New Independent Confirmation of C15:0 as an Essential Fatty Acid

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Welcome to Issue 110 of Science Says! Our weekly newsletter where you'll learn the latest healthy aging and C15:0 research news that our team of doctors, scientists, and experts are most excited about—without having to go search for it.

Eric and Steph
Co-Founders, Doctors, Nerds

What Dr. Stephanie Venn-Watson, our co-founder and author of over 80 peer-reviewed scientific publications, is reading.

HEALTHY AGING

So, How Do You Know C15:0 Is An *Essential* Fatty Acid?

Last week, we shared a study showing that C15:0 can enable critical early development *in absence of any other nutrients*—at least in worms. That's pretty darn essential.

This week, we get back to C15:0's essentiality in humans. In the journal *Biochimie*, a team in France independently evaluated specific elements of C15:0 (also known as pentadecanoic acid, which they refer to as "PDA") to determine whether it met the criteria of being an essential fatty acid. Their conclusion?

"Thus, considering these elements, PDA (C15:0) is currently meeting the described criteria of an EFA (essential fatty acid)."

Let's cover how Ciesielski et al. evaluated C15:0's critical role, and why it is important that this is the third team (initially starting with fatty15's founders) to make the same conclusion: C15:0 is essential.

I think I know, but what exactly is an *essential fatty acid*?

An essential fatty acid is a nutrient that our bodies require to maintain our baseline physiological health. Since our bodies don't make enough of these essential fats on their own, we must routinely get adequate amounts from our diet. As we've covered last week, there are only three known essential fatty acids:

- Linoleic acid (an omega-6 fatty acid)
- Alpha linolenic acid (an omega-3 fatty acid)
- Pentadecanoic acid (an odd-chain saturated fatty acid)

Okay. If we already knew that C15:0 is essential, what's the big deal about this latest study?

While our co-founder, Dr. Stephanie Venn-Watson, was the first to discover that C15:0 met the criteria of being an essential fatty acid, this is a giant, once-in-a-century discovery that continues to be evaluated by other scientists throughout the world.

Fun fact: Today, there are 100+ peer-reviewed studies, led by prestigious research teams throughout the world, demonstrating 1) how C15:0 works, and 2) its relevance to protecting our long-term health. You can nerd out on all this science at DiscoverC15.com.

Got it. How did the team in France evaluate C15:0 as an essential fatty acid?

In their review, Ciesielski et al. used the following two criteria to determine whether C15:0 is an essential fatty acid:

- ☐ It is not endogenously sufficiently synthesized by the body, hence it must be supplied by the diet.
- ☐ It is required to maintain a healthy physiological state.

Here's what they found.

Humans have a clear and long-standing dietary source of C15:0 (aka, milkfat).

As with the other essential fatty acids and several vitamins, C15:0 is present in milk - that perfect food that every mammal gets from birth.

Specifically, Ciesielski et al. detail how cows and other ruminants are particularly good at making C15:0 in their rumens, which then makes its way into their milk. They also explain why milkfat from cows (or goats or sheep) is *by far* our best dietary source of C15:0. In fact, the amount of C15:0 in our bodies is directly determined by how much milkfat we eat.

Additionally, this paper included studies showing that our own gut bacteria can use fiber to make some C15:0, but concluded that this does not appear to be an important pathway leading to sufficient and meaningful C15:0 body levels.

With that, Ciesielski et al. checked off their first box.

- ☑ It is not endogenously sufficiently synthesized by the body, hence it must be supplied by the diet.

Evidence that C15:0 has health protective effects.

Next up, Ciesielski et al. summarize a series of studies supporting that C15:0 has protective effects related to ***metabolic syndrome, type 2 diabetes, and fatty liver disease***. These studies showed the following:

- People with higher C15:0 levels consistently have better metabolic, glucose, and liver health.
- In relevant models, C15:0 directly improves and protects metabolic, glucose, and liver health.

Further, Ciesielski et al. describe how C15:0 has bioactivities (called mechanisms of action) that explain how it directly protects metabolic, glucose, and liver health, including:

- Activating AMPK and AKT, which support healthy glucose handling and insulin sensitivity.
- Lowering multiple pro-inflammatory cytokines and resultant inflammatory responses.
- Protecting the integrity of the gut barrier (aka protecting against leaky gut).

Thus, large human population studies, experimental research, and relevant mechanisms of action all support that C15:0 has an active role in protecting our health.

Evidence of additional health protective effects from a C15:0 metabolite.

As would be expected of an essential fatty acid, our very own Steph published in *Nature's Scientific Reports* in 2022 the discovery of a C15:0 metabolite, which is its own amazing and active molecule. In their paper, Ciesielski et al. summarize Steph's study, which shows that our bodies use C15:0 to make a special metabolite called pentadecanoylcarnitine (or PDC).

In turn, PDC fully activates the endocannabinoid system, including both CB1 and CB2 receptors. In fact, PDC is the second-ever discovered fully acting endocannabinoid. We care about this because endocannabinoids naturally activate key pathways that support deeper sleep, calmer mood, and less pain.

Given the last two sections, Ciesielski et al. were able to check off their second evidence-box of C15:0's role as an essential fatty acid:

- ☑ It is required to maintain a healthy physiological state (specifically, metabolic and liver health).

In their paper, which included a slew of other details, Ciesielski et al. concluded that C15:0 meets the criteria of being an essential fatty acid, agreeing with both the original Venn-Watson et al. paper and Dornan et al. You go, C15:0.

Where there is an essential nutrient, there is a nutritional deficiency.

At the end of their paper and given their conclusions that C15:0 is essential, Ciesielski et al. recommended that more is needed to understand nutritional C15:0 deficiencies.

Enter our recent paper in Metabolites, describing a nutritional C15:0 deficiency syndrome called Cellular Fragility Syndrome, the first nutritional deficiency syndrome to be discovered in 75 years. While we recently covered Cellular Fragility Syndrome in *Science Says!*, the following are the most important points:

- When our cell membranes have low C15:0 levels (~ 0.2% of total fatty acids), they become fragile, resulting in raised lipid peroxidation, damaged reactive oxygen species, damaged mitochondria, abnormal intracellular iron deposition, and cell death.
- This new form of cell death, originally discovered by a team of scientists at Columbia University in 2012, is called ferroptosis. Despite more than 10,000 peer-reviewed papers on ferroptosis, no one was able to explain what was actually causing ferroptosis (well, until now).
- In turn, C15:0 deficiency-driven ferroptosis accelerates aging and impairs our metabolic, liver, and heart health.
- Population-wide declines in C15:0 have resulted in as many as 1 in 3 people with Cellular Fragility Syndrome, which may explain observed accelerated aging-related conditions in younger people.
- Replenishing C15:0 directly reverses all aspects of ferroptosis and Cellular Fragility Syndrome.

Take home point: Fixing nutritional C15:0 deficiencies gives the world a whole lotta hope to help fix an urgent metabolic crisis and restore global health.

Indeed, our nerdy do-gooder movement to improve global health continues to gain momentum. Thanks for being with us on this decade-long journey, and have a great week, everyone!

Dive deeper into the science

READ THESE STUDIES

- Ciesielski et al. New insights on pentadecanoic acid with special focus on its controversial essentiality: A mini-review.
- Venn-Watson et al. Efficacy of dietary odd-chain saturated fatty acid pentadecanoic acid parallels broad associated health benefits in humans: could it be essential?
- Dornan et al. Odd chain fatty acids and odd chain phenolic lipids (alkylresorcinols) are essential for diet.
- Venn-Watson et al. Pentadecanoylcarnitine is a newly discovered endocannabinoid with pleiotropic activities relevant to supporting physical and mental health.
- Venn-Watson et al. The Cellular Stability Hypothesis: Evidence of ferroptosis and accelerated aging associated diseases as newly identified nutritional pentadecanoic acid (C15:0) deficiency syndrome.
- Nerd out on all the C15:0 science at DiscoverC15.com.