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# Oral Tocotrienols Are Transported to Human Tissues and Delay the Progression of the Model for End-Stage Liver Disease Score in Patients[1–4]

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## Abstract

The natural vitamin E family is composed of 8 members equally divided into 2 classes: tocopherols (TCP) and tocotrienols (TE). A growing body of evidence suggests TE possess potent biological activity not shared by TCP. The primary objective of this work was to determine the concentrations of TE (200 mg mixed TE, b.i.d.) and TCP [200 mg $\alpha$-TCP, b.i.d.)] in vital tissues and organs of adults receiving oral supplementation. Eighty participants were studied. Skin and blood vitamin E concentrations were determined from healthy participants following 12 wk of oral supplementation of TE or TCP. Vital organ vitamin E levels were determined by HPLC in adipose, brain, cardiac muscle, and liver of surgical patients following oral TE or TCP supplementation (mean duration, 20 wk; range, 1–96 wk). Oral supplementation of TE significantly increased the TE tissue concentrations in blood, skin, adipose, brain, cardiac muscle, and liver over time. $\alpha$-TE was delivered to human brain at a concentration reported to be neuroprotective in experimental models of stroke. In prospective liver transplantation patients, oral TE lowered the model for end-stage liver disease (MELD) score in 50% of patients supplemented, whereas only 20% of TCP-supplemented patients demonstrated a reduction in MELD score. This work provides, to our knowledge, the first evidence demonstrating that orally supplemented TE are transported to vital organs of adult humans. The findings of this study, in the context of the current literature, lay the foundation for Phase II clinical trials testing the efficacy of TE against stroke and end-stage liver disease in humans. J. Nutr. 142: 513–519, 2012.

## Introduction

The natural vitamin E family is composed of eight members equally divided into two classes: TCP[11] and TE. TCP are characterized by a saturated phytyl side chain with 3 chiral carbons, whereas TE possesses a farnesyl side chain with double bonds at carbons 3, 7, and 11. Within each class, isomers are differentiated by $\alpha$, $\beta$, $\gamma$, and $\delta$ according to the position and degree of methylation on the chromanol head (1,2). TCP represent the primary form of vitamin E in green leafy vegetables, whereas TE are found in highest concentrations in seeds of monocotyledons that include wheat, rice, barley, and palm (3).

A growing body of evidence suggests TE possesses potent biological activity not shared by TCP (2). In particular, $\alpha$TE and $\gamma$TE have emerged as vitamin E molecules with neuroprotective and anticancer properties that are not exhibited by $\alpha$TCP (1,4). Importantly, many of the unique therapeutic effects of the TE isomers occur at a concentration range achievable by dietary supplementation. A nanomolar concentration of $\alpha$TE in brain tissue of spontaneously hypertensive rats was achieved by oral supplementation and attenuated ischemic stroke-induced brain damage (5). Oral administration of $\delta$TE significantly increased its concentration in tumors of mice with pancreatic cancer and inhibited tumor growth (6).

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[3] This trial was registered at clinicaltrials.gov as NCT00678834.
[4] Supplemental Figures 1 and 2 and Tables 1 and 2 are available from the "Online Supporting Material" link in the online posting of the article and from the same link in the online table of contents at http://jn.nutrition.org.
[10] These authors contributed equally.
[11] Abbreviations used: TCP, tocopherol; TE, tocotrienol; $\alpha$TCP, $\alpha$-tocopherol; $\gamma$TCP, $\gamma$-tocopherol; $\alpha$TE, $\alpha$-tocotrienol; $\delta$TE, $\delta$-tocotrienol; $\gamma$TE, $\gamma$-tocotrienol; ESLD, end-stage liver disease; MCA, middle cerebral artery; MELD, model for end-stage liver disease.
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TTP selectively transports dietary αTCP into tissues (7). It is commonly held that TTP affinity is a critical determinant for the biological activity of the 8 natural vitamin E family members (8). The affinity of TTP to bind and transport αTE is 12% that of αTCP (9), which has led to the notion that TE biological activity is negligible (8). Interestingly, orally supplemented TE is transported to vital organs and restore fertility in TTP-deficient mice, suggesting TTP-independent mechanisms of transport for TE (3). The delivery and concentration of TE in vital organs of humans following oral supplementation remain unknown. A series of studies in our laboratory have demonstrated potent in vitro as well as in vivo neuroprotective properties of αTE against neurodegeneration and stroke (5,10–15). Recently, we concluded a randomized, blinded, preclinical trial in canines where orally supplemented TE proved to be substantially effective in protecting against stroke-induced brain lesions as evaluated by high resolution MRI (10). In particular, TE has been shown to significantly reduce hemispherical infarct volume and prevent loss of white matter fiber tract connectivity in canines subject to MCA occlusion (10). Additionally, a post hoc analysis of cerebral angiograms during MCA occlusion demonstrated that canines supplemented with TE had improved cerebrovascular collateral circulation to the ischemic MCA territory (10). αTE has also been shown to significantly attenuate MCA occlusion-induced stroke in mice (11). As we prepare to test the efficacy of αTE in attenuation of stroke outcomes in clinical trials, we sought to test whether orally supplemented TE reaches human brain tissue and whether it is safely tolerated at a much higher dose than what is commonly available by diet alone. This study employed daily dietary supplementation to examine the effects of TE or TCP supplementation on tissue vitamin E concentration in vital human organs. To acquire these tissues from orally supplemented humans, surgical patient populations were recruited for long-term oral TE or TCP supplementation.

## Participants and Methods

### Human participants

To ensure the ethical treatment of participants, the study protocol was reviewed and approved by the institutional review board of The Ohio State University (no. 2005C0034). All patients provided written informed consent. Due to limitations in obtaining healthy adult human tissue, whole blood and skin biopsy samples were taken from the healthy participants group, whereas vital organ tissue was acquired from the surgical patients group.

*Healthy participants group.* Whole blood and skin vitamin E concentration were compared at baseline (presupplementation) to samples collected after 12 wk of supplementation with TE. Healthy participants ($n$ = 16) received 400 mg of TE daily. Adult volunteers provided 2 skin biopsy and three blood samples. Skin biopsies were collected from the right (first biopsy at 0 wk) and left (second biopsy at 12 wk) inner thigh. Whole blood was taken at 0, 6, and 12 wk. Healthy participants were chosen for this study, because they could be supplemented for a defined time period (not bound by scheduled surgery as in the surgical patients group). This allowed us to collect presupplementation baseline samples. In this group, participants were not supplemented with TCP, because each participant was naive to TE and acted as their own control. Inclusion criteria for the healthy participants group included: age 21–40 y, good health, nonsmoker, nonpregnant or nonbreastfeeding, and no recent (past 6 mo) or current use of supplements containing vitamin E. Exclusion criteria for the healthy participants group included: diabetes or HIV infection, receiving immunosuppression therapy, neurological disease, and alcohol or drug use.

*Surgical patients group.* Adult surgical patients were randomized to supplementation of either 400 mg TCP or 400 mg TE daily. Vital organs for study included: cardiac muscle acquired from heart transplant recipients with end-stage heart failure (TCP, $n$ = 3; TE, $n$ = 5); liver from transplant recipients with end-stage liver (TCP, $n$ = 3; TE, $n$ = 4); adipose acquired from abdominal adipose tissue of morbidly obese patients undergoing reconstructive plastic surgery (TCP, $n$ = 4; TE, $n$ = 5); and brain tissue from recalcitrant epilepsy patients requiring resection (TE, $n$ = 4). Control brain samples were taken from autopsy participants donated to science and represented vitamin E concentrations of the general population without dietary TE consumption ($n$ = 4). Exclusion criteria included current or recent dietary supplementation of vitamin E and surgical patients <21 y of age. Both TCP- and TE-supplemented groups received comparable physician-prescribed diets that did not include additional dietary supplements.

### Supplementation regimen and compliance

Over the past 7 y, our laboratory has studied the neuroprotective properties of natural vitamin αTE (3,5,10–13,16–19). All of these studies were conducted with natural vitamin E from a single source to avoid variability in purity and mixed vitamin E formulation (Carotech). For the current study, vitamin E capsules were also manufactured by Carotech. For consistency, the entire study was conducted using vitamin E gel capsules manufactured in a single batch and immediately shipped to the clinic. Capsule content was validated using a sensitive coulometric electrode detection method developed by our laboratory (19).

The surgical patients group participants were randomized to receive either 400 mg TE (200 mg Tocovid SupraBio b.i.d.) or 400 mg TCP (200 mg b.i.d.). The healthy participants group received only 400 mg TE (200 mg b.i.d.). A single 200-mg Tocovid SupraBio softgel capsule contains 61.52 mg $d$-α-tocotrienol, 112.8 mg $d$-γ-tocotrienol, and 25.68 mg $d$-δ-tocotrienol. TCP gel capsules contained 200 mg of $d$-α-tocopherol. Vitamin E gel capsules were sealed in blister packs. To determine compliance, study participants mailed empty packages back to the clinic every 2 wk. Participant supplementation compliance for the study was >90%.

Supplementation length for surgical groups was determined by the initiation of vitamin E supplementation to the day before scheduled surgery. For all surgical patients, a minimum of 4 wk of supplementation was desired. However, in some cases, physician-directed necessity of surgery did not permit a full 4 wk. Tissue-specific mean, minimum, and maximum length of supplementation for patients is reported in **Supplemental Table 1**.

### Vitamin E extraction and analyses

Excised tissues were minced, rinsed in PBS to remove blood, and stored in liquid nitrogen until analysis. Vitamin E extraction was performed as previously described using a highly sensitive HPLC-coulometric electrode array detector (CoulArray Detector Model 5600 with 12 channels; ESA) (17).

### Statistical analysis

*Healthy participants group.* Box plots were used to determine outliers defined as values > the 75th percentile plus 1.5 times the IQR or values < the 25th percentile minus 1.5 times the IQR (20). Twelve outliers were identified and it was determined that laboratory procedural errors were the cause and thus removed from the analysis. Random-effects linear regression was used to compare the concentrations for vitamin E isoforms across weeks of TE supplementation for both the blood and skin samples. If the overall $P$ value was significant at the 0.05 level, we subsequently compared 0 vs. 6 wk, 0 vs. 12 wk, and 6 vs. 12 wk. The $P$ values were adjusted using the Holm's procedure to conserve the overall type I error at 5% (21). For skin samples, we compared 0 vs. 12 wk of supplementation with TE. Gender was included as an effect modifier (interaction with weeks of supplementation). If the interaction covariate was not significant, then gender was included as a main effect. Again, if gender by itself was not significant, it was removed from the regression model. The vitamin E isoforms were transformed using the natural logarithm to normalize the values within groups and stabilize the variance across groups. This is a necessary assumption when using random-effects linear regression. Data represent individual values for men and women as well as the mean ± SD for men, women, and both sexes taken together. $P < 0.05$ was considered significant.

*Surgical patients group.* Summary statistics for vitamin E concentration in adipose, brain, cardiac muscle, and liver of the surgical patients are presented according to supplementation group (TE or TCP). Wilcoxon's Rank Sum was used to test differences across vitamin E supplementation for the 5 detectable vitamin E isoforms. Nonparametric analysis (Wilcoxon's Rank Sum) was used due to small sample sizes (between two and five observations). $P < 0.05$ was considered significant. The US RDA is based on nutrient level that is sufficient for 97–98% of the population; therefore, we presented data as percentile values.

### MELD score analysis

Random-effects linear regression was used to estimate the individual slope and intercepts of the MELD score pre- and postsupplementation for each participant. This was performed separately for the TCP and TE supplementation groups. Random-effects regression takes into account the variability within participants due to repeated measures and the variability between participants in order to estimate the SE. Due to the serendipitous nature of our MELD score findings, the length of supplementation was not standardized between patients awaiting liver transplantation. The time scale is in days relative to the beginning of the patient's vitamin E supplementation. The estimated slopes presented in the "Results" were multiplied by 10,000, because the MELD score change was relatively small compared to the change in days of observations (1000–1500 d). The percent change in the slope from pre- to postsupplementation was calculated. Summary statistics are presented for pre- and postslope and the percent change across TE and TCP supplementation groups. Wilcoxon's Rank Sum was used to test differences in slope and percent change in slope between TCP and TE. Wilcoxon's Signed Rank test was used to compare pre- to postsupplementation. $P < 0.05$ was considered significant. All statistical analyses were run using Stata 10.1 software (Stata).

## Results

In peripheral whole blood of nonsupplemented participants baseline TE levels were negligible. TE supplementation significantly increased the concentration of TE in peripheral blood of both men and women (**Fig. 1**; **Supplemental Fig. 1**). The mean concentration of $\alpha$TE in whole blood of TE-supplemented participants was >1.5 $\mu$mol/L following 6 wk and 2.5 $\mu$mol/L following 12 wk of supplementation (Fig. 1*A*). TE supplementation also significantly increased whole blood $\alpha$TCP levels in study participants. TE supplementation modestly decreased whole blood $\gamma$TCP levels following 6 wk of supplementation. However, after 12 wk, the concentration did not differ from baseline. The data presented demonstrate that daily oral supplementation of TE in a typical human diet is significantly effective in increasing the concentration of TE in peripheral blood.

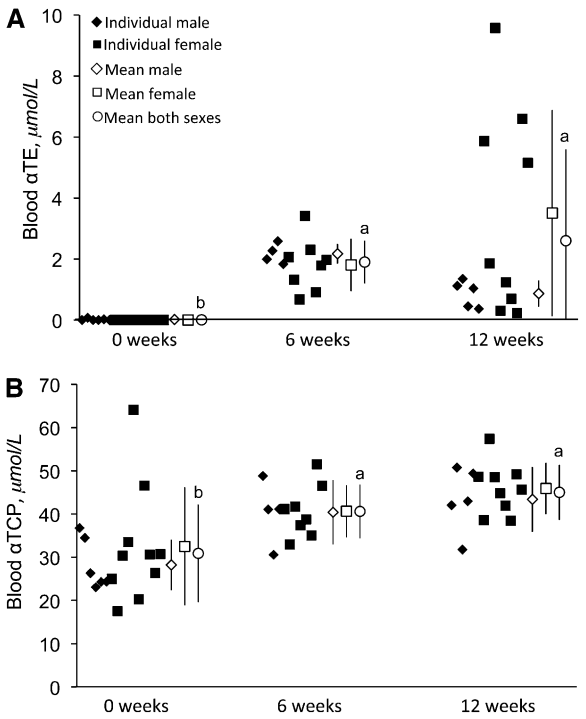


**FIGURE 1** Whole blood $\alpha$TE (*A*) and $\alpha$TCP (*B*) concentrations during 12 wk of oral TE supplementation in healthy participants. Data are individual values (males, $n$ = 6; females, $n$ = 10) and mean ± SD. Means for the sexes combined without a common letter differ, $P <$ 0.05. $\alpha$TCP, $\alpha$-tocopherol; $\alpha$TE, $\alpha$-tocotrienol; TE, tocotrienol.

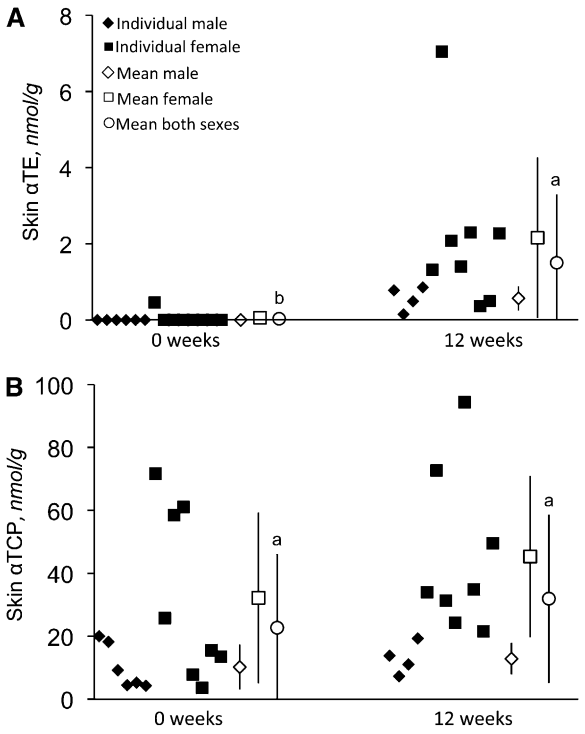


**FIGURE 2** Skin $\alpha$TE (*A*) and $\alpha$TCP (*B*) concentrations at baseline and following 12 wk of oral TE supplementation in healthy participants. Data are individual values (males, $n$ = 6; females, $n$ = 10) and mean ± SD at baseline (0 wk) and 12 wk. Means for the sexes combined without a common letter differ, $P < 0.05$. $\alpha$TCP, $\alpha$-tocopherol; $\alpha$TE, $\alpha$-tocotrienol; TE, tocotrienol.

As in whole blood, only trace baseline amounts of $\alpha$TE, $\gamma$TE, and $\delta$TE were detected in the skin of healthy participants not supplemented with TE (**Fig. 2**; **Supplemental Fig. 2**). Following 12 wk of TE supplementation, skin concentrations of $\alpha$TE, $\gamma$TE, and $\delta$TE were significantly elevated. The combined data for males and females showed a significant increase in all three isoforms at 12 wk. Oral TE supplementation had no significant effect on $\alpha$TCP or $\gamma$TCP skin concentration.

Adipose tissue emerged as a reservoir for TE in supplemented humans. The abdominal adipose concentration of TE-supplemented patients was significantly greater than in the other vital organs studied (**Table 1**). The adipose $\alpha$TE, $\gamma$TE, and $\delta$TE concentrations were ~10-fold greater than in controls ($P <$ 0.05). The ratio of $\alpha$TE:$\alpha$TCP in adipose of TE-supplemented participants was 1:4 compared to 1:25 in patients receiving TCP alone. TE supplementation had no discernable effect on adipose tissue TCP concentration (Table 1).

Trace levels of TE were detected in control brain tissue. TE supplementation significantly elevated $\alpha$TE, $\gamma$TE, and $\delta$TE concen-

**TABLE 1** Adipose, brain, heart, and liver vitamin E concentration in surgical patients supplemented with TCP or TE[1]

| | Percentile | | | | |
|---|---|---|---|---|---|
| | 25th | 50th | 75th | Mean ± SD | *P* value[2] |
| Adipose,[3] *nmol/g* | | | | | |
| TCP supplemented | | | | | |
| αTCP | 13.2 | 23.6 | 44.1 | 28.6 ± 20.7 | |
| γTCP | 5.57 | 13.2 | 21.0 | 13.3 ± 9.1 | |
| αTE | 0.30 | 0.66 | 1.61 | 0.95 ± 0.95 | |
| γTE | 0.71 | 1.72 | 3.21 | 1.96 ± 1.51 | |
| δTE | 0.05 | 0.50 | 1.36 | 0.71 ± 0.84 | |
| TE supplemented | | | | | |
| αTCP | 24.5 | 25.9 | 35.5 | 36.7 ± 24.9 | 0.46 |
| γTCP | 4.47 | 8.30 | 9.36 | 8.84 ± 6.47 | 0.46 |
| αTE | 7.49 | 7.89 | 13.6 | 9.94 ± 6.90 | 0.028 |
| γTE | 12.4 | 17.1 | 23.5 | 17.2 ± 9.67 | 0.014 |
| δTE | 6.82 | 7.00 | 11.9 | 8.73 ± 5.89 | 0.028 |
| Brain,[4] *nmol/g* | | | | | |
| TCP supplemented | | | | | |
| αTCP | 41.1 | 43.3 | 60.0 | 50.5 ± 17.2 | |
| γTCP | 0.98 | 2.51 | 10.6 | 5.77 ± 7.72 | |
| αTE | 0.03 | 0.04 | 0.05 | 0.04 ± 0.01 | |
| γTE | 0.03 | 0.05 | 0.08 | 0.06 ± 0.04 | |
| δTE | 0.09 | 0.15 | 0.17 | 0.13 ± 0.07 | |
| TE supplemented | | | | | |
| αTCP | 24.3 | 33.0 | 38.5 | 31.4 ± 10.4 | 0.043 |
| γTCP | 1.25 | 2.87 | 3.77 | 2.51 ± 1.60 | 0.56 |
| αTE | 0.71 | 0.80 | 1.87 | 1.29 ± 1.06 | 0.021 |
| γTE | 0.47 | 0.70 | 1.19 | 0.83 ± 0.50 | 0.021 |
| δTE | 0.24 | 0.38 | 0.67 | 0.45 ± 0.30 | 0.021 |
| Heart,[5] *nmol/g* | | | | | |
| TCP supplemented | | | | | |
| αTCP | 15.0 | 26.9 | 53.9 | 31.9 ± 20.0 | |
| γTCP | 2.23 | 10.3 | 13.7 | 8.76 ± 5.91 | |
| αTE | 0.08 | 0.08 | 0.12 | 0.09 ± 0.03 | |
| γTE | 0.02 | 0.23 | 0.26 | 0.17 ± 0.13 | |
| δTE | 0.05 | 0.06 | 0.17 | 0.09 ± 0.07 | |
| TE supplemented | | | | | |
| αTCP | 30.7 | 33.9 | 45.3 | 45.0 ± 25.4 | 0.99 |
| γTCP | 5.06 | 5.35 | 17.6 | 13.1 ± 12.9 | 0.65 |
| αTE | 1.70 | 6.23 | 7.25 | 5.37 ± 4.28 | 0.025 |
| γTE | 2.07 | 6.70 | 14.4 | 8.85 ± 8.40 | 0.025 |
| δTE | 0.70 | 1.70 | 3.39 | 2.32 ± 2.28 | 0.053 |
| Liver,[6] *nmol/g* | | | | | |
| TCP supplemented | | | | | |
| αTCP | 48.0 | 68.0 | 77.3 | 64.3 ± 14.9 | |
| γTCP | 4.71 | 4.75 | 8.67 | 6.04 ± 2.27 | |
| αTE | ND[7] | ND | ND | ND | |
| γTE | ND | ND | ND | ND | |
| δTE | ND | ND | ND | ND | |
| TE supplemented | | | | | |
| αTCP | 17.7 | 29.5 | 34.3 | 26.0 ± 12.8 | 0.033 |
| γTCP | 2.24 | 3.90 | 4.9 | 3.59 ± 1.79 | 0.16 |
| αTE | 0.05 | 0.37 | 0.78 | 0.42 ± 0.43 | 0.028 |
| γTE | 0.17 | 0.45 | 1.1 | 0.61 ± 0.62 | 0.028 |
| δTE | 0.04 | 0.16 | 0.38 | 0.21 ± 0.22 | 0.079 |

[1] Tissue-specific mean, minimum, and maximum length of supplementation for each organ are reported in Supplemental Table 1. Sample size for each organ is smaller than the total number of patients enrolled, because not all patients went to surgery. TCP, tocopherol; TE, tocotrienol; αTCP, α-tocopherol; αTE, α-tocotrienol; δTE, δ-tocotrienol; γTCP, γ-tocopherol; γTE, γ-tocotrienol.
[2] *P* value from Wilcoxon's Rank Sum test within respective organ, comparing the same isoform across supplementation groups, $^*P < 0.05$.
[3] TCP supplemented, $n = 4$; TE supplemented, $n = 5$.
[4] TCP supplemented, $n = 4$; TE supplemented, $n = 4$.
[5] TCP supplemented, $n = 3$; TE supplemented, $n = 5$.
[6] TCP supplemented, $n = 3$; TE supplemented, $n = 4$.
[7] ND, not detected. A numerical value of 0 was assigned to ND.

trations in the human brain (Table 1). Participants supplemented with TE had a significantly lower level of αTCP then cadaveric brains (Table 1). In heart muscle, αTE, γTE, and δTE levels were significantly higher in TE-supplemented patients compared to participants receiving TCP alone (Table 1). Heart α- and γTCP concentrations did not differ between treatment groups (Table 1). TE supplementation also significantly increased liver αTE, γTE, and δTE concentrations compared to patients supplemented with TCP (Table 1). However, similar to prior small animal research that examined dietary TE supplementation (3,17), the hepatic αTE concentration was markedly lower than αTCP in the liver of TE-supplemented patients. Unlike heart muscle and adipose tissues, the liver tissue of TCP-supplemented patients compared to their TE counterparts had significantly higher αTCP concentrations (Table 1). Although the concentrations of αTE, γTE, and δTE in liver tissue were <10% that found in adipose (Table 1), each isoform was detected in liver of TE-supplemented participants.

The MELD scoring system is clinically used to determine the severity of chronic liver disease and assess the priority and need for liver transplant allocation (22). We observed that oral TE supplementation blunted the time-dependent rise in MELD score compared to TCP-supplemented patients. Of the participants supplemented with TCP, only one patient (20%) showed improvement (i.e., lowering) in MELD score (**Fig. 3***A*). In contrast, 7 of the 14 (50%) participants supplemented with TE had a reduction in MELD score (Fig. 3*B*). Indeed, the slope of the mean fitted MELD score over time for TE-supplemented patients was significantly less than that of TCP-supplemented patients (Fig. 3*C*). This effect was most evident in patients with viral hepatic cirrhosis. When stratified on the basis of liver disease diagnosis, TE supplementation lowered the MELD score in 4 of 6 (67%) hepatitis C patients and the single hepatitis B patient (**Supplemental Table 2**).

## Discussion

To date, the majority of vitamin E clinical trials have reported negligible or detrimental outcomes across a range of diseases (23–27). Although title claims of these trials address vitamin E as a whole, they have primarily been focused to test only one of eight naturally occurring vitamin E family members, αTCP (28). With a growing body of literature demonstrating unique biological properties of the lesser-characterized vitamin E family members, the misnomer that αTCP and vitamin E are synonymous represents a blind spot in vitamin E research today. Members of the vitamin E family regulate specific cell signaling pathways independent of their antioxidant properties (29,30). αTE suppresses the activity of 3-hydroxy-3-methylglutary-CoA reductase, the hepatic enzyme responsible for cholesterol synthesis (31,32). Furthermore, TE, but not TCP, have been shown to suppress growth of human breast cancer cells (33). To date, the reported neuroprotective properties of αTE are the most potent function of any natural form of vitamin E on a concentration basis. At the nanomolar concentration range, αTE, but not αTCP, prevents glutamate-mediated neurotoxicity (5,12,13,15,34). Although orally supplemented TE circulate at one-tenth the concentration of TCP in blood, they are delivered in sufficient quantity to attenuate stroke-induced brain injury (5,10). Unlike the higher concentrations needed to combat oxidant insult, signaling regulatory functions of TE may therefore be executed at lower nanomolar concentrations (13–15).

In the current work, oral TE supplementation increased αTE in every vital organ tested, including brain. The whole blood αTE concentration following long-term oral supplementation is consistent with previously reported results (16). Importantly, the observed αTE concentration circulating in blood is 20-fold higher than that needed to afford neuroprotection (5). Indeed, αTE has demonstrated potent neuroprotective effects at the concentration detected in human brain tissue following oral supplementation (1,5,12,13,15). To our knowledge, this work is the first to demonstrate that oral TE supplementation increases tissue levels beyond therapeutic levels, suggesting that dietary TE may play an important role in human health.

As in other vital organs tested, the initial goal of collecting liver from transplant patients was to determine tissue TE content following long-term oral supplementation. On the basis of clinical feedback that TE-supplemented patients had a slower rise in MELD scores compared to TCP-supplemented patients, we were led to amend the trial to test the significance of TE on MELD score outcomes in ESLD patients. The MELD score was introduced in 1999 to quantify the prognosis of cirrhotic patients after transjugular intrahepatic portosystemic shunt (22). The MELD scale ranges from 6 to 40, with the highest scores indicating poor liver function and greater need for a transplantation surgery. The 3-mo mortality of ESLD patients with MELD scores in the range of 10–19, 20–29, 30–39, and >40 are 6.0, 19.2, 52.6, and 71.3%, respectively (35). The effect of oral TE on attenuating the time-dependent rise of MELD was most evident in patients with viral hepatic cirrhosis. A review of the recent literature on ESLD reveals the potential clinical impact of this finding. Of 124 ESLD patients evaluated in a study to assess variability of MELD score during the year before transplantation, the authors concluded that MELD score is a reliable marker for mortality, because it does not decrease over time. In fact, only 1 patient of the 124 reviewed had a reduction in MELD score > 5 (36). In the current study, 50% of ESLD participants receiving oral TE supplementation had a reduction in their MELD score. In contrast, a study by Huo et al. (37) demonstrated that participants receiving standard-of-care treatment had only a 16% reduction in MELD over time. Oral TE supplementation demonstrated promising effect in patients with viral hepatitis. Of the ESLD patients in the TE-supplemented group, 4 of 6 participants with hepatitis C and the sole participant with hepatitis B had a reduced MELD score following treatment. The importance of this observation is highlighted by a study comparing MELD scores in hepatitis C cirrhosis patients treated with or without standard-of-care therapy. Of 129 patients eligible, 66 received peginterferon, alfa-2b, and ribavirin for 24 wk, while 63 patients received no treatment. MELD scores for treated patients decreased significantly after 24 wk of therapy (14.1 ± 2.9 vs. 10.5 ± 2.3), whereas patients in the untreated control group had an increase in MELD score (14.5 ± 3.4 vs. 16.7 ± 3.2). However, only 27 patients in the treated group tolerated therapy, 26 patients had their dose reduced due to toxicity, and 13 patients had treatment discontinued due to intolerance. Despite such adverse effects, the authors conclude that in decompensated cirrhotics, hepatitis C virus clearance by therapy is life-saving and reduces disease progression (38). We recognize that the current work is limited by a small sample size. However, the outcomes of the work demonstrate the need for a double-blinded, prospective, clinical trial to test the therapeutic potential of TE in adjunctive therapy to either slow disease progression or allow a reduction in therapy in patients who do not tolerate standard therapeutic measures.

This work provides evidence on tissue availability of TE in vital organs of adult humans following oral supplementation and is the first to our knowledge to characterize multiple vital organ concentration of TCP in adults. The most effective method to acquire human vital organ tissue for determination of vitamin E content following oral TE supplementation was to enroll patients

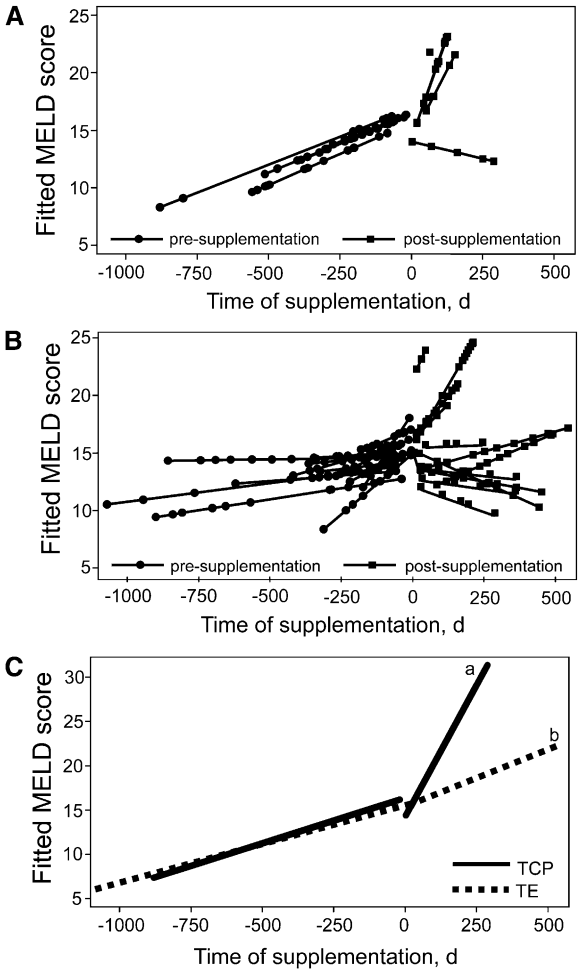


**FIGURE 3** Individual fitted MELD scores of ESLD patients supplemented with TCP (*A*) and TE (*B*) and mean fitted MELD scores of both groups (*C*). Data are the progression of MELD score relative to time. No significant difference was found in the mean fitted MELD score slope prior to supplementation. Within each postsupplementation group, mean fitted MELD score slopes without a common letter differ, $P < 0.05$. ESLD, end-stage liver disease; MELD, model for end-stage liver disease; TCP, tocopherol; TE, tocotrienol.

scheduled for target organ surgery. Logistical challenges of conducting research in a preoperative surgical patient population included enrollment of patients who never went to surgery. Another limitation of using a surgical population was not being able to tightly control for the length of oral supplementation prior to surgery. Such challenges contributed to a lengthy period of investigation lasting over 5 y. Although these weaknesses are recognized, patients supplemented for even the shortest duration had detectable levels of TE in tissue. That TE was delivered and accumulated in vital human organs supports future studies to identify specific mechanisms of tissue delivery and metabolism. The outcomes of this work provide clear evidence that oral TE supplementation enriches its concentration in whole blood, adipose, skin, brain, cardiac muscle, and liver.


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