

CAN A FATTY ACID SUPPLEMENT IMPROVE OUTCOMES IN OBESE PEOPLE WITH PREDIABETES?

Obesity is a vast and growing health problem that negatively affects many



systems in the body. It also increases the risk of diabetes, fatty liver disease, and cardiovascular disease, among other conditions.

Investigators at Brigham and Women's Hospital are now looking at novel ways to boost the natural mechanisms that the body uses to counteract the development of obesity and its related complications. An upcoming clinical trial will explore whether dietary supplementation with

palmitoleic acid (POA)—a monounsaturated fatty acid that is released by fat tissue during the metabolic process and part of the modern diet—can enhance key health measures in individuals who are obese and prediabetic.

In the lab, POA appears to reduce the accumulation of fat in the liver, improve the body's sensitivity to glucose, and decrease inflammation in the vascular vessels.

“POA is a molecule that is part of the body's own rescue system,” says physician-scientist Mehmet Furkan Burak, MD, an endocrinologist at the Brigham and instructor at Harvard Medical School, and a basic scientist in the Department of Molecular Metabolism within the Harvard T.H. Chan School of Public Health. “From an endocrinology standpoint, we want to see if we can mimic the body's own rescue mechanism to tackle obesity-related problems.”

Harnessing the Body's Natural Mechanisms

Researchers have known that when it comes to dietary fat, quality is more important than quantity for maintaining good metabolic health. This is where the idea of “healthy fats” comes from. But studies looking at supplementing the diet with so-called healthy fats like fish oil have had mixed results. One reason is that these oils contain a mixture of fatty acids, some of which may be beneficial and others of which are neutral or even detrimental.

POA is a key component of macadamia nut oil, which has been studied for its potential benefits. But in addition to high levels of POA, this oil also contains significant levels of palmitic acid, another fatty acid, which counteracts POA's beneficial effects. A technique that allows the purification and separation of clinical-grade POA from other fatty acids is one thing that has made this new trial possible.

The discovery that POA could be a good candidate for boosting the body's metabolism of fat came from laboratory studies by the Harvard T.H. Chan School of Public Health team, led by Gökhan S. Hotamisligil, MD, PhD (published in *Cell* in 2008). That research found that POA is an adipose tissue-derived lipid hormone that strongly stimulates muscle insulin action and suppresses fat accumulation in the liver.

Later work in mice revealed that POA could have beneficial health effects in disease models. “This molecule goes to the muscle and improves insulin sensitivity. It goes to immune cells and makes them less inflammatory. It also decreases fat formation,” Dr. Burak says. “If we supply it from the outside in patients, can it lead to the same therapeutic improvements?”

A Unique, Placebo-controlled Trial Involving POA

Dr. Burak's trial, which is expected to begin recruiting patients in November 2022, will be the first to look at supplementation with POA in people who are obese and prediabetic. The investigators plan to screen 120 individuals to ensure a distribution of individuals across the spectrum of glucose tolerance, ultimately enrolling 40 in the trial. Half of the participants will receive POA, with the other half receiving a placebo.

The primary measure of the trial will be POA's effects on insulin sensitivity. The patients will also receive liver MRIs and DEXA scans. A key factor enabling this study is the ability to measure insulin sensitivity with the hyperinsulinemic euglycemic clamp test. "This high-end technique is the gold standard for testing insulin sensitivity. It's not a calculation using a surrogate but is really the quantitative measurement," Dr. Burak says. "Very few centers in the world can do this test."

There will also be a lab component to this study in collaboration with Pau Sancho-Isabel Graupera of the Hospital Clínic de Barcelona. This research will investigate the molecular mechanisms of POA treatment on human liver organoids.

"If this trial proves successful, there are many implications for treating obesity-related complications," Dr. Burak concludes.

For more information on this study and Provinal® contact the study sponsor, Tersus Life Sciences LLC. 8000 Health Center Blvd., Bonita Springs, FL 34135
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