Amyotrophic Lateral Sclerosis and Frontotemporal Degeneration

ISSN: 2167-8421 (Print) 2167-9223 (Online) Journal homepage: https://www.tandfonline.com/loi/iafd20

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To cite this article: The Alsuntangled Group & Bedlack Richard (2020): ALSUntangled 55: vitamin E (α-tocopherol), Amyotrophic Lateral Sclerosis and Frontotemporal Degeneration, DOI: 10.1080/21678421.2020.1754024

To link to this article: https://doi.org/10.1080/21678421.2020.1754024

Published online: 02 May 2020.

Amyotrophic Lateral Sclerosis and Frontotemporal Degeneration, 2020; 0: 1–7

REVIEW ARTICLE

ALSUntangled 55: vitamin E (α-tocopherol)

THE ALSUNTANGLED GROUP

KEYWORDS: *Supplements; vitamins; vitamin E*

Overview

Vitamin E is a fat-soluble essential micronutrient from plants known chemically as α(alpha)-tocopherol. The typical American diet intake contains approximately 13.5 mg vitamin E daily (1) along with other non-essential forms of tocopherol (beta, gamma, and delta forms). The recommended daily allowance of vitamin E is 15 mg daily (2), which is the amount contained in many multivitamin preparations. Deficiency of vitamin E can affect multiple organ systems; ataxia is the most common and well-described neurological manifestation (3,4). ALS is not caused by vitamin E deficiency as blood levels (5–7) and CSF levels (7) of vitamin E in PALS are normal. Nonetheless, perhaps owing to its mechanisms of action (3,8,9), vitamin E is advertised on the Internet as an ALS treatment (10) and one of the more common supplements taken by PALS (11).

Mechanisms

The two main mechanisms by which vitamin E may be beneficial to PALS are reduction of neuroinflammation and oxidative stress. Although some have questioned the availability of vitamin E to the central nervous system (CNS), a randomized double-blinded placebo-controlled clinical trial (RCT) in Parkinson's disease patients showed that high dose (900 mg) daily oral vitamin E supplementation can increase lumbar CSF levels of vitamin E (12).

Neuroinflammation

Alterations in the immune system and neuroinflammation are thought to contribute to the pathophysiology of ALS (13). These alterations include activation of the NF-κB cellular signaling pathway (14). Down-regulating this pathway is beneficial in several mouse models of ALS (15–17), but the significance of this is controversial (18). Clinical trials to-date of immune-modulating therapies have been generally (19) but not always (20) unsuccessful.

Unmodified vitamin E does not appear to have any benefit on inflammatory processes, but addition of an acetate or succinate chemical functional group does have an effect on cellular immunologic signaling. In a human T cell line, α-tocopheryl acetate and α-tocopheryl succinate were both able to downregulate NF-κB signaling activation (21) although they apparently work by differing mechanisms (22). This is significant because most vitamin E supplements are α-tocopheryl acetate or α-tocopheryl succinate.

Oxidative stress

As discussed in a recent ALSUntangled paper (23), oxidative stress may play a role in ALS. Vitamin E has been demonstrated to be protective against oxidative stress in primary cultures of rat lower motor neurons (24), rat cortical neurons (25), rat astrocytes (26), cultured cells from the mouse NSC19 (27) and NSC34 motoneuron-like cell lines (28), and a mouse hippocampus neuron cell line (29). In healthy rats, oral vitamin E supplementation increases brain and CSF levels of vitamin E (30); intramuscular supplementation lowers brain markers of oxidative stress (31).

Multiple RCTs in humans have investigated the effect of vitamin E oral supplementation on biomarkers of oxidative stress (F2-isoprostanes) with mixed results. Three RCTs testing vitamin E

The ALSUntangled Group: ALSUntangled reviews alternative and off-label therapies on behalf of persons with ALS (PALS). Here, we review the use of vitamin E in PALS. See Appendix for ALSUntangled Reviewers.Correspondence: Richard Bedlack, E-mail: richard.bedlack@duke.edu Department of Neurology, Duke University, Durham, NC, USA

ISSN 2167-8421 print/ISSN 2167-9223 online
DOI: 10.1080/21678421.2020.1754024

supplements of up to 1200 mg per day in healthy participants for up to 2 months found no change in isoprostane urine levels (32–34) and a 3-month RCT with heart failure patients reported no effect on isoprostane blood levels (35). Vitamin E RCTs of longer durations have been more successful in lowering oxidative stress biomarkers. In healthy participants, 4 months of 1000 mg per day was sufficient to lower blood biomarkers (36). In patients with heart failure, 6 months of 800 mg per day yielded lower urine isoprostane levels (37). A 12-month RCT of 100 mg per day enrolling men (38) and a 36-month RCT of 180 mg per day enrolling smokers (39) reported lower blood and urine isoprostanes, respectively.

Based on the above evidence demonstrating the ability of vitamin E to lower a biomarker of oxidative stress in human clinical trials, ALSUntangled assigns a "Mechanisms" grade of A (Table 1).

Table 1. Evidence for vitamin E (α-tocopherol).

	Grade	Explanation
Mechanism	A	Multiple double-blind RCTs in participants without neurological disease show that moderately high doses of daily vitamin E supplementation for at least 4 months can lower blood and urine biomarkers of oxidative stress.
Pre-clinical	C	2 flawed studies in the SOD1 mutant mouse model showed a benefit of delayed disease onset, but no benefit on survival was observed.
Cases	A	There has been at least one published case report where the ALS diagnosis was clear and the patient had a substantial benefit on vitamin E with adequate follow-up. We however caution that there have also been over 200 published case reports with no benefits.
Trials	F	2 randomized double-blinded placebo-controlled trials showed no benefit of vitamin E on accepted ALS outcome measures despite adequate statistical power, high dosage, and long duration.
Risks	A	It is likely safe for PALS to take up to 1000 mg per day of vitamin E long-term. Vitamin E is should not be taken with an anticoagulant such as warfarin.

Pre-clinical models

There have been several studies in cultured cells testing the ability of vitamin E to protect against toxins potentially relevant to ALS. In one study, the human neural cell line SH-SY5Y was exposed to the neurotoxin BMAA (see ref. 40) which increased markers of cellular stress. When vitamin E was co-incubated with the BMAA, markers of oxidative stress and cell death pathway activation were reduced relative to cells treated with BMAA only (41). In another study, primary cultures of cortical neurons from rats were exposed to human CSF. At baseline, cells demonstrated a 90% survival over 48 hours. If the cells were incubated with healthy human CSF, the survival was still 90%, but when exposed to PALS CSF, the survival decreased to 70%. With the addition of vitamin E to the CSF from PALS, survival improved to 80% (42). Another study used rat adrenal medulla cells that were induced to express mutant SOD1. Expression of mutant SOD1 led to cell death but a significantly lower number of cells died when they were incubated with vitamin E (43). Another study used primary spinal cord cultures from mutant SOD1 mice. At baseline, the cultured cells had 80% survival and this decreased to 40% when exposed to glutamate. When vitamin E was added to the cells prior to glutamate exposure, survival increased to 70% (44). Similarly, another study exposed the mouse motoneuron-like NSC34 cell line to glutamate that reduced the number of living cells. Vitamin E was able to partially block this effect (28).

In a study of the mutant SOD1 G93A mouse model of ALS, vitamin E supplementation from an early age delayed onset of disease but did not improve survival relative to control mice (45). The same effect of delayed disease onset but similar survival was found in this mouse model by another research group when vitamin E was used in a drug cocktail as compared with the drug cocktail without vitamin E (46). Both studies were small and possibly underpowered to find a survival effect.

Based on the above evidence, ALSUntangled assigns "Pre-Clinical Models" a grade of C (Table 1).

Cases

In the early 1940s, neurologist Israel Wechsler treated over 60 PALS with vitamin E in an unblinded manner. He believed that approximately 10 PALS benefited (47–50). He published details of 20 of these patients whom took up to 200 mg of vitamin E daily either administered orally or intramuscularly (48,49). The follow-up for these patients was generally very short and the "improvements" were minimal in some of these patients, hence we will only discuss the most compelling cases. C.B. was a 36-year-old woman whom had progressive limb weakness and trouble swallowing. On exam, she was unable to walk and had atrophy of the limbs and tongue and hyperreflexia. Labs and spine X-ray were normal. Over 2 months of vitamin E supplementation, her swallowing improved, the tongue gained muscle bulk, she regained limb strength and was able to "walk with assistance." At 6-month follow-up, she was continuing to regain strength (48,49). Her disease

progressed slightly when seen at 9 months follow-up, but she still retained much of her original improvement (50). R.E. was a 39-year-old woman with 18 months of progressive weakness of her hands and legs. On exam, she had widespread upper and lower motor neuron signs including tongue fasciculations, intrinsic hand muscle atrophy, and hyperreflexia. She was started on vitamin E and had improvements in gait and hand strength that were sustained for the 3-month follow-up period (48). Wechsler also treated the famous baseball player Lou Gehrig (L.G.) after 10 months of progressive weakness of his legs and hands. On exam L.G. was hyperreflexic with widespread fasciculations and upper extremity atrophy. Treatment with vitamin E reportedly improved his walking and his "thumb" strength with no progression over 3 months of follow-up (48). L.G. eventually progressed and died a year later.

In 1940, a London physician reported that in a group of 4 PALS, one experienced remission of his disease on vitamin E supplementation; however, this patient's ALS diagnosis was not straightforward because of atypical features that included hand numbness and no increase in reflexes. The other three PALS did not benefit (51). Another physician reported that two PALS benefited from vitamin E, but no other information was given which makes this claim impossible to evaluate (52). In 1941, another physician reported on nine PALS, of which eight were reported to have experienced benefit, but these "benefits" were modest and subjective with short follow-up periods (53). In 1942, another physician described a 60-year-old man whom had progressive leg weakness leading to paraplegia, dysarthria, and weight loss over 18 months. On exam he had atrophy of his calves and intrinsic hand muscles, widespread fasciculations, and diffuse hyperreflexia including extensor plantar responses. He was started on 25 mg three times daily vitamin E by mouth (later decreased to 12.5 mg three times daily after 6 months). Over the next 18 months, he slowly regained strength to the point he was able to climb stairs without assistance. His fasciculations and hyperreflexia also appeared to improve. These improvements were reportedly sustained through publication of the case report 30 months after initiation of vitamin E (54).

Despite these several cases where vitamin E appeared to be of some benefit, more than 200 additional case reports published during the 1940s from a number of renowned neurologists described only transient or subjective small benefits (47,50,55–69). In the 1960s, some researchers hypothesized that vitamin E deficiency and pancreatic dysfunction may contribute to ALS pathophysiology (70), but a subsequent case series of 12 PALS at the NIH showed no benefit of supplementation with vitamin E and pancreatic enzymes given over periods of at least 7 months (71). In the 1980s, researchers questioned if historical vitamin E doses were simply too low to benefit ALS, hence a consecutive case series was conducted in which 20 PALS received 10,000 mg of vitamin E per day by mouth and 20 PALS received 100 mg twice weekly by intramuscular injection for a total of six months. The researchers reported that the 40 PALS treated did not benefit from this high-dose vitamin E supplementation (72).

In the online community PatientsLikeMe, 279 PALS reported taking vitamin E at various doses and durations (73). Of the 55 who reported outcomes, one rated benefits as "major," four "moderate," two "slight", 14 "none," and 34 "can't tell" (73).

Within the Duke University cohort of 47 validated "ALS reversals," four were taking vitamin E in addition to multiple other supplements when their motor improvements occurred (74,75). As we have previously stated, there are multiple possible explanations for these remarkable cases. (74).

Based on the above evidence, ALSUntangled assigns "Cases" a grade of A (Table 1).

Trials

There have been several clinical trials of vitamin E in PALS. The best designed one was a 12-month double-blind study that enrolled 289 PALS to be randomized to either 500 mg twice daily of vitamin E acetate by mouth or placebo. Both the vitamin E and placebo groups also took riluzole. Three months into the study, the vitamin E group had higher blood vitamin E levels and a subset had decreased levels of oxidative stress biomarkers. Despite this, there was no clear clinical benefit at 12 months as measured by the main outcomes selected: Norris limb score, Norris bulbar score, forced vital capacity (FVC), or manual muscle testing. There was also no difference in survival, i.e. time to death, between the two groups (76). Participants on vitamin E were slightly less likely to progress to more severe disease states according to a little-used measure called the ALS Health State Scale. Several additional ALS clinical trials of variable quality assessed cocktails of antioxidants that included vitamin E. None showed any benefits in PALS (77,78).

It was subsequently hypothesized that larger doses of vitamin E were required to confer a benefit in PALS. An 18-month double-blinded study enrolled 160 PALS to be randomized to vitamin E 5000 mg daily or placebo. Again, both groups took riluzole. At 18 months, there was no statistically significant difference between the two groups in

Norris limb score, Norris bulbar score, FVC, or survival (79).

Of potential interest, several studies have attempted to find a correlation between vitamin E consumption with the likelihood of ever developing ALS. Three case-control studies (two American and one Japanese) comparing PALS to control subjects showed no difference in dietary intake of vitamin E (80–82), but one Dutch case-control study showed that healthy control subjects consumed more vitamin E than PALS (83). While case-control studies like these can sometimes help answer research questions, they may be biased. A more scientifically sound design is prospective studies that enroll participants, monitor their vitamin E consumption and then follow-up to see if they develop ALS. In one American prospective study, there was a lower risk of developing ALS when vitamin E supplements were taken over a long duration (84). In another study, the data from three American prospective cohorts pooled together indicated that the risk of ALS decreased with increasing duration of vitamin E supplementation (85). The most recently published prospective study utilized a cohort of 30,000 male smokers in Finland. The results showed that if the cohort was divided into two groups based on blood levels of vitamin E, the group with higher vitamin E bloods levels had a decreased risk of developing ALS as compared with the participants with lower levels (86).

In summary, although vitamin E appears to be possibly protective against getting ALS, it was not effective in slowing or stopping progression in clinical trials. This is consistent with two studies of the SOD1 mutant mouse model that showed vitamin E delayed disease onset, but did not improve survival (45,46). Based on this evidence, ALSUntangled assigns "Trials" a grade of F (Table 1).

Risks

As stated above, the recommended daily allowance of vitamin E is 15 mg daily (2). Available safety data from animal studies and clinical trials suggests that daily doses of up to 1000 mg are likely to be safe for periods of at least 18 months (87). Safety analyses in PALS from both the 1000 mg per day for 12 months trial and the high dose vitamin E for 18 months trial suggested that there is no discernable difference in adverse events between vitamin E and placebo for the regimens used in these trials (76,79). PALS receiving mega dosages (10,000 mg daily) for 6 months in a case series were said to "tolerate" the dose but no formal listing of adverse events was provided (72). Unless under a physician's close supervision, no one should initiate a vitamin E supplement if they have a bleeding disorder or are taking an anticoagulant like warfarin. Vitamin E supplementation can lead to decreased vitamin K, inhibited platelet aggregation and reduced platelet–endothelial adhesion that can cause life-threatening hemorrhage (88–90). One large, randomized, placebo-controlled trial in healthy men suggested that vitamin E supplementation over very long periods of time (7–10 years) can slightly increase the risk of prostate cancer (91). However, two other large long-duration trials did not find this same increased risk (92,93).

Based on all this evidence, ALSUntangled assigns "Risks" a grade of A for vitamin E (α-tocopherol) supplementation up to 1000 mg total daily dose in PALS not taking anticoagulants (Table 1).

Dosing and costs

Vitamin E is available in natural (D-α-tocopherol) and synthetic forms (DL-α-tocopherol). Synthetic vitamin E is half as potent as natural vitamin E; however, this is corrected for on the label so both 900 mg synthetic vitamin E and 450 mg natural vitamin E will be sold simply as "450 mg vitamin E." PALS may notice IU as a form of measurement, but this is being phased out by the FDA in favor of milligrams. One IU of the natural form is equal to 0.67 mg vitamin E, while one IU of the synthetic form is equal to 0.45 mg (2).

The cost of a month's supply of vitamin E (α-tocopherol) will vary depending on brand and dose. For a 500 mg twice daily dose of α-tocopherol acetate as in the first ALS trial (76), the cost will be approximately $5 US dollars per month (94).

Conclusions

Vitamin E (α-tocopherol) is perhaps the most studied supplement in the history of ALS and was taken by one of the most famous ALS patients. Vitamin E has mechanistic potential in ALS as an antioxidant but appears in the SOD1 mutant mouse model to only have an effect on delaying disease onset. This bears out in human populations as large prospective cohorts show that long-duration vitamin E supplementation may decrease the risk of ALS, but randomized clinical trials show that even high dose vitamin E does not benefit the disease once ALS has been diagnosed. Although it is inexpensive and safe, we do not recommend vitamin E to slow, stop or reverse ALS based on the lack of efficacy in clinical trials.

Declaration of interest

ALSUntangled is sponsored by the ALS Association. Richard Bedlack has research support from ALSA and Orion, and consulting support from ALSA, Biogen, Brainstorm Cell, ITF

Pharma, Mallinkrodt, New Biotic and Woolsey Pharma.

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Appendix

ALSUntangled Reviewers who contributed to this paper include the following: Jesse Crayle (lead author), Richard Bedlack (senior author), Carmel Armon, Paul Barkhaus, Benjamin Barnes, Michael Benatar, Tulio Bertorini, Robert Bowser, Mark Bromberg, Benjamin Brooks, Lev Brylev, James Caress, Greg Carter, Merit Cudkowicz, Jon Glass, Volkan Granit, Michael Graves, Terri Heiman-Patterson, Leann Jiang, Christopher McDermott, Gary Pattee, Erik Pioro, Michael Rivner, Jeffrey Rothstein, Kristiana Salmon, Kim Staats, and Paul Wicks. *Note*: This paper represents a consensus of those weighing in. The opinions expressed in this paper are not necessarily shared by every investigator in this group.