Calorie restriction trial reveals key factors in extending human health

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Decades of research has shown that limits on calorie intake by flies, worms, and mice can enhance life span in laboratory conditions. But whether such calorie restriction can do the same for humans remains

unclear. Now a new study led by Yale researchers confirms the health benefits of moderate calorie restrictions in humans—and identifies a key protein that could be harnessed to extend health in humans.

The findings were published Feb. 10 in *Science*.

The research was based on results from the Comprehensive Assessment of Long-term Effects of Reducing Intake of Energy (CALERIE) clinical trial, the first controlled study of calorie restriction in healthy humans. For the trial, researchers first established baseline calorie intake among more than 200 study participants. The researchers then asked a share of those participants to reduce their calorie intake by 14% while the rest continued to eat as usual, and analyzed the long-term health effects of calorie restriction over the next two years.

The overall aim of the clinical trial was to see if calorie restriction is as beneficial for humans as it is for lab animals, said Vishwa Deep Dixit, the Waldemar Von Zedtwitz Professor of Pathology, Immunobiology, and Comparative Medicine, and senior author of the study. And if it is, he said, researchers wanted to better understand what calorie restriction does to the body specifically that leads to improved health.

Since previous research has shown that calorie restriction in mice can increase infections, Dixit also wanted to determine how calorie restriction might be linked to inflammation and the immune response.

"Because we know that chronic low-grade inflammation in humans is a major trigger of many chronic diseases and, therefore, has a negative effect on life span," said Dixit, who is also director of the Yale Center for Research on Aging. "Here we're asking: What is calorie restriction doing to the immune and metabolic systems and if it is indeed beneficial, how can we harness the endogenous pathways that mimic its effects in humans?"

Dixit and his team started by analyzing the thymus, a gland that sits above the heart and produces T cells, a type of white blood cell and an essential part of the immune system. The thymus ages at a faster rate than other organs. By the time healthy adults reach the age of 40, said Dixit, 70% of the thymus is already fatty and nonfunctional. And as it ages, the thymus produces fewer T cells. "As we get older, we begin to feel the absence of new T cells because the ones we have left aren't great at fighting new pathogens," said Dixit. "That's one of the reasons why elderly people are at greater risk for illness."

For the study, the research team used magnetic resonance imaging (MRI) to determine if there were functional differences between the thymus glands of those who were restricting calories and those who were not. They found that the thymus glands in participants with limited calorie intake had less fat and greater functional volume after two years of calorie restriction, meaning they were producing more T cells than they were at the start of the study. But participants who weren't restricting their calories had no change in functional volume.

"The fact that this organ can be rejuvenated is, in my view, stunning because there is very little evidence of that happening in humans," said Dixit. "That this is even possible is very exciting."

With such a dramatic effect on the thymus, Dixit and his colleagues expected to also find effects on the immune cells that the thymus was producing, changes that might underlie the overall benefits of calorie restriction. But when they sequenced the genes in those cells, they found there were no changes in gene expression after two years of calorie restriction.

This observation required the researchers to take a closer look, which revealed a surprising finding: "It turns out that the action was really in the tissue microenvironment not the blood T cells," Dixit said.

Dixit and his team had studied adipose tissue, or body fat, of participants undergoing calorie restriction at three time points: at the beginning of the study, after one year, and after two. Body fat is very important, Dixit said, because it hosts a robust immune system. There are several types of immune cells in fat, and when they are aberrantly activated, they become a source of inflammation, he explained.

"We found remarkable changes in the gene expression of adipose tissue after one year that were sustained through year two," said Dixit. "This revealed some genes that were implicated in extending life in animals but also unique calorie restriction-mimicking targets that may improve metabolic and anti-inflammatory response in humans."

Recognizing this, the researchers then set out to see if any of the genes they identified in their analysis might be driving some of the beneficial effects of calorie restriction. They honed in on the gene for PLA2G7—or group VII A platelet activating factor acetylhydrolase—which was one of the genes significantly inhibited following calorie restriction. PLA2G7 is a protein produced by immune cells known as macrophages.

This change in PLA2G7 gene expression observed in participants who were limiting their calorie intake suggested the protein might be linked to the effects of calorie restriction. To better understand if PLA2G7 *caused* some of the effects observed with calorie restriction, the researchers also tracked what happened when the protein was reduced in mice in a laboratory experiment.

"We found that reducing PLA2G7 in mice yielded benefits that were similar to what we saw with calorie restriction in humans," said Olga Spadaro, a former research scientist at the Yale School of Medicine and lead author of the study. Specifically, the thymus glands of these mice were functional for a longer time, the mice were protected from diet-

induced weight gain, and they were protected from age-related inflammation.

These effects occurred because PLA2G7 targets a specific mechanism of inflammation called the NLRP3 inflammasome, researchers said. Lowering PLA2G7 protected aged mice from inflammation.

"These findings demonstrate that PLA2G7 is one of the drivers of the effects of calorie restriction," said Dixit. "Identifying these drivers helps us understand how the metabolic system and the immune system talk to each other, which can point us to potential targets that can improve immune function, reduce inflammation, and potentially even enhance healthy lifespan."

For instance, it might be possible to manipulate PLA2G7 and get the benefits of calorie restriction without having to actually restrict calories, which can be harmful for some people, he said.

"There's so much debate about what type of diet is better—low carbohydrates or fat, increased protein, intermittent fasting, etc.—and I think time will tell which of these are important," said Dixit. "But CALERIE is a very well-controlled study that shows a simple reduction in calories, and no specific diet, has a remarkable effect in terms of biology and shifting the immuno-metabolic state in a direction that's protective of human health. So from a public health standpoint, I think it gives hope."

More information: Timothy W. Rhoads et al, Reverse Translation Delivers New Insights on Immunometabolic Regulation, *Science* (2022). DOI: 10.1126/science.abn6576.
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