

Dogma vs. data:

Rethinking linoleic acid

Stacy Kish

- Fats play a critical role in nutrition but are often viewed through the narrow lens of the omega-6:omega-3 ratio. The western diet skews the ratio toward omega-6, which has been maligned for different health conditions, from chronic heart disease to diabetes.
- New research confirms linoleic acid, an omega-6 fatty acid, has many positive implications on human health, including promoting the accumulation of lean mass, the proper functioning of the mitochondria, and the ability to stave off heart disease, diabetes, and fatty liver disease.
- Martha Belury, the Carol S. Kennedy professor of human nutrition in the Department of Human Sciences at the Ohio State University, in Columbus, Ohio, USA, has followed the data throughout her research career, shifting her focus from omega-3 to the health benefits of omega-6 fatty acids.
- Because of the strong evidence for linoleic acid as a protective fat for many chronic diseases, the omega-6:omega-3 ratio is now considered a misleading or outdated method of categorizing dietary fats and has been replaced by the omega-3 Index, which has been shown in clinical studies to predict coronary heart disease more accurately.

Humans have evolved to eat a variety of foods. No one component is entirely bad or entirely good. Many diets popular today, approach nutrition through a narrow, simplified lens. Every decade one component of our diet is placed center stage as the villain that is responsible for all of our woes. In recent decades, the spotlight has been turned on fats.

Fat is essential, providing a source of energy and a feeling of satiety. There are essential fatty acids that humans cannot produce, including linoleic acid (omega-6) and alpha-linolenic acid (omega-3). Both fatty acids are obtained from the food we eat and play a critical role in major cellular events, including metabolism, inflammation, cell differentiation, and cell death. Some dietitians and nutritionists have advocated for eating an equal amount of omega-6 and omega-3 fatty acids, resulting in a 1:1 ratio. This diet is presumed to mimic the ancient human diet, though no definitive data supports what early humans actually ate consistently. The modern American diet ranges from a value of 10:1 to 15:1.

The overarching nutritional message has been that the modern diet suffers from an “omega imbalance.” The imbalance is a ‘concern,’ because omega-6 fatty acids, which skews the index to higher numbers, have been assumed to promote poor health outcomes and disease, including increased ‘bad’ cholesterol (LDL), inflammation, and coronary heart disease. Surprisingly, no randomized controlled clinical trials actually support any of these claims. (<https://doi.org/10.1007/s11883-006-0019-7>).

The concept of the omega-6:omega-3 ratio is “flawed and unhelpful,” says William Harris, professor of basic biomedical sciences at the University of South Dakota, in Vermillion, South Dakota, USA.



Harris is the founder and president of the Fatty Acid Research Institute, a non-profit research and education organization created to further the study of fatty acids and disease. To expand on Harris's point, measuring the ratio is difficult because each fatty acid appears as various species in different ratios in different reservoirs in the body. According to Harris, this simple metric has "both theoretical and practical complications" that create fundamental misunderstandings that have cascaded through the field. He has published numerous articles describing the lack of scientific validation to support using this ratio as an indicator of healthful diet (<https://doi.org/10.1016/j.plefa.2018.03.003>).

Martha Belury, Carol S. Kennedy professor of human nutrition in the Department of Human Sciences at the Ohio State University, Columbus, Ohio, USA, concurs with Harris's assessment. She believes it is time to move away from the omega-6:omega-3 ratio and re-evaluate the benefits of the much maligned omega-6 fat.

"Science and health are short-changed if we oversimplify," said Belury. "While omega-3 has an important role in health, omega-6 has a pivotal role to play as well. This is an important message for consumers and practitioners."

LINOLEIC ACID: THE VILLAIN OF MODERN GLUTTONY?

Belury began her career arguing for omega-3 fatty acids. One of her studies during her doctoral program aimed to evaluate the protective nature of omega-3 fatty acid in a mouse model for skin cancer. As is standard, she set up a control, in this case

an omega-6 fatty acid, to compare the results. To her surprise, the results showed omega-6 fatty acid offered unanticipated protection too.

"Dogma exists in science like it does everywhere and sometimes scientists are blind to results that go against what they anticipate," said Belury. "Shifting the paradigm is difficult. It requires time, patience, and money."

Belury was fortunate to have an advisor and mentor who encouraged her to pursue the truth no matter where the data took her. She is now confident in one thing—lipids are not a simple or straight forward story.

Belury says nutrition does not operate like a binary system where one fat is good and one is bad. Rather, fatty acids require a more nuanced approach to illustrate the complexity of the natural world. Her research follows a series of clues, supported by studies around the world, to unravel the complex interactions this fatty acid has in human health.

WHEN RESEARCH COUNTERS CONVENTIONAL WISDOM

Linoleic acid is the most common form of omega-6 fatty acid. It is found in vegetable oils, nuts, seeds, and animal products. As the American diet has evolved, linoleic acid, a component of soybean and many other vegetable oils, has increasingly found its way into processed foods. Today, soybean oil accounts for as much as 45 percent of the dietary intake of linoleic acid in the United States (<https://doi.org/10.3945/an.113.003772>).

In 2014, a team of researchers from Uppsala University and the Karolinska University Hospital in Sweden published

Linoleic Acid Revs Up the Mitochondria

New research is finding that mitochondrial dysfunction may play a role in many diseases, from diabetes to Parkinson's disease. Mitochondria are critical in the cell, producing ATP that powers all activities as well as generating heat and regulating cell death. Healthy mitochondria are lined with tetralinoleoyl-cardiolipin. Unlike other phospholipids that are constructed with two chains of fatty acids that could include linoleic acid, palmitate or oleate, the structure of tetralinoleoyl-cardiolipin consists of four linoleic fatty acid chains. The unusual structure lies in its bacterial origin.

"Cardiolipin is a very understudied fat," said Genevieve Sparagna, research assistant professor at the University of Colorado Anschutz Medical Campus in Aurora, Colorado, USA, who has worked with Belury on previous research projects. "It is derived from ancient bacterial phospholipids, so it is unique," she says.

The four fatty acids are connected via two phosphates linkages at either end of a glycerol backbone. This construction produces a super strong mesh with a chevron-like pattern. The mesh forms the scaffold of the electron chain transport super complex that allows electrons

to flow through the mitochondrion creating ATP energy without leaking.

Advances in technology have opened new opportunities to study the mitochondrial function beyond the normal process of monitoring changes in oxygen consumption. Subtle changes in the cardiolipin mass are detected using mass spectrometry.

According to Sparagna, other fatty acids can replace linoleic acid in the tetralinoleoyl-cardiolipin mesh inside the mitochondrion. These substitutions reduce the efficiency of the ATP creation and increase electron loss. As a result, the mitochondrion provides less energy for the cell.

By looking at the mass of the mitochondrion, it is possible to determine exactly which fatty acids are being substituted on the tetralinoleoyl-cardiolipin curtain. This information opens opportunities to understand why the mitochondria is not performing optimally. Sparagna is now running these tests on peripheral blood mononuclear cells—immune cells with a single, round nucleus that originate in bone marrow, rather than the traditional but more invasive skeletal muscle tissue obtained with a biopsy.

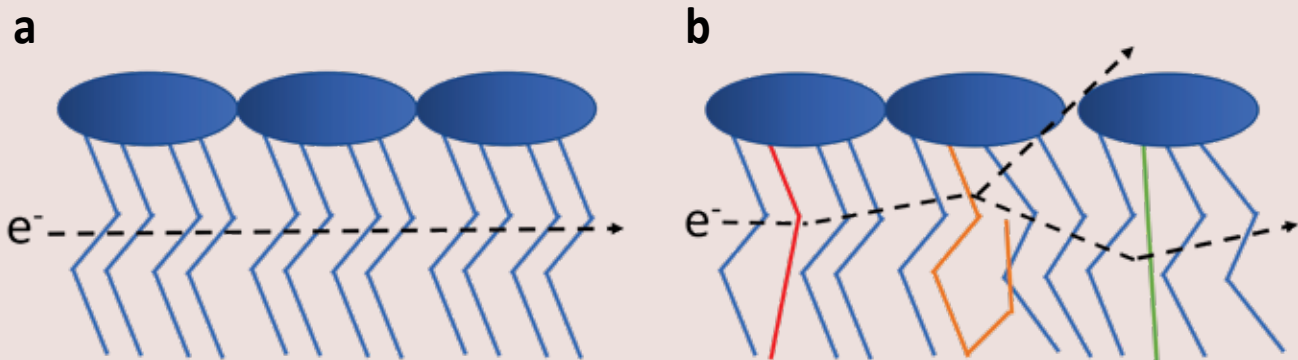


FIG. 1. a) Linoleic acid fatty acid chains (blue lines) formed on a cardiolipin molecule. b) Other fatty acids, represented by red, orange, and green lines, formed on a cardiolipin molecule. Electrons (e^-) follow the electron transport chain (dashed path) through the cardiolipin molecule. In a), the electrons flow straight through the tetralinoleoyl-cardiolipin. In b), the electron path is less efficient and electrons may leak from the membrane. Source: Sparagna

the results of the Lipogain clinical trial (<https://clinicaltrials.gov/ct2/show/NCT01427140>). The double-blind, randomized, seven-week study examined the role of two dietary fats on body fat accumulation and ectopic fat storage. The study while small—only 39 participants were enrolled—revealed that the type of fat consumed has a powerful impact on liver fat accumulation, fat distribution, and body composition. Participants were fed either muffins baked with linoleic-rich sunflower oil or palm oil, a saturated fatty acid that is commonly used in food around the world. While both groups gained weight, the group fed the palm oil muffins gained more liver fat, total fat, and abdominal fat. The group fed the sunflower oil-rich muffin

gained more lean tissue. The study supported much of Belury's research on the positive health outcomes of linoleic fatty acid.

In 2020, Belury published the results of a similar study that measured the effect of linoleic acid on measurements associated with body fat and metabolism on 15 post-menopausal, nondiabetic women with metabolic syndrome (<https://doi.org/10.1093/cdn/nzaa136>). During menopause, estrogen plummets. A woman's body composition changes, leading to weight gain around the abdomen. Metabolic syndrome is characterized by abdominal obesity, low good cholesterol (HDL), and elevated triglycerides, glucose, and blood pressure. These conditions increase the risk for heart disease and diabetes. During

the 16-week study, participants received two teaspoons of linoleic acid-rich vegetable oil per day.

The study results showed that supplementing the diet with linoleic oil increased total and high molecular weight adiponectin concentration, a hormone released by fat tissue that helps cells in the body use blood glucose more effectively. The linoleic oil also increased the concentration of oxylipins, a family of oxygenated products produced by fatty acids that may play a role in mitigating cardiovascular disease. These findings suggest linoleic supplements deserve greater scrutiny in patients with metabolic syndrome.

Belury was curious if the mitochondria could be a target of linoleic acid. To delve deeper into the role of linoleic acid on mitochondrial function, her lab examined dietary fat in a mouse model. For 25 weeks, mice were fed a lard diet that mimicked the fat intake pattern in the western diet or one rich in linoleic-rich safflower oil. Following a series of lipodomic analyses, they found that the mice fed the linoleic-rich diet increased the concentration of tetralinoleoyl-cardiolipin, the phospholipids lining mitochondria.

An earlier study found rats bred to have heart failure responded positively to a diet supplemented with linoleic acid. Cardiac mitochondria are especially powerful organelles that supply the energy needed to keep the heart beating 24 hours a day, seven days a week. The linoleic-rich diet supercharged the mitochondria compared to carbohydrate- or lard-rich diets. The heart-challenged rats should have died young, but the linoleic acid intervention allowed them to live into old age. More surprisingly, the rats responded to the change in diet in less than 24 hours (<https://doi.org/10.1161/HYPERTENSIONAHA.108.114264>).

This previous finding provoked Belury to continue her mitochondrial studies in humans. Her team developed a blood test using protocols published by her peers to evaluate mitochondrial function. Healthy mitochondria convert fat into energy efficiently. As a result, a person with healthy mitochondria have less fat tissue, more lean mass, and respond to insulin more effectively. Belury confirmed these findings in a small study where participants were given either a cookie made with linoleic-rich safflower oil or a cookie rich in oleic oil. They found the linoleic-rich diet increased the concentration of tetralinoleoyl-cardiolipin in blood samples. The oleic-rich diet increased oleic-rich cardiolipin, which had a blunting effect on mitochondrial function.

To pursue these initial findings further, Belury constructed the WELL (Weight, Energy, Lipids & the Liver) Study. The on-going, 18-week clinical intervention aims to evaluate the role of two dietary fats—palm oil and soybean oil—on liver fat and abdominal fat. According to Belury, 30 percent of Americans have non-alcoholic fatty liver disease. This disease sets up a detrimental positive-feedback loop. As the liver accumulates fat, it becomes insulin resistant, allowing nonlipid precursors to produce more fatty acids. The more fat the liver accumulates, the worse the health outcomes. Forthcoming results from the WELL Study could provide additional information about the protection conferred by omega-6 fatty acids (<https://clinicaltrials.gov/ct2/show/NCT05199948>).

FROM A RATIO TO AN INDEX

Some researchers are still confounded by the notion that omega-3 and omega-6 were ever embroiled in a zero-sum competition. Both are components of a healthful diet and play an important role in the body and human health. While many nutritionists now see the error in the simplicity of the omega-6:omega-3 ratio, the concept has become enmeshed in the conventional dietary narrative. This concept has also influenced research funding trends, stifling researchers' ability to explore the health implications of fatty acids on a variety of diseases. However, a more reliable indicator has emerged—the omega-3 index, a measure of the weight percent of total red blood cell membrane fatty acids.

The omega-3 index focuses on the sum of two omega-3 fatty acids: eicosapentaenoic acid and docosahexaenoic acid. An optimal omega-3 index is 8 percent or higher. The index has been shown in multiple observational and cohort studies to be a better predictor for coronary heart disease, sudden cardiac death, and impaired cognitive function (<https://doi.org/10.1016/j.atherosclerosis.2017.05.007>). The omega-3 index is also easier to measure than the omega-6:omega-3 ratio. Similar to the A1C test that is used to evaluate the glycemic status for patients with diabetes, the omega-3 index can be measured with a simple blood test.

Beyond the omega-6:omega-3 ratio or omega-3 index, the science provides a clear and powerful argument for the benefits of linoleic acid. It is now time for fellow researchers, practitioners, reporters, and funding agencies to take a more holistic approach to fat and begin the slow shift in how we view this critical component of our diet. In the future, Belury wonders if there will also be a place for a Recommended Dietary Allowance for linoleic acid.

“Fatty acids are among the simplest molecules in nutrition, but there is still so much we do not understand,” said Belury. “My hope is that in the future researchers can study linoleic acid to understand its role in human health.”

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