REDOX EXPERIMENTAL MEDICINE

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REVIEW

Current evidence of the role of vitamin E in prolonging a healthy life

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Abstract

This is a narrative review of the evidence of α-tocopherol importance in human health, especially with regards to its vitamin role. α-Tocopherol is a potent peroxyl radical scavenger, and this role is prominent in its efficacy in maintaining the metabolic health of tissues. Vitamin E deficiency is discussed as a tool to understand the impact of α-tocopherol's absence promoting increased lipid peroxidation and polyunsaturated fatty acid depletion. Downstream deficiency consequences include impacts on choline and one-carbon metabolism, glucose and energy metabolism, and their interactions with critical thiols, such as glutathione. Importantly, human vitamin E deficiency, caused by genetic defects in the α-tocopherol transfer protein (α-TTP), provides important clues for the necessity of α-tocopherol for the peripheral nervous system. Moreover, α-TTP expression in the liver, brain, eyes, and placenta illustrates that these tissues are especially vulnerable and require this specific α-tocopherol delivery mechanism for their protection. Although clinical trial evidence is limited and equivocal about the health benefits of vitamin E supplements, there is epidemiologic evidence of the long-term benefits of increased α-tocopherol intakes in 'healthy' diets (high in vegetables and fruits, fish, nuts, and seeds, as well as fiber).

Significance statement

The elaborate regulation of α-tocopherol concentrations by the human body suggests that the consistent consumption of the recommended amounts of dietary α-tocopherol (15 mg) over a lifetime are protective of the at-risk tissues, as well as providing protection from chronic diseases.

Keywords

- antioxidants
- ataxia with vitamin E deficiency (AVED)
- zebrafish
- humans

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Introduction

The free radical theory of aging was first proposed based on the idea that radiation-caused free radical damage was similar to that observed in aging tissues (Harman 1956). Although the theory gained adherents, the numerous experiments carried out over the intervening seven decades have not proven the theory. Interestingly, Harman (Harman 1981) proposed that 'the healthy lifespan can be increased by minimizing deleterious free radical reactions while not significantly interfering with those essential to the economy of the cells and tissues ... this can be done by keeping body weight down, at a level compatible with a sense of well-being,

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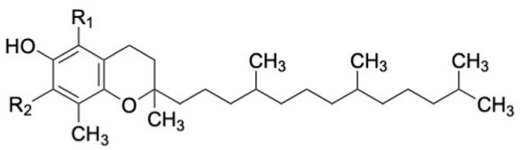
while ingesting diets adequate in essential nutrients but designed to minimize a random free radical reactions in the body. Such diets would contain minimal amounts of components prone to enhance free radical reactions, for example copper and polyunsaturated lipids, and increased amounts of substances capable of decreasing free radical reaction damage such as α-tocopherol, ascorbic acid, selenium, or one or more synthetic antioxidants'. This prescient dietary recommendation for healthy aging is not unlike the current recommendations of the Linus Pauling Institute (https://lpi.oregonstate.edu/mic), although polyunsaturated fats, especially plant oils and fish oils, are now recognized to be an important part of a healthy diet (US Department of Health and Human Services and US Department of Agriculture 2015).

A key part of this dietary recommendation is vitamin E (α-tocopherol) (Harman 1981). The general consensus is that in test-tube chemical reactions α-tocopherol acts as an antioxidant. However, there are numerous antioxidants in nature, why is this specific one needed as a vitamin by humans? This question has remained unanswered since the time α-tocopherol was found to be a necessary nutrient (Evans & Bishop 1922). The present article seeks to describe and to evaluate the current evidence as to its role in prolonging a healthy life.

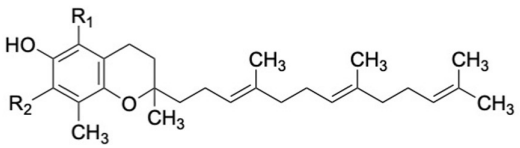
Vitamin E is α-tocopherol

We can look at other fat-soluble vitamins to provide clues as to α-tocopherol's *in vivo* vitamin role. For example, vitamin A (retinol) has a specific plasma transport protein (Blaner *et al.* 2016) and has a metabolic derivative, retinoic acid, which acts a ligand in various nuclear receptors (Chambon 1996, Petkovich & Chambon 2022). Similarly, vitamin D is hydroxylated and 1,25 hydroxycholecalciferol is a ligand of the vitamin D nuclear receptor, which acts as a nuclear transcription factor (Bikle 2014). Vitamin K1 (phylloquinone) is converted by the body to menaquinone-4 (vitamin K2), and both K1 and K2 can function as ligands for the vitamin K-dependent carboxylase (Shearer & Okano 2018). This enzyme converts various vitamin K-dependent proteins (Ferland 2012) such that certain of their glutamic acids are enzymatically converted to gamma-carboxy glutamic acids. These vitamin K-dependent proteins have numerous functions from coagulation to ferroptosis (Mishima *et al.* 2023).

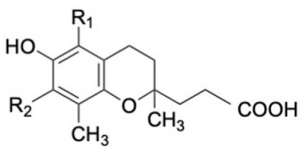
All of the previously discussed various mechanisms have been explored in an effort to define a molecular role for vitamin E, specifically for α-tocopherol. Many of these functions have been more broadly studied for the eight tocochromanols synthesized by plants (α-, beta-, gamma-, delta-tocopherols, or tocotrienols) (Fig. 1). Currently, there is great interest in the tocochromanol-carboxy catabolites as anti-inflammatory agents (Jiang 2014, Pein *et al.* 2018). Nuclear receptor binding has been reported for the catabolites (Bartolini *et al.* 2020), but this activity seems to be confined largely to the Pregnane X Receptor (PXR in rodents, SXR in humans) with greater xenobiotic activities observed for products derived from the tocotrienols (Landes *et al.* 2003, Zhou *et al.* 2004). Additionally, vitamin K2 (menaquinone 4) has an unsaturated side chain similar to that of tocotrienols and binds to SXR (Hirota & Suhara 2019). Importantly, this nuclear receptor activity is apparently only related to xenobiotic catabolism of the tocochromanols and not to some apparently needed α-tocopherol vitamin function. Overall, there have been no obvious linkages of α-tocopherol activity



Tocopherol



Tocotrienol



CEHC

TC or CEHC	R_1	R_2
α-	$-CH_3$	$-CH_3$
ß-	$-CH_3$	-H
γ-	-H	$-CH_3$
δ-	-H	-H

Figure 1
Shown here are the tocochromanol (TC) structures of the four tocopherols and the four tocotrienols. The locations on the chromanol ring are hydroxyl group at position 6, R_1 at position 5, R_2 at position 7. The most important chiral center for α-tocopherol activity is at position 2, the location of attachment of the phytyl tail to the chromanol ring. The other chiral centers in the phytyl tail are at positions 4′ and 8′. Also shown is the carboxyethyl hydroxychromanol structure of the TC catabolites.

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to nuclear receptor or signal transduction pathways (Blaner *et al.* 2021). Thus, the apparent reason humans require α-tocopherol is because of its potent lipid peroxyl radical scavenging activity. This vitamin action remains mystifying since all of the tocochromanols have peroxyl radical scavenging activities. Even more mystifying is the apparent preference for natural α-tocopherol (*RRR*-) compared to synthetic (*all racemic*, or *all rac*-) α-tocopherols since all eight stereoisomers in the latter have the identical 6-hydroxychromanol head groups and the same peroxyl radical scavenging activities.

The naturally occurring tocochromanols and synthetic α-tocopherol have different vitamin E activities as a result of the α-tocopherol transfer protein (α-TTP) structural requirements for a specific ligand. The α-tocopherol-binding site in α-TTP requires three methyl groups on the chromanol ring and also requires that the side chain is in the correct conformation (Min *et al.* 2003). Although synthetic α-tocopherol meets the head group requirements, the side chain does not. The side chain has three chiral carbon centers that can be either *R* (from the Latin rectus, meaning 'right') or *S* (from the Latin sinister, meaning 'left'), giving rise to eight stereoisomers (*RRR*-, *RSR*-, *RRS*-, *RSS*-, *SRR*-, *SSR*-, *SRS*-, *SSS*-). Thus, *all rac*-α-tocopherol contains equal amounts of each of the eight stereoisomers, but only half of these are in the 2*R*-conformation. α-TTP binds not only to *RRR*- but also to 2*R*-α-tocopherols. Because *all rac*-α-tocopherol is only half 2*R*-α-tocopherols, natural has twice the vitamin E activity on a per milligram basis. In the United States, vitamin E is defined for nutrient requirements and food labeling by the US Food and Drug Administration (FDA) (Food and Drug Administration 2016) as 2*R*-α-tocopherols (*RRR*-, *RSR*-, *RRS*-, and *RSS*-α-tocopherols), as recommended by the Institute of Medicine (Food and Nutrition Board and Institute of Medicine 2000).

The rationale for the α-TTP requirements for α-tocopherol rather than other TCs are more speculative. The apparent explanation is that the tocochromanol heads that have fewer than three methyl groups are susceptible to Michael addition reactions when they form peroxyl radicals. These addition products can become cytotoxic (Cornwell *et al.* 2003, Wang *et al.* 2006). The α-tocopheryl peroxyl radical cannot participate in these Michael addition reactions, suggesting that the α-tocopherol antioxidant activity is key to its vitamin role.

Lipid peroxidation and α-tocopherol antioxidant activity

α-Tocopherol has a critical role to halt lipid peroxidation and its induced damage. Polyunsaturated fatty acids (PUFAs) are present in every cell membrane and are highly susceptible to lipid peroxidation (Wagner *et al.* 1994, Atkinson *et al.* 2021). The reason there is limited destruction of these PUFAs is because α-tocopherol intercepts the peroxyl radical and halts the lipid peroxidation chain reaction faster than the radical can react with other PUFA (Burton & Ingold 1981, Conrad & Pratt 2019). In the process, α-tocopherol becomes a radical, the tocopheroxyl radical, that is reduced by other water-soluble antioxidants such as ascorbic acid or glutathione (Buettner 1993). Thus, under 'normal' conditions, neither the accumulation of oxidized lipids nor oxidized tocopherol (tocopheryl quinone – the two-electron oxidation product) occurs. By contrast, α-tocopherol deficiency, when studied *in vivo* in a closed system such as zebrafish embryos, was lethal (McDougall *et al.* 2017*a*). α-Tocopherol deficiency allowed lipid peroxidation to proceed, induced depletion of PUFA, especially phosphatidyl choline containing docosahexaenoic acid (DHA). Additionally, choline was depleted, which led to alterations in one-carbon (methyl group) metabolism. The increased oxidative damage also depleted glucose and NADPH, a reductanct needed both for tissue synthesis in the embryo, as well as for various antioxidant repair mechanisms, such as glutathione reductase. As glutathione is a major antioxidant needed for reducing the tocopheroxyl radical, its increased use also increases its synthesis, which also depletes other thiols such as methionine and cysteine (Head & Traber 2021).

Evidence that humans require α-tocopherol

Ataxia with Vitamin E Deficiency (AVED, Online Mendelian Inheritance in Man® MIM #277460) occurs in humans as a result of defect(s) in the gene for α-TTP (Schuelke 2005 May 20 (updated 2023 March 16)). Importantly, α-tocopherol supplementation (approximately 1000 mg/day) can prevent or halt progression of the vitamin E deficiency symptoms (Sokol *et al.* 1988, Di Donato *et al.* 2010, Kohlschutter *et al.* 2020). There is at least one individual who has been supplemented for over 30+ years who has a α-TTP

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genetic defect but not any obvious progression of the neurodegenerative abnormalities (Kohlschutter *et al.* 2020). By contrast, α-tocopherol supplementation does not reverse the damage once it has occurred (Thapa *et al.* 2022).

The α-tocopherol deficiency symptoms in AVED show that the peripheral nervous system is especially vulnerable (Schuelke 2005 May 20 (updated March 16, 2023)). Measurements of α-tocopherol concentrations in peripheral nerves from persons with AVED showed α-tocopherol depletion before the onset of clinical symptoms (Traber *et al.* 1987). Ataxia is caused by the dying back of the peripheral sensory nerves (Ulatowski *et al.* 2014) with the large-caliber, myelinated axons of peripheral sensory nerves the predominant targets (Sokol 1988). Axonal dystrophy has also been observed in the posterior columns of the spinal cord and the dorsal and ventral spinocerebellar tracts (Sokol 1988). Thus, the large-caliber, myelinated axons of peripheral sensory nerves are the predominant targets in human α-tocopherol deficiency. There is little central nervous system involvement until severe α-tocopherol deficiency occurs.

Notably, persons with AVED do not appear to have an increased prevalence of coronary heart disease, atherosclerosis, or Alzheimer disease. In part, this lack of prevalence may have more to do with the relatively few patients that have been found. Further, AVED is generally detected in children, who are now aggressively supplemented with α-tocopherol to prevent the adverse neurologic consequences of α-tocopherol deficiency (Schuelke 2005 May 20 (updated March 16, 2023)).

Roles of the liver and intestine in nutrient trafficking

α-TTP was first described as a liver α-tocopherol binding protein (Catignani & Bieri 1977). Later it was recognized that the hepatic α-TTP in humans (and most animals) transfers α-tocopherol from the liver to maintain plasma α-tocopherol concentrations (Traber *et al.* 1990, 1992). The liver is the body's most important tissue with regards to α-tocopherol trafficking because the dietary α-tocopherol that is delivered to the liver is rapidly salvaged by hepatic α-TTP and prevented from being excreted (Traber *et al.* 2019, Traber & Head 2021).

Liver α-tocopherol trafficking by α-TTP

The preferential enrichment of the plasma with α-tocopherol is dependent upon a multi-step process involving α-TTP (Arai & Kono 2021). Following uptake of chylomicron remnants by the liver, the hepatic α-TTP selects α-tocopherol then transfers it to the inner plasma membrane (Chung *et al.* 2016), where α-tocopherol is exchanged for phospholipid inositol phosphates (PIPs) (Arai & Kono 2021). The membrane α-tocopherol is subsequently transferred by ATP-binding cassette A1 (ABCA1) to an external acceptor, such as nascent very low density (VLDL) or high density (HDL) lipoproteins (Shichiri *et al.* 2010). These lipoproteins then transfer α-tocopherol to the circulating lipoproteins, which can deliver it to tissues (Traber 2013). Notably, the supplemental α-tocopherol intakes recommended for those with AVED obviate the necessity for the hepatic α-TTP because during chylomicron catabolism α-tocopherol is non-specifically incorporated into circulating lipoproteins, which can deliver α-tocopherol to the tissues (Traber 2014). Thus, large (~1000 mg daily) α-tocopherol supplements are needed by persons with AVED for the non-specific α-tocopherol transport mechanisms to allow normalization of plasma and tissue α-tocopherol concentrations. As discussed earlier, if supplements are started prior to damage, such supplements are sufficient to prevent neurologic damage.

α-Tocopherol and fatty liver disease

Although fatty liver disease (NAFLD, now termed metabolic dysfunction-associated steatotic liver disease (MASLD) (Rinella *et al.* 2023)) has not been reported frequently in persons with AVED, there is a case report of siblings with AVED, who developed fatty liver (along with premature atherosclerotic vascular disease and ischemic heart disease) in the absence of relevant risk factors (Trotta *et al.* 2019). By contrast in persons diagnosed with MASLD, α-tocopherol supplements (800 IU/daily) compared with pioglitazone improved hepatic steatosis, lobular inflammation, and hepatocellular ballooning (Sanyal *et al.* 2010). A meta-analysis of five randomized α-tocopherol supplement trials further concluded that supplements reduced circulating markers of liver dysfunction [aspartate transaminase (AST), alanine aminotransferase (ALT), alkaline phosphatase (ALP)] and steatosis relative to control groups (Sato *et al.* 2015). Thus, MASLD may be a result of inadequate α-tocopherol antioxidant protection

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in the liver (Podszun *et al.* 2020), but this conclusion is by no means proven.

α-TTP is present in the liver, not the intestine; implications for tocochromanol absorption

It should be noted that despite the clear importance of the liver and the hepatic α-TTP in α-tocopherol trafficking, the various tocochromanols are absorbed by the intestinal cells for secretion in chylomicrons without α-TTP assistance. Indeed, the liver specifically secretes α-tocopherol and metabolizes other tocochromanols, while the intestine facilitates the absorption of all tocochromanols (Traber 2013).

We studied the role of the liver and the intestine in α-tocopherol trafficking using stable isotopes (Traber *et al.* 2019). Plasma, fecal, and urine samples were collected to quantitate α-tocopherol absorption during a clinical trial in healthy women, who were administered intravenously an emulsion containing a stable-isotope-labeled α-tocopherol (hexadeuterium (d_6)-α-T) and orally a stable isotope-labeled α-tocopherol (tri-deuterium (d_3)-α-T) (Traber *et al.* 2019). α-Tocopherol absorption ranged on average between 55% and 74%, as evaluated using multiple methodologies. Absorption was unaffected by dietary fat (40% vs 0% fat in a defined liquid meal (DLM) accompanying the oral dose) or by a 12 h fast after participants consumed d_3-α-T with the 0% fat DLM (0% fat-fast) (Traber *et al.* 2019).

Our investigations into the role of fat on α-tocopherol absorption (Traber *et al.* 2019) have provided an explanation for the observation that the liver requires an α-TTP, but the intestine does not (Traber *et al.* 1990, 1993, 1994). During digestion of a meal, tocochromanol uptake into enterocytes can be facilitated by a number of transporters (Niemann-Pick C1 like 1, scavenger receptor class B type I, cluster of differentiation 36, and ABCA1) that also promote cholesterol absorption (Yamanashi *et al.* 2017, Reboul 2019). Our findings suggest that during the 0% fat trials (despite the absence of sufficient fat for chylomicron secretion), the oral d_3-α-T was taken up into the intestinal enterocytes. When a meal was consumed subsequently, the enterocytes secreted chylomicrons containing the retained d_3-α-T. Our studies are consistent with the dual track model of fat absorption (Cook *et al.* 2022). Studies examining fat absorption have documented that lipid droplets are formed rapidly inside enterocytes during fat consumption (Soayfane *et al.* 2016). These enterocytes control circulating triglyceride (TG) fluctuations by transiently storing TG in lipid droplets (Demignot *et al.* 2014), rather than secreting TG in chylomicrons (Khalifeh-Soltani *et al.* 2016). Data from apolipoprotein B48 (apo B) knockout mice that cannot form chylomicrons or absorb α-tocopherol show that large lipid droplet accumulations are found in enterocytes (Young *et al.* 1995). Therefore, it seems reasonable to suggest that during our clinical trial, the d_3-α-T could have been retained in the enterocytes during 0% fat or 0% fat-fasting interventions until a subsequent meal, when enterocyte TG uptake was sufficient for chylomicron secretion (e.g. after fat uptake from the next meal).

Our findings also suggest that the various tocochromanols accumulate in enterocyte lipid droplets, that these droplets can then coalesce with nascent chylomicrons, and that this process facilitates the incorporation of TG, various fat-soluble compounds, and tocochromanols into chylomicrons (Fig. 2). Once the chylomicrons reach the circulation, catabolism of the particles is rapid based on the kinetics of the IV dose (Traber *et al.* 2019). Once the chylomicron remnants reach the liver, then α-TTP is needed to facilitate α-tocopherol secretion into plasma VLDL (Fig. 3). The VLDL are catabolized in the circulation and α-tocopherol is swiftly distributed to all of the lipoprotein fractions. By contrast, the other tocochromanols can be catabolized in the liver via xenobiotic mechanisms and/or excreted in bile, similarly to γ-tocopherol (Leonard *et al.* 2005).

It should also be noted that the proposed mechanisms for chylomicron transport of tocochromanols facilitates the absorption of a variety of fat-soluble compounds, which may or may not be beneficial. Their delivery to the liver allows selection of desirable compounds, such as α-tocopherol, and promotes xenobiotic and/or catabolism of non-desirable or toxic compounds. It is generally accepted excretion that various fat-soluble vitamins (e.g. A, D, and K) are absorbed in chylomicrons, but transport from the liver needs specific proteins. The exception to the latter is vitamin K (Erkkila *et al.* 2004, Shearer & Okano 2018).

Catabolism of α-tocopherol and the tocochromanols

We also studied catabolism of the oral and IV doses in the clinical trial described earlier (Traber *et al.* 2021). The d_6-α-T in the IV dose was cleared from the plasma with an estimated at a half-life of ~3–4 min, virtually 100% of a relatively large bolus (30 mg or 68.8 μmol d_6-α-T) was delivered to the liver in <1 h (Traber *et al.* 2019).

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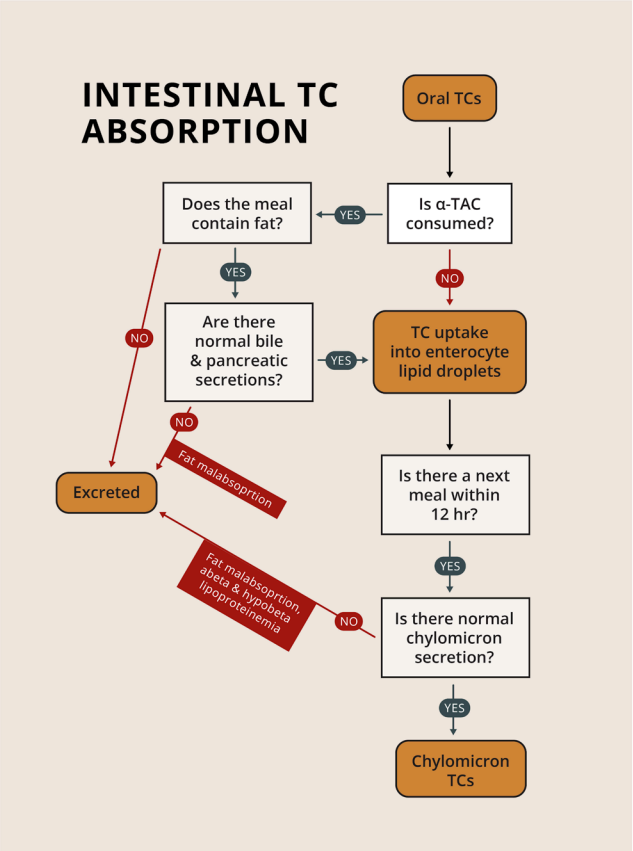

Figure 2
Intestinal tocochromanol absorption requires chylomicron secretion. During digestion of a meal, TCs are taken up into enterocytes. Fat seems only to be needed to facilitate absorption of supplements containing α-tocopheryl acetate (α-TAC) (Leonard *et al.* 2004). Both biliary and pancreatic secretions are needed for fat absorption, which also facilitates TC uptake by enterocytes (Traber & Sies 1996). During fat absorption, lipid droplets accumulate inside enterocytes (Cook *et al.* 2022). These enterocytes control circulating triglyceride (TG) fluctuations by transiently storing TG in lipid droplets until the next meal is consumed. This subsequent meal allows sufficient TG uptake into the cells for chylomicron secretion. Enterocyte lipid droplets coalesce with nascent chylomicrons, a process that facilitates the incorporation of TG, various fat-soluble compounds, and TCs into chylomicrons (Traber *et al.* 2019, 2021). This TC absorption process does not need α-TTP. Notably, this process requires the synthesis of apolipoprotein B48 (apo B) (Cook *et al.* 2022). Vitamin E deficiency occurs in the absence of apo B, such as in abetalipoproteinemia or hypobetalipoproteinemia (Bredefeld *et al.* 2022) due to the inability to absorb or transport dietary α-tocopherol levels in apo B-containing lipoproteins.

It was anticipated that this large α-tocopherol amount might increase liver α-tocopherol catabolism to α-carboxyethyl hydroxychromanol (CEHC). Surprisingly, the interventions changed catabolism of the IV d_6-α-T dose rather than the oral d_3-α-T dose. The 0% fat-fast intervention caused a roughly 50% decrease in the cumulative urinary d_6-α-CEHC excretion, while the switch from 40% to 0% fat had no effect on excretion.

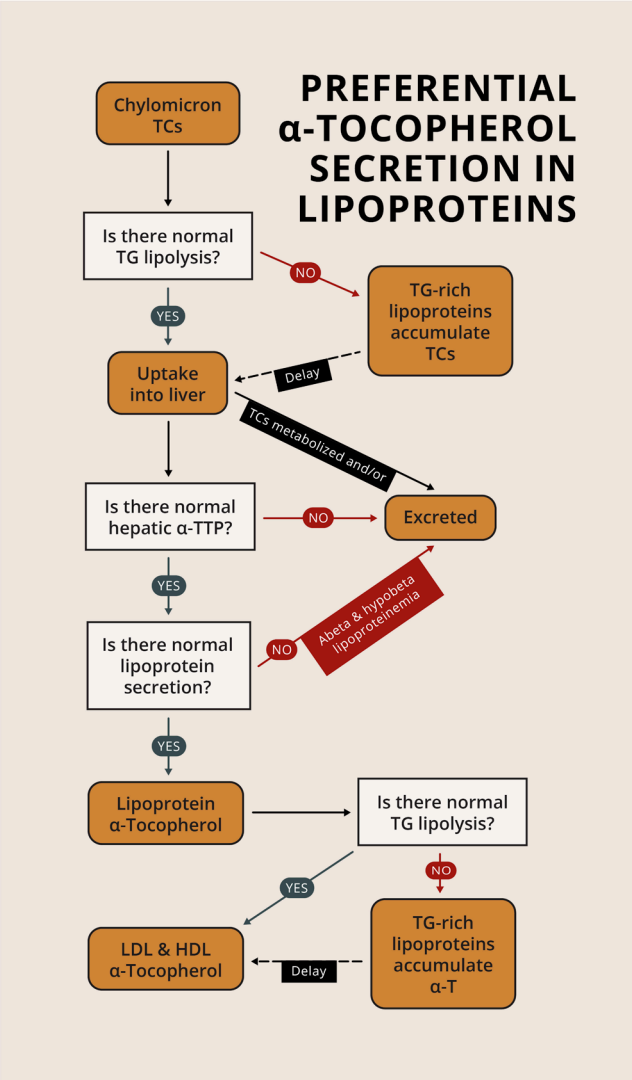

Figure 3
All TCs are absorbed by the intestine, but only α-tocopherol secretion is preferentially secreted by the liver. Once the chylomicron remnants reach the liver following some TG lipolysis, α-TTP is needed to facilitate α-tocopherol secretion to an external acceptor, such as nascent very low density (VLDL) or high density (HDL) lipoproteins (Shichiri *et al.* 2010). The preferential enrichment of the plasma with α-tocopherol is dependent upon a multi-step process involving α-TTP (Arai & Kono 2021). The VLDL are catabolized in the circulation and α-tocopherol is swiftly distributed to all of the lipoprotein fractions (Traber *et al.* 2019). These lipoproteins then transfer α-tocopherol to the circulating lipoproteins, which can deliver it to the tissues (Traber 2013). Notably, the supplemental α-tocopherol intakes recommended for those with AVED obviate the necessity for the hepatic α-TTP because during chylomicron catabolism α-tocopherol is non-specifically incorporated into circulating lipoproteins, which can also deliver α-tocopherol or TCs to tissues (Traber 2014). Vitamin E deficiency occurs in the absence of apo B, such as in abetalipoproteinemia or hypobetalipoproteinemia (Bredefeld *et al.* 2022) due to the inability to absorb or transport dietary α-tocopherol levels in apo B-containing lipoproteins. Persons with AVED need daily vitamin E supplements of approximately 1 g, while persons lacking apo B-containing lipoproteins need supplements of approximately 10 g daily (100 mg/kg body weight).

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Additionally, during the fasting intervention, the amount of urinary unlabeled-α-CEHC and unlabeled-γ-CEHC excreted were also both decreased. A plausible explanation for the decrease is dependent on regulation of xenobiotic metabolism in the liver. Hepatic α-tocopherol catabolism may be affected given that (i) CYP4F2 initiates tocochromanol catabolism (Jiang 2022), (ii) the *CYP4F2* gene is regulated by SREBP (Hsu *et al.* 2007, Hardwick *et al.* 2009), and (iii) fasting decreases SREBP-1c (Lee *et al.* 2017). Taken together, these findings suggest that during fasting there is decreased α-tocopherol or tocochromanol catabolism in the liver, while simultaneously there is inadequate fat in the intestine for tocochromanol absorption.

Evidence that specific human extra-hepatic tissues require α-tocopherol

α-TTP appears to be important for transferring α-tocopherol within some specific tissues, such as eyes, brain/central nervous system, as well as yolksac and placenta, as discussed further. In these examples, α-TTP functions to move circulating α-tocopherol into the tissue of interest.

α-Tocopherol and α-TTP during pregnancy

Vitamin E was discovered in 1922 because it is required by pregnant rats to carry their fetuses to term (Evans & Bishop 1922). The embryonic defects included exencephaly (Cheng *et al.* 1957, Verma & Wei King 1967) dorsal root ganglia degeneration and a defective blood–brain barrier (Verma & Wei King 1967). Neural tube defects are also present in α-tocopherol-deficient mice (Homanics *et al.* 1995, Kim *et al.* 1998, Raabe *et al.* 1998, Jishage *et al.* 2001, Santander *et al.* 2017).

Since α-TTP's role is to transfer α-tocopherol, it is of interest that this protein is expressed in fetal and maternal tissues during human pregnancy. α-TTP is increased at the site of fetal implantation in the placenta (Jishage *et al.* 2001, Kaempf-Rotzoll *et al.* 2002), specifically in the syncytiotrophoblast and trophoblast cells of the human placenta (Kaempf-Rotzoll *et al.* 2002, 2003, Rotzoll *et al.* 2008). Indeed, placental α-TTP concentrations are estimated to be second only to those of the liver (Muller-Schmehl *et al.* 2004). Additionally, α-TTP is expressed by the human yolk sac (Jauniaux *et al.* 2004), which is an important embryonic structure that provides nourishment to the embryo prior to implantation.

Given that α-tocopherol deficiency was first identified in embryos, we studied α-tocopherol deficiency in the premier model of vertebrate embryogenesis, the zebrafish. α-Tocopherol-deficient zebrafish embryos had increased lipid peroxidation, which led increased phospholipid turnover (McDougall *et al.* 2016) and to metabolic dysregulation (McDougall *et al.* 2016, 2017*a*,b,d, Head *et al.* 2021, Zhang *et al.* 2021). α-Tocopherol deficiency also caused morphological changes at very early stages in development (Head *et al.* 2020, Head *et al.* 2021), which occur prior to an analogous time to when a woman knows she is pregnant. α-Tocopherol protects the developing nervous system of zebrafish and rodents during the time frame in which neural tube defects occur in human embryos (18–19 hours post-fertilization (hpf) in zebrafish (Kimmel *et al.* 1995), 9–12 days in rats (Altman & Katz 1962), and 22–30 days in humans (O'Rahilly 1979, Wilcox *et al.* 1999, Gilbert 2010). A more severe neurologic phenotype is caused by *ttpa* knockdown in zebrafish embryos with 100% lethality by 24 hpf (Miller *et al.* 2012). Similarly, *ttpa* null mice experienced increased fetal mortality (Finno *et al.* 2018). The pup lethality could be overcome by feeding parental heterozygote (*ttpa*$^{+/-}$) mice α-tocopherol (Ranard *et al.* 2020).

Critically, our studies in zebrafish have shown that both α-TTP (Miller *et al.* 2012) and α-tocopherol (McDougall *et al.* 2017*a*,b, Head *et al.* 2020) are essential for neurogenesis and embryonic development. The deficiency of either is embryonically lethal in the zebrafish. α-TTP knockdown is 100% lethal by 24 hpf (Miller *et al.* 2012), suggesting that α-TTP is a key regulator during embryogenesis. Although α-tocopherol deficiency is lethal to 70% of deficient embryos (McDougall *et al.* 2017*a*), some embryos survive with neural tube defects, impaired brain formation, and defective neurogenesis (Head *et al.* 2020, 2021). A small percentage survive without apparent morphologic defects but when refed α-tocopherol, these animals were found to have metabolic, as well as learning and behavior, defects (McDougall *et al.* 2017*d*).

α-Tocopherol deficiency causes severe developmental impairment at early embryonic stages in the zebrafish (Fig. 4). α-Tocopherol is required for brain (forebrain, midbrain, and hindbrain) development at 12 hpf and by later stages (>24 hpf) for formation of the dorsal root ganglia (DRG) and notochord (Head *et al.* 2020).

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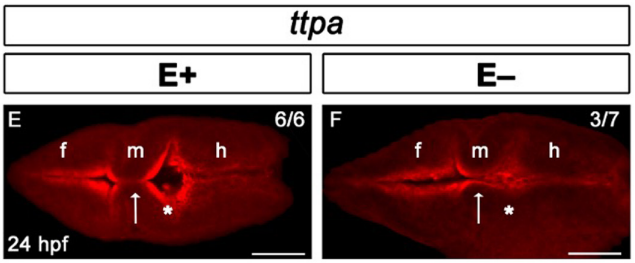

Figure 4
α-tocopherol deficiency impairs zebrafish embryo brain formation. *Ttpa* expression (indicated with red fluorescence) in representative α-tocopherol-sufficient and -deficient (E+ and E–) embryos shows E– embryos do not have closure at midbrain–hindbrain boundary and have reduced hindbrain ventricle inflation (*).The dorsal direction is indicated by arrow. At 24 h post-fertilization (hpf), *ttpa* is expressed at brain ventricle borders and within cells of the forebrain (f), midbrain (m), and hindbrain (h). Arrows indicate the midbrain–hindbrain boundary where diencephalic ventricle expansion was altered; *represent inflation in E+ embryos (E, *n* = 6/6) or lack thereof in E– embryos (F, *n* = 3/7). Scale bar represents 50 μm. α-Tocopherol deficiency did not change *ttpa* expression, as measured by qPCR. Further, *ttpa* expression is localized along brain ventricle borders regardless of diet. Adapted from: 'Head, *et al.* Vitamin E is necessary for zebrafish nervous system development'. Scientific Reports. Published (September 21, 2020), Springer Nature' (Head *et al.* 2020).

Clearly, both α-TTP and α-tocopherol are necessary molecules during embryonic development because uptake and trafficking in the embryo occurs in the nervous system prior to liver or circulatory system development (Head *et al.* 2020). Although α-tocopherol concentrations did not regulate *ttpa* expression levels or patterns (Head *et al.* 2020), α-tocopherol deficiency instead altered the tissue structures containing α-TTP (Head *et al.* 2020) (Fig. 4). Thus, α-tocopherol appears to be needed subsequent to 6 hpf, such as during the formation of the neural keel, rod folding and neural tube cavitation, and neural stem cell migration which occur in the zebrafish between 12 and 24 hpf. Data from both gene expression and evaluation of the metabolome in α-tocopherol-deficient embryos suggest that the activity of the mTOR signaling pathway is dysregulated (Head *et al.* 2021) – mTOR is a regulator mechanism that impacts both metabolism and neurodevelopment (Zoungrana *et al.* 2022).

Persons heterozygous for genetic α-TTP defects are able to successfully carry the pregnancy to term (Cavalier *et al.* 1998, Di Donato *et al.* 2010, Schuelke 2005 (updated March 16, 2023)); however, there are no published reports of successful pregnancies in persons with the homozygous or compound heterozygous forms of AVED, despite the apparent success of α-tocopherol supplements staving off neurologic symptoms (Kohlschutter *et al.* 2020). The findings in zebrafish also suggest that α-tocopherol is required for human pregnancy – a statement supported by a report showing that mothers with low serum α-tocopherol concentrations early in pregnancy have a doubled risk of miscarriage (Shamim *et al.* 2015). Thus, miscarriage, as well as neural tube defects, may be overlooked in human α-tocopherol deficiency symptoms. Of concern is a recent report documenting that compared to whites, non-white pregnant women in the USA are more likely to have both low α-tocopherol intakes and low circulating α-tocopherol concentrations (Hanson *et al.* 2018).

The roles of α-TTP and α-tocopherol in eyes

α-TTP in Müller cells of the retina traffics α-tocopherol in the eyes (Tanito *et al.* 2007, Shichiri *et al.* 2012). Certain eye disorders, especially retinitis pigmentosa and occasionally macular degeneration both caused by retinal degeneration, have been reported in persons with AVED (Mariotti *et al.* 2004, Iwasa *et al.* 2014). With regards to healthy aging humans, 'AREDS' (Age-Related Eye Disease Study) showed that α-tocopherol in a cocktail of micronutrients, including zinc, could delay the progression of age-related macular degeneration (Age-Related Eye Disease Study Research Group 2001, Age-Related Eye Disease Study 2 Research Group 2013, Chew *et al.* 2022). Mechanistically, α-tocopherol likely protects the eye by halting lipid peroxidation of the phospholipids and carotenoids in the macula (Johra *et al.* 2020), thus reducing the oxidative stress burden in the eye. Due to the AREDS study design and the fact that vitamin E was part of the initial beneficial nutrient cocktail and therefore considered 'standard of care', subsequent supplementation AREDS trials evaluated other micronutrient/antioxidant components. Thus, it is unclear as to the specific α-tocopherol benefit in preventing or delaying the progression of macular degeneration (Evans & Lawrenson 2017*a*,*b*). There also may be difficulty in delivering α-tocopherol to the macula.

The roles of α-TTP and α-tocopherol in the central nervous system

The brain has the highest rate of oxygen consumption of any body tissue and the highest peroxidation-susceptible lipids (e.g. those containing docosahexaenoic acid, DHA), which is why it is highly susceptible to lipid peroxidation (Cobley *et al.* 2018). Remarkably, during

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dietary α-tocopherol deficiency, the brain compared with other tissues is better able to retain α-tocopherol, as illustrated in dogs (Pillai *et al.* 1993) or rats (Terada *et al.* 2011). Adult zebrafish fed with α-tocopherol-deficient diets for prolonged periods experienced increased defects in learning and behavior (McDougall *et al.* 2017*c*) and showed increased lipid peroxidation and dysregulation of lysophospholipid metabolism (Choi *et al.* 2015) as well as metabolic dysregulation (McDougall *et al.* 2017*c*), similar to that observed in embryos (McDougall *et al.* 2016, 2017*a*,*b*). Yassine *et al.* (2022) emphasize the metabolic disturbances and the potential for dietary components to forestall defects observed with aging.

The high level of brain oxidative damage during Alzheimer's disease (Butterfield & Boyd-Kimball 2018) has led to studies investigating the potential for α-tocopherol benefit in age-related-dementias or Alzheimer's disease. Clinical trials have shown that α-tocopherol supplements slowed the onset of dementia in Alzheimer's disease patients (Sano *et al.* 1997, Dysken *et al.* 2014). However, meta-analyses of Alzheimer's disease trials using α-tocopherol supplements have shown no statistical benefit (Farina *et al.* 2012, 2017). Nonetheless, high Alzheimer's disease incidence was associated with low-circulating α-tocopherol levels (de Wilde *et al.* 2017). Moreover, measurements of gray and white brain antioxidants from persons with Alzheimer's disease showed that α-tocopherol concentrations were almost 50% lower than brains of healthy elderly (Dorey *et al.* 2023). Lloret *et al.* (Lloret *et al.* 2019), in a comprehensive review of this topic, posit that α-tocopherol supplements are unlikely to show benefit due to the complexity of the brain and the difficulty in delivering α-tocopherol into the brain.

Retention of α-tocopherol by the brain is likely dependent on α-TTP as α-TTP null mice were not able to accumulate brain α-tocopherol (Leonard *et al.* 2002). However, α-TTP is not found in most brain tissues with the exception of Purkinje neurons and associated Bergmann glial cells (Ulatowski *et al.* 2014). In the brain, certain astrocytes (glial fibrillary acidic protein-positive) can deliver α-tocopherol to neighboring neurons by an α-TTP-facilitated process (Ulatowski *et al.* 2022).

Purkinje neurons are a class of inhibitory GABAergic neurons that use gamma-aminobutyric acid (GABA) as a neurotransmitter. Both Purkinje neurons and Bergmann glia cells are found in the Purkinje layer of the cerebellum, a brain region derived from the primordial hindbrain (Hoshino 2012). α-TTP gene expression is found in the developing 24 hpf zebrafish embryo in anatomically similar regions to where Purkinje progenitor neurons are found during rodent brain development (Muguruma *et al.* 2010). Yokota et al (Yokota *et al.* 2000) concluded based on autopsy findings of a person with AVED due to the His101Gln mutation that α-TTP functions in delivering α-tocopherol to the cerebellum, and that α-TTP mutations cause Purkinje cell loss. They noted that the AVED subject's ataxia was caused by a posterior column lesion and that α-TTP was not expressed in the DRG, which is the parent neuron of the posterior column axon. The oral α-tocopherol supplementation of the person with AVED raised his tissue concentrations both in the DRG and cerebral cortex to those of normal persons. These findings support the conclusion that α-tocopherol supplementation for more than 10 years partially ameliorated or prevented the progression of the person's ataxia symptoms (Yokota *et al.* 2000).

Conclusion

The health benefits of α-tocopherol for humans are hard to prove, except in the cases where deficiency due to genetic deficits in α-TTP are known, e.g., AVED, where α-tocopherol supplements have prevented the vitamin E deficiency symptoms, as discussed earlier.

Some health benefits of dietary α-tocopherol in preventing chronic disease have been shown in epidemiologic studies. A follow-up report from the Alpha-Tocopherol Beta-Carotene cancer prevention trial assessed baseline vitamin E status and dietary intakes of the 29,092 men who had been followed for 19 years since the study's initiation, during which time 13,380 deaths ensued (Wright *et al.* 2006). The men at baseline in the highest compared with the lowest serum α-tocopherol quintiles had significantly lower risks of total and cause-specific mortality, including cardiovascular disease and cancer (Wright *et al.* 2006). High dietary vitamin E intakes also include beneficial effects on the microbiome – higher serum α-tocopherol concentrations were associated with higher bacterial diversity (Frankenfeld *et al.* 2022), which is generally believed to be beneficial to the host. Higher dietary α-tocopherol was also associated with a lower incidence of Alzheimer's disease (Yassine *et al.* 2022). Since these are associations, it is not clear whether the

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α-tocopherol levels are reflective of certain dietary patterns, socioeconomic status, or other factors. As most people do not consume the recommended 15 mg α-tocopherol daily, they may be at increased risk for various chronic diseases. Nonetheless, there is generally universal support for a healthy diet that contains vegetable oils (such as olive and canola), nuts (such as almonds and hazelnuts), and green leafy vegetables (kale, spinach, and collard greens), which all are high in α-tocopherol and whose routine consumption will achieve the goal of 15 mg α-tocopherol daily.

Declaration of interest

The author declares that there is no conflict of interest that could be perceived as prejudicing the impartiality of this review.

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Author contribution statement

MGT conceived the study and wrote the paper.

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