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When Iron Wreaks Havoc On Our Liver & Metabolism

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Welcome to Issue 175 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 *The Longevity Nutrient* and over 80 peer-reviewed scientific publications, is reading.

HEALTHY AGING

Metabolic Hyperferritinemia: An Emerging Syndrome

A meta-analysis was published in *Liver International* this month that looked at the prevalence of hyperferritinemia among people with liver disease - specifically, metabolic dysfunction-associated steatotic liver disease (aka, MASLD). This latest research by Souza et al. feeds into a series of studies rallying around a distinct syndrome called "metabolic hyperferritinemia", which appears to be affecting a good number of us. With that, let's dive in...

Okay, what is hyperferritinemia?

First off, "ferritin" is a protein that stores iron in our cells. As described by Knovich et al., this is why the amount of ferritin in serum can serve as a useful biomarker to detect either iron deficiency (low ferritin) or iron overload (high ferritin).

Hyperferritinemia is defined as high serum ferritin levels. Chronically high ferritin levels are indicative of too much iron sitting around in tissues (aka, iron overload). While we typically think of iron as a good thing, too much iron can damage tissues - including our liver, heart, pancreas and brain. As shared by Adams et al., ***hyperferritinemia is present between approximately 6% to 19% of apparently healthy individuals.***

Got it. What is "metabolic hyperferritinemia"?

Back in the day, iron overload was primarily a hereditary condition caused by a genetic mutation in which people absorb too much iron. Since the 1990s, however, there have been increasing numbers of people who have *non-hereditary* iron overload. This trend is being validated by physicians, who are seeing more and more patients with high ferritin during routine blood tests.

While high ferritin can be caused by inflammation, the recent increasing trend in hyperferritinemia has been attributed to unwanted iron overload in tissues. Importantly, this type of hyperferritinemia has been closely linked to more severe cardiometabolic and liver conditions, especially type 2 diabetes, cardiovascular disease, and fatty liver disease. It also has a few distinct features that helps this type of ferritinemia stand out, including deposition of iron inside specific cells in the liver, called Kupffer cells.

To better detect and understand this emerging type of hyperferritinemia in humans without requiring a liver biopsy, an international consortium of physicians specializing in endocrinology, iron metabolism, cardiology, and liver disease published a consensus statement to formally define the term “metabolic hyperferritinemia” (or MHF). In their publication in *Nature Reviews*, Valenti et al. describe the inclusion criteria and three stages of MHF:

Inclusion criteria for metabolic hyperferritinemia: Presence of metabolic conditions, including MASLD.

Stage 1 (early metabolic hyperferritinemia)

- Ferritin levels: > 300-550 ng/ml for women, > 400-550 ng/ml for men.
- Liver iron levels: Normal
- Overall iron stores: Normal
- Organ damage due to iron: Absent

Stage 2 (dysmetabolic iron accumulation)

- Ferritin levels: 550-1,000 ng/ml
- Liver iron levels: Increased
- Overall iron stores: Increased
- Organ damage due to iron: Rare

Stage 3 (dysmetabolic iron overload syndrome)

- Ferritin levels: > 1,000 ng/ml
- Liver iron levels: High
- Overall iron stores: Very high
- Organ damage due to iron: Present

In the most recent study by Souza et al., they found that approximately 1 in 4 people with MASLD had metabolic hyperferritinemia…along with more severe metabolic dysfunction and liver injury. Another study by Gensluckner et al., evaluating 8,407 adults aged 40 to 77, showed that 13% of this baseline population had hyperferritinemia. Of these, a whopping 81% met the criteria of metabolic hyperferritinemia.

So, to sum up…a test routinely used by physicians is increasingly detecting people with high ferritin levels (aka hyperferritinemia) caused by a specific type of iron overload linked to more severe cardiometabolic and liver conditions. This is now being referred to as “metabolic hyperferritinemia”. Bottom line - we all need to be paying attention to our ferritin levels to protect our bodies against damaging iron deposition.

Here’s where C15:0 comes in.

As we published in 2012, we found that about 1 in 3 bottlenose dolphins had fatty liver disease and hyperferritinemia caused by liver iron overload - ***which specifically showed iron deposition inside those Kupffer cells.*** We didn’t know it at the time, but dolphins were revealing a clean and clear picture of what would later be called metabolic hyperferritinemia in humans.

Most importantly, dolphins showed us the pathophysiology of three concurrently emerging phenomena in humans: specifically, MASLD, metabolic hyperferritinemia, and ferroptosis (a new form of iron-driven cell death).

Here’s what dolphins taught us that brings all three of these conditions together:

- Lower dietary C15:0 results in more fragile red blood cells (RBCs)
- These fragile RBCs are engulfed by Kupffer cells in the liver
- Over time, this results in liver iron overload

(specifically in the Kupffer cells) and fatty liver disease that manifests as Stages 1-3 of metabolic hyperferritinemia.

- On the positive side, increasing dietary C15:0 levels increases RBC C15:0 levels, which reverses this syndrome. These early studies supported that dietary C15:0 deficiency may cause MASLD, MHF, and ferroptosis.

This hypothesis is playing out in the broader scientific community - including the demonstrated ability for C15:0 to reverse this emerging picture of a nutritional deficiency syndrome by independent teams across four different models, including humans.

The bottom, bottom line? There is an increasingly urgent need not only to identify people with metabolic hyperferritinemia, but to fully understand the roles of: 1) low dietary C15:0 driving a distinct and potentially common deficiency syndrome, and 2) restoring healthy C15:0 levels to fix it.

Have a great week, everyone!

Dive deeper into the science

READ THESE STUDIES AT
DISCOVERC15.COM/RESOURCES

- Souza et al. Prevalence and characteristics of hyperferritinemia in metabolic dysfunction-associated steatotic liver disease: a meta-analysis
- Knovich et al. Ferritin for the clinician
- Adams et al. Hemochromatosis and iron-overload screening in a racially diverse population
- Valenti et al. Consensus Statement on the definition and classification of metabolic hyperferritinemia
- Gensluckner et al. Prevalence and characteristics of metabolic hyperferritinemia in a population-based central-European cohort
- Venn-Watson et al. Hemochromatosis and fatty liver disease: building evidence for insulin resistance in bottlenose dolphins
- Mazzaro et al. Iron indices in bottlenose dolphins
- Johnson et al. Use of phlebotomy treatment in bottlenose dolphins with iron overload
- Venn-Watson et al. Modified fish diet shifted metabolome and alleviated chronic anemia in bottlenose dolphins: potential role of odd-chain saturated fatty acids
- 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?
- Aabis et al. Pentadecanoic acid attenuates thioacetamide-induced liver fibrosis by modulating oxidative stress, inflammation, and ferroptosis pathways in rat
- Robinson et al. C15:0 Supplementation in Young Adults at Risk for Metabolic Syndrome: A Randomized Controlled Trial
- 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

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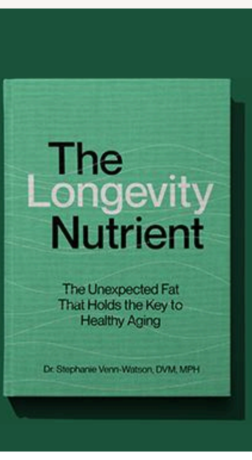
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