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CALERIE Trial - Benefits of Calorie Restriction in Humans

There is significant evidence to show that limits on calorie intake by flies, worms, and mice can enhance life span in laboratory conditions. However, it is still unclear whether such calorie restriction can do the same for humans.

A new study led by Yale researchers confirms the health benefits of moderate calorie restrictions in humans. The researchers have also identified a key protein that could be harnessed to extend health in humans. Their findings are published in *Science*.

The research is based on the Comprehensive Assessment of Long-term Effects of Reducing Intake of Energy (CALERIE) trial results. CALERIE is the first controlled study of calorie restriction in healthy humans. For the trial, researchers established baseline calorie intake for over 200 study participants. A share of these participants was asked to reduce their calorie intake by 14%, while the rest continued to eat as usual. The long-term effects of calorie restriction on health were analysed over the next two years.

The aim of the study was to see if calorie restriction is as beneficial for humans as it is for lab animals and to understand what calorie restriction does to the body that leads to improved health. The researchers also wanted to determine how calorie restriction is linked to inflammation and the immune response.

Study researchers analysed the thymus, a gland that sits above the heart and produces T cells. The thymus ages faster than other organs, and in most healthy adults, the thymus is fatty and nonfunctional by the age of 40. As it ages, the thymus produces fewer T cells. That is one of the reasons why elderly people are at a greater risk for illness.

The research team used 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. On the other hand, participants who weren't restricting their calories had no change in functional volume.

These findings suggest that this organ can be rejuvenated. It was also observed that the action was in the tissue microenvironment, not the blood T cells. A study of the adipose tissue of participants undergoing calorie restriction at three time points - at the beginning of the study, after one year, and after two years - showed changes in the gene expression that were sustained through year two. This showed that some genes had unique calorie restriction-mimicking targets that could improve metabolic and anti-inflammatory response in humans.

Specifically, the researchers 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 in participants with limited calorie intake suggested the protein might be linked to the effects of calorie restriction. In a laboratory experiment, the researchers tracked what happened when the protein was reduced in mice. They found that reducing PLA2G7 yielded benefits similar to calorie restriction in humans. The thymus glands of these mice were functional for a longer time, and the mice were protected from diet-induced weight gain and age-related inflammation.

These findings show that PLA2G7 is one of the drivers of the effects of calorie restriction. The researchers state that it might be possible to manipulate PLA2G7 and get the benefits of calorie restriction without having to actually restrict calories. Hence, the study shows that a reduction in calories without any specific diet could have a beneficial effect in terms of biology and shifting the immuno-metabolic state in a direction that's protective of human health.

Source: Science
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