LINUS PAULING INSTITUTE

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RESEARCH NEWSLETTER

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NEW WEBINAR ON ZINC AND HEALTH FROM DR. EMILY HO LOOK INSIDE ►

VITAMIN C AND E IN CYSTIC FIBROSIS

Maintaining adequate blood levels of vitamin E can be challenging for people with cystic fibrosis. New research by Dr. Maret Traber and her colleagues shows that this problem might be solved indirectly by supplementing with vitamin C. Results of their recent clinical trial reveal that vitamin C supplementation increases vitamin E bioavailability in patients with cystic fibrosis. Additionally, these findings suggest that this strategy may help improve the vitamin E status of millions of people with chronic inflammation worldwide, leading to improved global health outcomes.

Although commonly thought of as a lung disease, cystic fibrosis affects many organs throughout the body, including the pancreas and liver. Because of this, people with cystic fibrosis have limited ability to digest and absorb fats and often struggle with malnutrition.

Cystic fibrosis is a genetic disorder often accompanied by high levels of inflammation. With inflammation comes an increased production of free radicals and oxidative stress, increasing the need for antioxidants. Many different antioxidant therapies have been proposed and studied in patients with cystic fibrosis, with limited success.

Dr. Maret Traber, a world-renowned expert on vitamin E and Ava Helen Pauling Professor at the Linus Pauling Institute, is concerned with the issues that surround poor fat absorption. These problems can dramatically impact health and quality of life.

The inability to properly absorb dietary fat concurrently decreases the uptake of the fat-soluble vitamins A, D, E, and K. Since both vitamins A and E contribute to antioxidant defenses, inadequate levels of these vitamins can exacerbate cycles of inflammation within the body.

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Emily Ho, PhD
Endowed Chair and Director,
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FROM THE DIRECTOR

On December 6, I presented Galvanizing Your Health: Why You Need Zinc, a webinar on my favorite element. The presentation and Q&A touched on several aspects of zinc and health. The recording is now available online (see below).

As planning begins for our 2023 webinar series, we are looking forward to February when we will produce another edition of our immensely popular Linus Pauling Day webinar focused on vitamin C. Stay tuned for the details.

We are also excited to bring you more in-person events once again. Personally, I am eager to connect face-to-face with you once more – it has been too long!

I look forward to holding social events at the Linus Pauling Science Center in the coming year. We are also planning speaking engagements across the country – and hopfeully at a location near you.

Next year's big event is the Diet and Optimum Health conference, which returns to the Corvallis campus in September. The theme of Diet and Optimum Health 2023 will be "Precision Health: Living Longer, Better," which pays homage to Dr. Linus Pauling's book *How to Live Longer and Feel Better*.

This is fitting because this conference – and the Linus Pauling Institute as a whole – will be focused on precision health and extending the healthspan, which are extensions of the ideas that Dr. Pauling introduced nearly 40 years ago.

Everyone is welcome to attend. Information can be found on the back page of this issue. The conference content will be more technical than our webinar series, which is designed for a general audience. If you can't join us in person at the conference, we plan to bring you summaries of some of the presentations and themes in future *LPI Research Newsletter* issues.

This is only the beginning of what we have planned. Other webinars and in-person events will follow throughout the year, so please keep your eye on this newsletter and our emails to know when an event is happening near you. Hopefully, you can join us to make 2023 an unforgettable year for the Institute.

Here's to your good health in the new year!

LPI STUDENTS: A FOCUS ON ALZHEIMER'S

Cellular senescence is one mechanism of normal aging. During this process, cells enter a special metabolic state where they no longer divide or grow but remain metabolically active. However, some senescent cells produce inflammatory signals that disrupt the function of neighboring cells.

An increased number of senescent cells is one hallmark of human neurodegenerative disorders, including Alzheimer's disease. Since these diseases are more common with advanced age, it is logical to hypothesize that senescent cells play a role in their development. However, the importance of senescent cells in the progression of Alzheimer's disease is still under debate.

As a PhD candidate, Ruben Riordan sought to shed light on the information surrounding Alzheimer's disease and cellular senescence. His doctoral mentors were Dr. Viviana Pérez, an expert on cellular senescence and aging, and Dr. Kathy Magnusson, an expert on cognitive decline and aging.

Testing several different mouse models for Alzheimer's disease, Ruben found that only two supported a cellular senescence theory, meaning that the senescent cell numbers increased concurrently with the onset of cognitive decline. On the other hand, three other mouse models exhibited cognitive decline without an increase in senescent cells.

This is an important finding but perhaps not surprising. Researchers in the field of Alzheimer's disease have struggled to develop animal models that mimic the mechanisms and progression of symptoms observed in most people, pointing to the importance of Ruben's work.

Focusing on the mice that did display cellular senescence, Ruben examined the interaction with a protein called Nrf2, a master regulatory protein for detoxification responses. To do so, he bred mice that exhibited cellular senescence during Alzheimer's disease progression and that also could not make Nrf2.

The mice that could not produce Nrf2 exhibited symptoms of Alzheimer's disease earlier and more rapidly than similar mice that produced Nrf2, suggesting that Nrf2 activity influenced the onset of the disease. It is thought that Nrf2 activity is likely helping brain neurons cope with the stress of the disease, preserving memory and bodily function for longer periods of time.

Strangely, the absence of Nrf2 did not increase or decrease the number of senescent cells in these animals. This suggests that senescent cells are not an integral part of the disease – at least as it presents in this animal model. Alternatively, it could suggest that senescence is important for some aspects of the disease but not those influenced by Nrf2.

Ruben recently graduated from the Department of Biochemistry and Biophysics and the Linus Pauling Institute with his doctoral degree. He accepted a postdoctoral research position with Dr. Brian Kraemer at the University of Washington, researching Alzheimer's disease and related dementias.

Congratulations, Ruben!

Ruben Riordan, PhD
Recent Graduate from the Linus Pauling Institute and Oregon State University

Dr. Viviana Pérez was recently selected for a position in the Cell Biology Program at the National Institute on Aging within the National Institutes of Health. All of us at the Linus Pauling Institute wish her the best in her new position promoting cellular senescence research at the national level.

Continued from Cover

However, just providing more vitamin E to patients with cystic fibrosis might not be the best solution. High levels of systemic inflammation increase the likelihood that vitamin E oxidizes before it reaches tissues, making supplementation ineffective. Therefore, Dr. Traber wondered if there was another strategy: adding vitamin C.

Vitamins C and E are both antioxidants, contributing to cellular antioxidant defenses. When vitamin E is oxidized and deactivated by free radicals, vitamin C can rejuvenate the oxidized vitamin E back to its active state (see below). This allows vitamin E to continue protecting cells for longer periods of time.

Vitamin C might also help lower persistent levels of inflammation, particularly in the intestine, where increased inflammation could diminish vitamin E absorption. Additionally, vitamin C may help protect vitamin E from oxidation as it travels in the blood, allowing it to remain active longer.

In a recent clinical trial by Dr. Traber and her colleagues at the University of California, Davis, six participants with cystic fibrosis (3 female, 3 male) took 500 mg of vitamin C orally twice a day for 25 days. Before and after vitamin C supplementation, the research team gave each participant a labeled form of vitamin E as a supplement, so they could more accurately monitor vitamin E blood levels over time.

After vitamin C supplementation, more labeled vitamin E was detected in plasma as compared to the period before supplementation. Vitamin E also remained in circulation at least six hours longer after the supplementation period than before.

After taking vitamin C, every participant had lower blood concentrations of a key oxidative stress biomarker called malondialdehyde, as compared to pre-supplementation levels. This suggests that the addition of vitamin C supplements – combined with the noted improvements in circulating levels of vitamin E – reduced the free radical damage to cells.

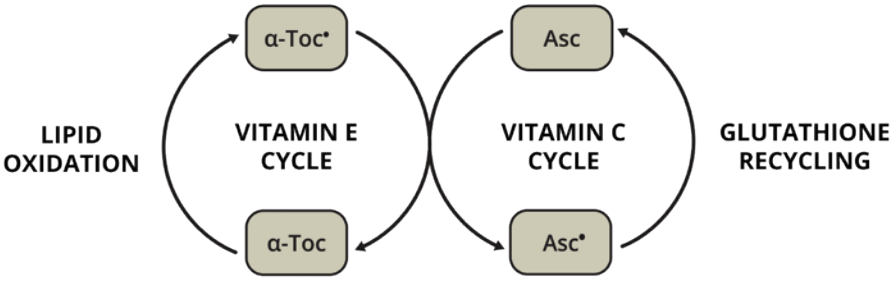
These findings suggest that extra vitamin C can provide a protective environment for vitamin E. This longer circulation period could allow vitamin E more time to enter tissues and protect cell membranes. The combination of vitamins C and E may then be responsible for the reduced levels of inflammation.

Although this was a small trial with limited scope, it does reinforce the idea that supplementation with antioxidant vitamins can have great benefits for those who suffer from persistent inflammation. Dr. Traber emphasizes that the implications of this work may can extend far beyond patients with cystic fibrosis, as the interplay between vitamin C and E is especially important for anyone with high levels of inflammation.

References:

Traber et al. *Nutrients* **14 (2022);** doi: 10.3390/nu14183717

Traber et al. *Am J Clin Nutr* **105 (2017);** doi: 10.3945/ajcn.116.138495



Vitamin C and vitamin E work together in the antioxidant network. When lipids in our cell membranes become oxidized, they can spread that oxidation to other lipids. Vitamin E (α-Toc) will block that from happening, but only by becoming oxidized itself. Vitamin C (Asc) can restore vitamin E, which itself is recycled by glutathione.

VITAMIN E WEBINAR Q&A FOLLOW-UP

In our June webinar, Dr. Maret Traber presented *All You Wanted To Know About Vitamin E But Were Afraid To Ask*. Dr. Traber discussed what vitamin E is, what it does, and why people aren't getting enough from the foods they eat. She also addressed the persistent myth that vitamin E supplements are dangerous.

Due to time constraints, Dr. Traber was not able to address all of your questions, so she addresses some of the most common questions here.

The recording of the webinar is available at **lpi.pub/Traber2022**

Who is at high risk for vitamin E deficiency?

People with impaired fat absorption may be at an increased risk for a vitamin E deficiency (see cover article). Also, taking certain fat-blocking drugs like cholestyramine and orlistat can result in a deficiency.

My colleagues and I believe that some people with really high blood levels of cholesterol may also have issues with vitamin E metabolism. While they appear to have normal vitamin E levels in their blood, our research indicates that they have trouble getting vitamin E into the tissues that need it.

Do I need to get all the different forms of vitamin E?

There are eight different molecules that are very similar in shape and function: alpha-, beta-, gamma-, and delta-tocopherol, and alpha-, beta-, gamma-, and delta-tocotrienol. However, alpha-tocopherol (sometimes written as α-tocopherol) is the only form of vitamin E required by the human body.

While individual tocotrienols and delta-tocopherol are thought to be better scavengers of some free radicals than alpha-tocopherol, the body cannot store these versions of vitamin E. Therefore, we have trouble evaluating their overall importance in health.

How does vitamin E act as an antioxidant?

Vitamin E is found where fats exist in the body, most commonly in cell membranes, protecting the cell against oxidation. When fats in your cell membranes are oxidized, a "runaway" oxidation reaction can occur. This means that one oxidized fat molecule will cause another one to become oxidized, and so on, and so on – spreading damage throughout the cell.

Thankfully, vitamin E reacts with these oxidized fats 1,000 times faster than the oxidation reaction. Just one molecule of vitamin E in a cell membrane is enough to break the chain reaction and prevent some oxidative damage from occurring.

What foods have the most vitamin E?

The most abundant dietary sources of vitamin E are wheat germ, sunflower seeds, hazelnuts, almonds, and their oils. But other excellent sources of vitamin E are fortified cereal, a fruit called mamey sapote, peanut butter, avocado, and canned tomato sauce.

Green leafy vegetables like collard greens and chard also contain vitamin E. While not the richest sources of the vitamin, these vegetables are excellent choices because they are nutrient dense.

Does heat from cooking destroy vitamin E?

For the most part, no. Vitamin E is more stable than many other vitamins, so the cooking method does not matter too much.

RESEARCH IN BRIEF: LICORICE EXTRACTS

Licorice, the name given to the roots and rhizomes of the plants in the Glycyrrhiza genus, has been used as a medicinal herb and flavoring agent since antiquity. Licorice supplements may have potent antioxidant, anti-inflammatory, and antimicrobial effects that may help ease the symptoms of upper respiratory infections, treat ulcers, and aid digestion.

Licorice contains a variety of unique phytochemical compounds. Some of these compounds have estrogenic activity, which has made licorice a popular dietary supplement to alleviate menopausal symptoms.

As part of a larger study on natural products, Dr. Richard van Breemen, one of the experts in natural products at the Linus Pauling Institute, wanted to see if women taking licorice supplements for menopausal symptoms could have unanticipated drug interactions.

This study was conducted with Dr. van Breemen's collaborators at the University of Chicago and involved 14 healthy perimenopausal and postmenopausal women. These participants consumed 75 mg of a standardized licorice extract twice daily for two weeks. To measure the impact on drug metabolism, the participants also took a mixture of four drugs representing common drug metabolism pathways before and after the licorice treatment.

In brief, the results showed that there was no impact of this licorice extract on the metabolism of the drugs tested, at least at the concentrations tested in this study (150 mg per day of licorice extract).

It is important to note that **the licorice extract used in this study contained very little glycyrrhizic acid (<1%)**. Glycyrrhizic acid is a potent phytochemical that can cause high blood pressure and low blood potassium levels if taken in excess. Some data also indicate that glycyrrhizic acid can strongly affect enzymes involved in drug metabolism.

If you choose to use licorice supplements, consider using those with glycyrrhizic acid removed or in amounts that have been measured and controlled. As with any botanical supplement, it is important to purchase from trustworthy sources that can provide you with detailed analyses of their products. Also, make sure to discuss supplement use with your healthcare provider.

References:
Liu et al. Drug Metab Dispos **50 (2022);** doi: 10.1124/dmd.122.001050

Muchiri et al. J Am Soc Mass Spectrom **33 (2022);** doi: 10.1021/jasms.1c00318

While this work did not explore the health benefits of licorice extracts, previous work by Dr. van Breemen and his research team showed that a licorice compound called licochalcone A might be able to bind to the spike protein in SARS-CoV-2. This would suggest that licorice extracts might be a potential therapeutic agent against COVID-19, but further testing is needed to confirm this with a live virus.

RESEARCH IN BRIEF: ZINC AND THE MICROBIOME

Many older adults are at increased risk for zinc deficiency. In part, this is because the ability to absorb and distribute zinc throughout the body naturally declines with age, making it hard to get zinc into cells where it is needed. Since zinc is important for immune function and the response to oxidative stress, deficiency can lead to uncontrolled immune responses and excessive inflammation.

Alterations in the number and variety of microbes living in our intestines can also promote inflammatory responses. Known collectively as the gut microbiome (the bacteria, yeast, and fungi that inhabit our gastrointestinal tract), these microbes influence the overall health of the human body. There is concern that age-related changes in the gut microbiome could also drive inflammation in older adults.

Since both low zinc levels and pro-inflammatory changes in the gut microbiome are more likely as we age, it is possible they are connected. Dr. Emily Ho and her research team wanted to see if changing the amount of zinc in the diet could influence the microbiome and explain some of its effects on inflammation.

To test this hypothesis, the team started with a group of young mice and a group of old mice receiving a zinc-adequate diet. Using fecal samples, the researchers determined the number and variety of bacterial species living inside the gut of both age groups of animals.

Then they separated the animals into groups that received either a low-zinc diet (20% of the amount in the adequate diet) or a high-zinc diet (1,000% of the amount in the adequate diet). After six weeks, the researchers examined the intestinal bacteria again to determine the effects of the low- and high-zinc diets.

In older animals eating a high-zinc diet, the researchers observed small changes in the gut microbiome that correlated with lower blood inflammatory markers than those eating a low-zinc diet. This appeared to support the hypothesis that zinc, bacteria, and age are interconnected. Overall, however, the dietary level of zinc was a minor factor in determining the types and numbers of gut microbes present in the animals.

By contrast, the age of the mice was a much greater factor in microbiome composition. The microbiomes of older mice were very different from those of younger mice, regardless of diet. Overall, 150 out of 186 genera were significantly different between the two age groups (a genus is made up of dozens of bacterial species).

What would be important to determine in future studies is if the age-related changes in the microbiome reduce the ability of the intestinal cells to absorb zinc. If this is indeed the case, interventions designed to reverse these microbiome changes may be an important step in restoring optimum zinc status and limiting inflammation.

Zinc deficiencies in older adults can come from many sources. Aside from issues with absorption, avoiding certain foods can make zinc deficiencies worse. People who choose to eat less meat, beans, and nuts are the most likely to be low in zinc.

Reference:
Davis II et al. *Manuscript in Preparation;* Preprint article at doi: 10.1101/2022.09.16.508248v1

Wong et al. Biometals **34 (2021);** doi: 10.1007/s10534-020-00279-5

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Photo: Ascorbic Acid Crystals by Henri Koskinen