufactured by Novo Nordisk, which had a monopoly on all agents in the U.S. until Nov. 8, when tirzepatide became available from Eli Lilly.

With Novo Nordisk's Wegovy, or semaglutide, to be safe there are five doses that you have to titrate up—0.25, 0.5, 1 milligram, 1.7 and 2.4 milligrams. This is an essential titration, you cannot skip doses. If you try to skip doses, it's like someone never in the kiddie pool deciding they want to jump in the middle of the Atlantic Ocean. They're not ready.

What I think has happened is that the three lower doses—0.25, 0.5, and 1 milligram—had massive shortages. They're almost impossible to get. But the two big doses, 1.7 and 2.4 milligrams, you can get almost anywhere. I think people have been skipping the low doses.

Have there been signs of the supply improving?

On Nov. 10, Novo Nordisk announced they would spend $6 billion to improve the supply chain. Today the shortage of semaglutide has slightly improved. This new agent, tirzepatide, I have found to be readily available.

Many companies want a piece of this market, but with others having a head start, can they still get one?

I think they will. Worldwide, we're talking over 1 billion people with obesity, and no company has the ability right now to supply even the U.S. market. We're going to need multiple players to conquer the global market.

More information: Ank A. Agarwal et al, Body Composition in Anti-Obesity Medication Trials—Beyond Scales, *JAMA Internal Medicine* (2024). DOI: 10.1001/jamainternmed.2023.7733