Fat mice bred to have more muscle give insight

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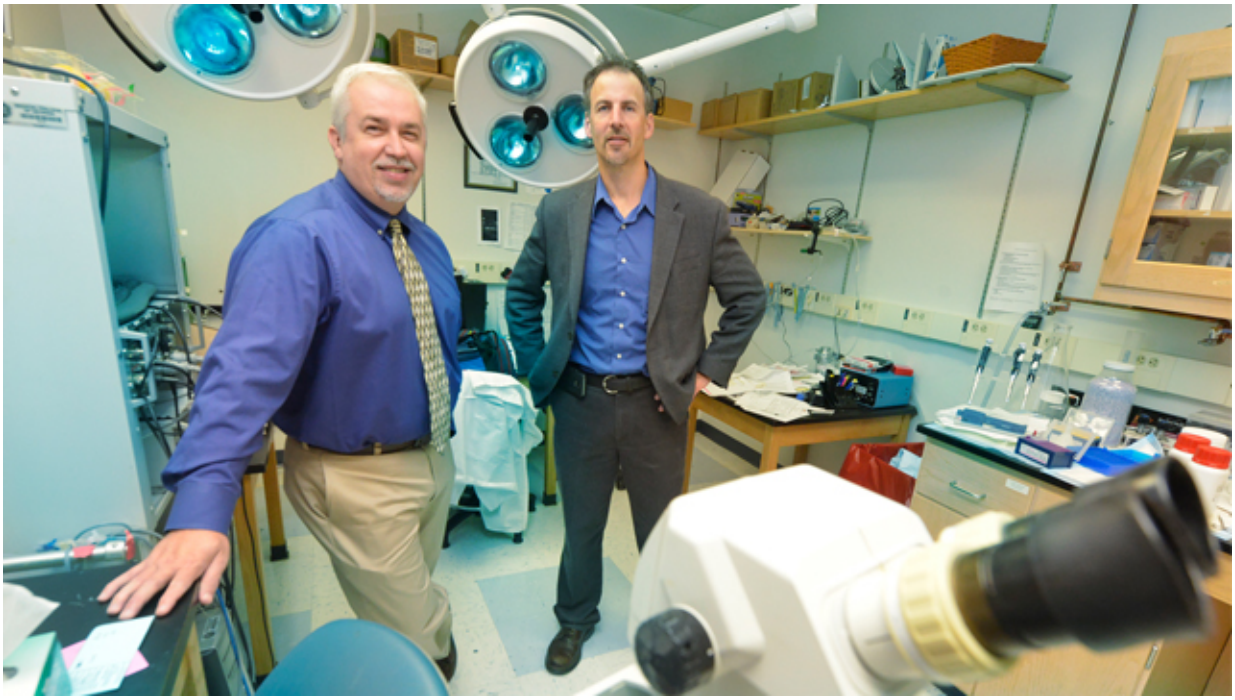

Drs. David Stepp (left), vascular biologist in the Vascular Biology Center at the Medical College of Georgia at Georgia Regents University and David Fulton, Director of the MCG Vascular Biology Center and Co-Principal Investigator with Stepp on the grant. Credit: Phil Jones

Even without losing fat, more muscle appears to go a long way in fighting off the bad cardiovascular effects of obesity.

That emerging evidence has scientists looking hard for new targets to uncouple the unhealthy relationship between fat and cardiovascular disease.

"If you look at the exercise literature, we understand very well that if you exercise, things get better. What we don't really understand is what about exercise is good; what does it tell us about physiology and how disease starts, and how can you customize it to different populations?" said Dr. David Stepp, vascular biologist in the Vascular Biology Center at the Medical College of Georgia at Georgia Regents University.

Stepp and his colleagues have evidence that an increase in muscle mass - a huge consumer of glucose, a natural energy source that is often elevated in obesity - could mean a healthier ticket for some.

While fat has the unhealthy habit of storing fuel, "muscle is a much more metabolically active tissue, even when it's just sitting there," Stepp said. "It burns more oxygen at rest; it burns more energy at rest; so it burns more calories at rest." Some of things scientists don't know is if muscles secrete something that improves glucose metabolism or if just having more glucose-consuming muscle is the apparent magic.

A new $2.2 million grant from the National Heart, Lung, and Blood Institute is helping fill in those important blanks as it illuminates new points for intervening in one of the worst consequences of obesity.

"We are trying to establish links between the health of skeletal muscles and the circulatory system," said Dr. David Fulton, Director of the MCG Vascular Biology Center and Co-Principal Investigator with Stepp on the grant. "When you eat, most of the glucose ends up in your skeletal muscle. When you are young, most of your body mass is skeletal muscle, so that glucose is efficiently distributed in the places where it should go to get used for energy and work."

Stepp and Fulton were authors on a 2014 study in the *Journal of the American Heart Association* that showed the benefits of adding muscle when fat is monopolizing the body. They looked at normal mice and mice genetically altered to be obese - mice with voracious appetites that soon doubled their normal weight - as examples of a healthy and unhealthy human. When they deleted myostatin, a natural, negative regulator of muscle growth, from both, both groups developed bigger muscles. The normal mice also had less fat tissue.

But it was the obese-with-muscles mice that truly benefited in the cardiovascular sense: glucose tolerance and blood vessel dilation went up and insulin resistance and superoxide production went down. More muscle didn't result in these additional changes in the leaner mice.

"If the insulin burner gets bigger and the storage (fat) gets smaller, that's good," Stepp said. "What we have demonstrated is that if the burner gets bigger, no matter what the storage does, it's still good."

When they looked further at the obese mice, minus the muscles, they also found the superoxide- producing gene Nox1 is a major culprit in obesity-related vascular disease. In fact, the gene is overexpressed in the blood vessels of the fat mice, apparently driven by high glucose levels in the blood.

Obese mice with no muscle added but Nox1 removed also experience cardiovascular improvement, an observation that Postdoctoral Fellow Dr. Jennifer Thompson is pursuing further with a new American Heart Association grant.

Meanwhile, Stepp and Fulton are exploring how elevated blood glucose elevates Nox1, acknowledging that while it makes intuitive sense, the science needs to be clear. Because while the search is on for Nox1 inhibitors, there aren't any at this moment. Fulton and Stepp hope their

studies will further inspire the search and identify additional points of intervention as well.

"We know that high glucose goes to Nox1 goes to superoxide, and superoxide goes to cardiovascular disease. What we don't know is what is in between glucose and Nox1," Stepp said. A possibility is galectin-3, a receptor for proteins that get coated with glucose when circulating levels of the sugar get too high. At least in culture, when glucose is added to cells, they produce more Nox1. But when the scientists block galectin-3 and add glucose, Nox1 doesn't increase.

While it's known that sugar-coating messes up protein function, the scientists aren't certain what galectin-3 is doing. Is it clearing the dysfunctional proteins, telling them to die, and/or driving up Nox1? So they are looking at the signaling between all of the above. They are also developing additional mice models, where Nox1 and galectin-3 are removed from already genetically fat mice, to further explore their role in vascular dysfunction. They will also explore the cardiovascular impact, such as blood pressure and how well blood vessels dilate in response to stress, in their fat mice models with added muscle as well as the two new knockouts.

The bottom line: they want to know if they can break "the metabolic connection" between fat and cardiovascular disease. "Where is the key event that causes all these bad things to happen?" Stepp said, and, of course, where and how best to intervene.

Myostatin is part of the yin and yang of muscle growth that enables us, with some effort, to have good, but not excessive, muscle mass. High myostatin levels can produce muscular dystrophy; low ones can mean incredible bulk. Myostatin levels tend to decrease with exercise and increase with aging.

Injectable or infusible myostatin inhibitors are under study for muscular dystrophy and frailty syndrome, where older individuals lose so much muscle mass that they fall frequently. But the drugs are not generally available, even to scientists. While experience with the inhibitors is limited, life with less myostatin appears to be a good thing: Stepp said mice short one copy of the myostatin gene live longer, and humans with documented myostatin deficiency tend to be Olympic athletes.

Provided by Medical College of Georgia