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Vitamin E: A New Perspective

by Andreas M. Papas, Ph.D.

Vitamin E is a family of eight compounds

Mention vitamin E and most people will think alpha-tocopherol. Even many scientists will make the same connection. It is only recently that scientists, and now the consumers, have been reminded that vitamin E is more than alpha-tocopherol.^{1,2}

Unlike some vitamins, which consist of a single compound, vitamin E consists of eight different compounds, four tocopherols and four tocotrienols (designated as alpha, beta, gamma and delta). Our food contains all eight compounds.

Tocopherols and tocotrienols have similarities and differences in their molecules. They consist of a head (chroman ring in the technical jargon) and a tail (known as phytol tail for tocopherols). The chroman ring carries the active antioxidant group. Each tocotrienol has an identical chroman ring as the corresponding tocopherol. Tocotrienols differ from tocopherols on their tail; the tocotrienols have three unsaturated sites while tocopherols have none.

Natural vs. synthetic vitamin E: The difference is real and big!

The discussion for natural and synthetic vitamin E refers to alpha-tocopherol only. This is because only alpha-tocopherol is produced commercially both in the natural and synthetic forms. The other three tocopherols (beta, gamma and delta) are available only in their natural form as mixtures. Also, the tocotrienols (alpha, beta, gamma and delta) are available commercially in their natural form and only as mixtures containing tocopherols.

The crux of the difference: For most vitamins the synthetic forms are identical to the natural and have identical function in our body. Not so for alpha-tocopherol.

All molecules in d-alpha-tocopherol, the naturally occurring form, are identical. In contrast, the synthetic dl-alpha-tocopherol is a mixture of eight different molecular entities known in the chemical jargon as stereoisomers. Of these eight, only one is identical to the natural form. The other seven do not exist in nature.^{1,2}

There is no argument that the natural d-alpha-tocopherol, gram for gram is more potent than the synthetic dl-alpha-tocopherol. It was made official decades ago by the likes of the Food and Drug Administration (FDA), the World Health Organization (WHO) and the United States Pharmacopoeia (USP). The natural form was officially recognized as 36% more potent than the synthetic.

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The argument has been whether 36% underestimates the true advantage of the natural. According to a number of studies in humans using powerful new techniques developed by researchers at the National Research Council of Canada, the natural d-alpha-tocopherol is twice as bioavailable (available for use by our body) compared with the synthetic.³ In another study with pregnant women, the natural d-alpha Tocopherol passed from the mother through the placenta to the baby in her womb three times more efficiently than the synthetic.⁴ Based on this and other research, the Food and Nutrition Board of the National Academy of Sciences recommended that the biopotency of the naturally occurring d-alpha-tocopherol is twice that of the synthetic dl form.⁵

The International Unit (IU) – What it tells us (and, more important, what it doesn't)

The IU is a measure of vitamin E activity. One IU is defined as one milligram of synthetic dl-alpha-

tocopheryl acetate. For nutritional supplements the claimed IU content is from alpha-tocopherol content only. The other tocopherols and tocotrienols are assumed to have zero IU value.

The Food and Nutrition Board of the National Research Council (NRC) scrapped the IU and replaced it with the alpha-tocopherol equivalent (alpha-TE). One alpha-TE is one milligram of natural d-alpha-tocopherol. It also allowed credit for beta and gamma-tocopherols and alpha-tocotrienols for foods only, not supplements.^{1,2}

Despite the recommendation of the NRC, vitamin E content of nutritional supplements and in fortified foods continues to be expressed as IU.

It is important to note that IU provides partial information on the true vitamin E value of a product. Specifically, IUs do not tell us whether:

1. The product has tocopherols other than alpha tocopherol or tocotrienols.
2. The alpha-tocopherol is natural or synthetic.
3. The alpha-tocopherol is esterified.

Absorption, transport and metabolism

Vitamin E is fat-soluble and it is absorbed in the same manner as fat. Specifically unique tiny spheres with a water-loving (hydrophilic) outer layer called micelles engulf the vitamin E and help ferry it across the gut. Chylomicrons, produced by the small intestine, carry the micelles into the lymph, the milky fluid containing white blood cells, proteins, and fats. In the lymph the enzymes lipoprotein lipases break down the majority of chylomicrons to produce chylomicron remnants, which go into the blood. The majority of the chylomicron remnants reach the liver, which strips away the vitamin E from the remnants and puts it into the freshly produced very low-density lipoproteins (VLDL). VLDL is broken down by lipoprotein lipases to produce the low-density lipoproteins (LDL, bad cholesterol.) In our blood LDL is the largest carrier of vitamin E. LDL freely exchanges vitamin E with high-density lipoproteins (HDL, the good cholesterol.) HDL and LDL seem to deliver vitamin E to our tissues.^{1,2}

Our blood and tissue contains much more alpha-tocopherol than any of the other tocopherols and tocotrienols. This is not because we consume more alpha-tocopherol in our diet. Quite the opposite. In the typical American diet we take twice as much gamma-tocopherol than alpha. Absorption cannot explain this phenomenon either, because there is evidence that tocopherols and tocotrienols are absorbed in a similar



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manner. At the heart of this mechanism is a special protein, called the alpha-tocopherol transfer protein. It recognizes the alpha-tocopherol and preferentially puts more of it in the blood. It has also been proposed that this is the mechanism that puts more of the natural d-alpha-tocopherol than the synthetic dl-alpha-tocopherol in the blood.

If alpha-tocopherol is selectively put in the blood does this mean that the other members of the vitamin E family are not important? That was the prevailing assumption; the emerging research, however, increasingly indicates that this assumption is wrong. This research will be reviewed below.

The function of vitamin E: A master antioxidant and much more

Vitamin E is an important component of our antioxidant system. It is considered a master antioxidant because:^{1,2}

1. Tocopherols and tocotrienols are chain-breaking antioxidants – they break the chain reaction of lipid peroxidation, the process that turns lipid rancid.
2. The structure of vitamin E makes it unique and indispensable in protecting cell membranes. Vitamin E, primarily alpha-tocopherol, anchors itself strategically in the membrane with the hydrophobic (water hating) tail in the interior of the membrane. The hydrophilic (water loving) head is in the hydrophilic area of the membrane.
3. Vitamin E is the master inhibitor of oxidation of the bad cholesterol LDL - which is believed to be the first step in atherosclerosis.

Vitamin E is more than the master antioxidant, it has additional important functions. For example:^{1,2}

1. Vitamin E inhibits the activity of the enzyme PKC (protein kinase C) which is associated with inflammation.
2. Vitamin E exhibits anticoagulant properties. Oxidized alpha-tocopherol (called alpha-tocopheryl quinone) is also a powerful anticoagulant.
3. Vitamin E compounds reduce the production of inflammatory compounds such as prostaglandins.
4. Tocotrienols and gamma-tocopherol have other unique functions (please see below.)

Focus on gamma-tocopherol and tocotrienols

Underscoring the importance of viewing vitamin E as a family of compounds is the evidence that gamma-tocopherol and tocotrienols have unique functions different from those of alpha-tocopherol.

Gamma-tocopherol

- gamma-Tocopherol appears to be more potent than alpha-tocopherol in increasing superoxide dismutase (SOD) activity in plasma and arterial tissues as well as Mn SOD and Cu/Zn SOD protein expression in arterial tissues. SOD is a major antioxidant enzyme.⁶
- While both alpha and gamma-tocopherol increase nitric oxide (NO) generation and nitric oxide synthase (cNOS) activity, only gamma-tocopherol increased cNOS protein expression. NO is important for cardiovascular health because in atherosclerosis, the endothelium has a reduced capacity to produce NO.⁶
- gamma-Tocopherol has been reported to be more effective than alpha in quenching nitrogen radicals.⁷ These radicals are major culprits in arthritis, multiple sclerosis (MS) and diseases of the brain such as Alzheimer's.
- gamma-Tocopherol and its major metabolite reduced PGE2 synthesis in both lipopolysaccharide-stimulated macrophages and IL-1 β -treated human epithelial cells. In contrast, alpha-tocopherol reduced slightly PGE2 formation in macrophages, but had no effect in epithelial cells.⁸ The corresponding metabolite of alpha-tocopherol was not active. We reported preferential uptake of gamma-tocopherol and potential synergy with alpha-tocopherol in macrophages.⁹
- A metabolic product of gamma-tocopherol, code-named LLU-alpha, appeared to be a natriuretic factor which affects how much fluid and electrolytes pass through the kidney to the urine.¹⁰

Tocotrienols

Tocotrienols and, in particular, gamma-tocotrienol appear to act on a specific enzyme called 3-hydroxy-3-methylglutaryl-coenzyme A reductase (HMG-CoA) involved in cholesterol production in the liver.¹¹ Tocotrienols suppress the production of this enzyme, which may result in less cholesterol being manufactured by liver cells. This may in turn result in an overall reduction of plasma cholesterol levels.

Laboratory studies indicate that tocotrienols may affect the growth and/or proliferation of some types of human cancer cells. Researchers at the University of Texas at Austin confirmed earlier results from a Canadian group that tocotrienols slow down the growth of human breast cancer cells.¹² This study showed that the naturally occurring tocotrienols and RRR-delta-tocopherol induced apoptosis (death) of these cancer

cells. The gamma and delta-tocotrienols were the most effective. Alpha, beta, and gamma tocopherols were ineffective in this system. Researchers at the University of Wisconsin found that gamma-tocotrienol suppressed the growth of rat melanoma cells, and with greater potency, the growth of human breast adenocarcinoma and human leukemic cells.¹³ Our research indicated that γ -tocopherol, added to a sumipurified diet, was more effective than α -tocopherol in reducing ras-p21 oncogenes in the colonocyte of rats.¹⁴

Tocotrienols and cardiovascular health – Promising initial results

The strongest evidence yet for tocotrienol benefit on cardiovascular health comes from a clinical study conducted by the Kenneth Jordan Heart Research Foundation in New Jersey. The five-year study evaluated fifty patients who had stenosis of the carotid artery.¹⁵

Stenosis means constriction or narrowing – the buildup of plaque over time causes stenosis of the arteries. Stenosis of the carotid artery can cause stroke. Advanced stenosis of the carotid artery is treated with medical procedure called angioplasty; a small balloon is inserted in the artery and inflated in order to widen the artery.

This procedure can save lives but it has its drawbacks. During the procedure pieces of plaque can detach and cause the stroke that the doctor is trying to prevent. About one-third of patients undergoing this procedure have renewed narrowing (restenosis) of the widened segment within about six months. With the passing of time many more patients develop restenosis. Restenosed arteries may have to undergo another angioplasty.

In this study one group of 25 patients received approximately 650 milligrams of tocotrienols plus tocopherols. The other group of 25 received a placebo. All patients were examined every 6 months for the first year and every year after that with ultrasonography. This medical procedure measures the narrowing after 4 years:

- **Placebo group:** Fifteen patients showed worsening of the stenosis, 8 remained stable and 2 showed some improvement.
- **Tocotrienol (plus tocopherol) group:** Three patients showed minor worsening and 12 remained stable. What is remarkable is that 10 patients showed regression of stenosis – their condition improved.

The treated group had also significant reduction in

TBARS, a test that measures oxidation. The researchers have also looked at the effect of tocotrienols on total cholesterol, LDL and triglycerides.¹⁶ Although their data suggest a substantial drop in triglycerides and LDL and increase in HDL, this observation needs to be confirmed in other clinical studies because evidence to-date has been mixed.^{17,18}

Vitamin E and cardiovascular health – The emerging controversy

Vitamin E has been linked to the prevention of cardiovascular disease (CVD) based on the hypothesis that oxidation of LDL initiates the development of atherosclerotic plaque.^{1,2} This hypothesis, although not universally accepted, is supported by studies in vitro, in animals, and in humans. This background in basic science and a number of epidemiological studies, led to the initiation of clinical intervention trials.

The results from clinical intervention trials have been mixed leading to a controversy on the role of vitamin E in heart disease.

- The Cambridge Heart Antioxidant Study (CHAOS) with 2,000 patients who had atherosclerosis indicated that 400 or 800 IU of vitamin E each day as d-alpha-tocopheryl acetate reduced their risk of suffering a heart attack within a year and a half by 77 percent compared to the control group. There was no decrease, however, in fatal heart attacks; actually the number was slightly higher in the vitamin E group.¹⁹
- The Italian study known as GISSI involved 11,324 men and women who had suffered a heart attack no more than three months before. They were divided into four groups and followed for 3 1/2 years. One group was given 1 gram of omega-3 fish oil a day, the second 300 mg dl-alpha-tocopheryl acetate pill, the third group was given both, and the rest were the control. While fish oil reduced subsequent heart attacks, the effects of dl-alpha-tocopheryl acetate were not significant.²⁰
- The Heart Outcomes Prevention Evaluation Study (HOPE), an international study with over 9,000 high-risk people from Canada, the United States, Europe, Mexico, and Latin America evaluated vitamin E (400 IU d-alpha-tocopheryl acetate) and Ramipril, (ACE inhibitor, blood pressures drug). Ramipril showed significant benefit in reducing deaths from heart disease and stroke while d-alpha-tocopheryl acetate was ineffective.²¹

In evaluating these conflicting results it is important to

consider that these studies evaluated only one member of the vitamin E family, namely alpha-tocopherol and were limited to a single dose. The emerging information on the role of gamma-tocopherol and tocotrienols strongly indicates that the complete vitamin E of tocopherols plus tocotrienols might be more effective.²¹

Other health benefits of vitamin E

The following is a very brief overview of the role of vitamin E in wellness and disease prevention.

Alzheimer's disease: A collaborative study at major medical centers across the United States found that in Alzheimer's patients taking large doses of vitamin E (2,000 IU/day), progression of the memory-robbing disease was delayed by approximately seven months.²⁴

Aging and immunity: Studying healthy elderly people, researchers at Tufts University, reported that vitamin E increased the power of disease-fighting T-cells, improved delayed-type hypersensitivity skin response (DTH) by 65 percent and antibody response to hepatitis B six-fold. It also increased significantly the antibody titer to tetanus vaccine.²⁵ A recent study in Netherlands reported no benefit in acute respiratory tract infections in elderly person from vitamin E supplementation.²⁶

Cataracts: A Canadian study compared the consumption of vitamin supplements by 175 cataract patients with that of 175 cataract-free controls. People in the control group were taking significantly more supplements of vitamins C and E than the cataract group.^{1,2,27}

Skin health: Vitamin E has been shown to reduce the damage to skin from exposure to UV radiation and ozone.^{1,2}

Safe and effective use levels

It is estimated that intake of vitamin E from our diet is less than 15 mg/day. Rich sources of vitamin E include vegetable oils, nuts, and whole grains.

The USDA RDA is 30 IU and the NRC RDI is 15 IU. It is generally assumed that the vitamin E requirement is for α -tocopherol and there is no official RDA for other tocopherols and tocotrienols. Considerably higher doses are believed to be necessary for prevention of disease and promotion of wellness. The most common supplemental doses are 100, 200, 400, and 800 IU. The author recommends that supplements should contain the complete vitamin E family of tocopherols plus tocotrienols.

Unlike other fat-soluble vitamins, toxicity of vitamin E is very low probably because it is not stored in the liver. Side effects have been rare, mostly gastrointestinal,

with doses of over 1200 IU/day. Large doses may exacerbate blood coagulation in persons with vitamin K deficiency or those taking anticoagulant drugs. Pro-oxidant effects of vitamin E have been shown in vitro but have not confirmed in humans.^{1,2}

Additional tocotrienols are recommended for people at high risk or with family history of heart disease and breast cancer. Additional gamma-tocopherol is recommended for people at high risk of prostate cancer, Alzheimer's and diseases associated with inflammation.

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Vitamin E Malabsorption: Common, Extremely Serious and Preventable

by *Andreas M. Papas, Ph.D.*

It may be hard to believe that in the midst of an abundance of food and a plethora of supplements, many people would develop clinical vitamin E deficiency. A dramatic example is cholestasis, a condition in which excretion of the bile is stopped. Cholestatic children develop very serious and often fatal degenerative neurological diseases due to malabsorption of vitamin E. While serious cholestasis is rare, many other common diseases and physiological conditions cause varying degrees of malabsorption with subclinical deficiency. Unfortunately vitamin E deficiency may go undetected for decades but the cumulative damage to muscle and nerves is debilitating and irreversible.

Absorption of vitamin E: oil and water do not mix or do they?

We are water-based organisms – water makes more than half of our weight. The blood, the lifeline that carries the nutrients and nourishes all our tissues is water-based. Vitamin E, however, is fat-soluble. Oil and water do not mix. The body has to overcome this problem and micelles are the body's solution. The fat-soluble material is put into these unique tiny spheres with a water-loving (hydrophilic) outer layer and is ferried from the gut across the intestinal wall into the blood stream.

To make micelles two major components are absolutely required.

- Bile – a yellow-green liquid produced in the liver and secreted into the gut. The bile helps emulsify the fat in our diet and provides components of the outer layer of the micelles.
- Pancreatic juice – a secretion delivered into the upper part of the small intestine (duodenum), where it aids digestion.

In the blood stream vitamin E is transported by lipoproteins, the vehicles that transport lipid materials in our body. These are minute spheres with a water friendly outer layer, which allows them to circulate freely in the blood. They carry vitamin E and other lipids in their lipophilic interior.

Which conditions cause malabsorption?

A large number of diseases and physiological conditions may cause poor absorption of vitamin E.

1. Fat malabsorption due to liver and pancreatic insufficiency. Because the bile and the pancreatic juices are critical for absorption of vitamin E, any condition that compromises the function of the liver and pancreas can cause malabsorption. These include:

- Cholestasis, a condition in which excretion of the bile is stopped or reduced. Cholestasis may be caused by inherited genetic defects and diseases and injury of the liver. Liver diseases such as hepatitis, alcoholic hepatitis and damage or inflammation of the liver from the use of powerful medicines or chemotherapy can affect the production of bile.
- Cystic fibrosis, a genetic disease in which the secretion of the pancreatic juice is blocked by thick mucous. Liver function and secretion of the bile may also be affected.
- Steatorrhea, the inability to absorb fat, causes serious vitamin E deficiency. Steatorrhea is caused by other conditions causing malabsorption such as cystic fibrosis, pancreatitis, and celiac disease.

2. Malabsorption due to inflammation and surgical removal of part of the gut, infection, disturbance of its flora, and diarrhea. These include:

- Inflammatory bowel disease (IBD) includes diseases that cause inflammation in the intestines such as Crohn's and ulcerative colitis.
- Short bowel syndrome is the result of half or more of the small intestine being removed primarily in order to treat Crohn's disease.
- HIV is associated with fungal and other infections of the small intestine, which cause poor absorption of the nutrients particularly the fat-soluble ones. Other infectious diseases of gut may cause malabsorption.
- Irritable Bowel Syndrome (IBS; also known as spastic colon or mucous colitis) can cause diarrhea and malabsorption.
- Bariatric surgery to treat obesity is often associated with nutrient deficiency proportional to the length of absorptive area.

3. Defects in the transport of vitamin E in the body have a serious indirect effect on absorption. These, mostly genetic defects, include:

- Abetalipoproteinemia is a rare inherited disease which prevents the formation of normal chylomicrons

and very-low density lipoproteins (VLDL) which are essential for the transport of vitamin E. Patients with abetalipoproteinemia 'absorb' vitamin E but most of the vitamin E never goes past the gut wall because the patients cannot produce these special vehicles which carry vitamin E.

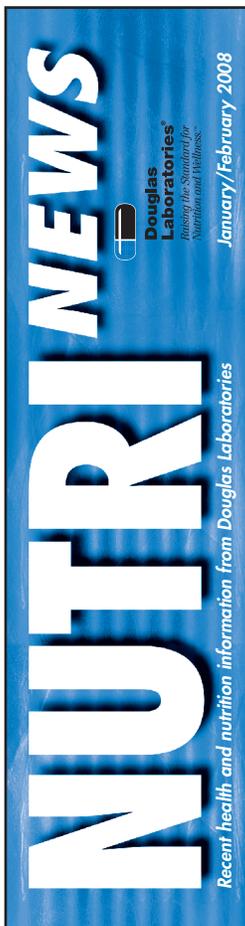
- Ataxia with vitamin E deficiency, or familial isolated vitamin E deficiency, is an extremely rare genetic disease with symptoms very similar to those of another very rare disease called Friedreich ataxia. This genetic disease prevents the transfer of absorbed vitamin E from the liver to the blood and the tissues.

Overcoming vitamin E malabsorption

Water-soluble vitamin E formulas can help to overcome malabsorption. Formulas which are particularly rich in the natural unesterified gamma tocopherol and tocotrienols are of particular interest to malabsorbers because of the increased oxidative stress.

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