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Serum vitamin E concentrations among highly functioning hip fracture patients are higher than in nonfracture controls

Christopher R. D'Adamo^{a,*}, Michelle D. Shardell^a, Gregory E. Hicks^b, Denise L. Orwig^a, Marc C. Hochberg^c, Richard D. Semba^d, Janet A. Yu-Yahiro^e, Luigi Ferrucci^f, Jay S. Magaziner^a, and Ram R. Miller^a

^aDepartment of Epidemiology and Public Health, University of Maryland, Baltimore, MD 21201

^bDepartment of Physical Therapy, University of Delaware, Newark

^cDepartment of Medicine, University of Maryland, Baltimore, MD

^dThe Johns Hopkins Medical Institutions, Baltimore, MD

^eDepartment of Orthopedic Research, The Union Memorial Hospital, Baltimore, MD

^fClinical Research Branch, National Institute on Aging, Baltimore, MD

Abstract

Malnutrition after hip fracture is common and associated with poor outcomes and protracted recovery. Low concentrations of vitamin E have been associated with incident decline in physical function among older adults and may, therefore, be particularly important to functionally compromised patients hip fracture patients. Serum concentrations of α -tocopherol and γ -tocopherol, the 2 major forms of vitamin E, were assessed in 148 female hip fracture patients 65 years or older from the Baltimore Hip Studies cohort 4 around the time of fracture (baseline) and at 2, 6, and 12 month postfracture follow-up visits (recovery). It was hypothesized that mean concentrations of both forms of vitamin E among these hip fracture patients would be lowest at the baseline visit and increase at each study visit during the year after fracture. Linear regression and generalized estimating equations were used to assess changes in vitamin E concentrations after adjustment for covariates and to determine predictors of vitamin E concentrations at baseline and throughout recovery. It was also hypothesized that vitamin E concentrations shortly after hip fracture would be lower than those in nonfracture controls after adjustment for covariates. To evaluate this hypothesis, linear regression was used to perform adjusted comparisons of baseline vitamin E concentrations among Baltimore Hip Studies cohort 4 participants to 1076 older women without history of hip fracture from the Women's Health and Aging Study I, Invecchiare in Chianti Study, and the National Health and Nutrition Examination Surveys. Mean α -tocopherol was lowest at baseline, and time from fracture to blood draw was positively associated with baseline α -tocopherol ($P = .005$). Mean γ -tocopherol did not change appreciably throughout the year after fracture, although it fluctuated widely within individuals. Serum concentrations of α -tocopherol and γ -tocopherol were highest among the hip fracture population after adjustment ($P < .0001$). In general, highly cognitively and physically functioning hip fracture patients

demonstrated higher vitamin E concentrations. Thus, the relatively high degree of function among this cohort of hip fracture patients may explain their higher-than-expected vitamin E concentrations.

Keywords

Vitamin E; Tocopherols; Antioxidants; Micronutrients; Hip fracture; Older women

1. Introduction

Hip fracture is a problem of increasing public health concern. Each year, there are 1.6 million hip fractures worldwide [1]; and the annual incidence is projected to more than double by the year 2050 [2], due in large part to the continuing growth of the population of older adults in whom this injury is most common. The consequences of hip fracture are severe. Between 16% and 32% of patients with hip fracture die within a year after the injury [3–5], and survivors are typically burdened with considerable physical, cognitive, and social impairments [6]. Thus, the identification of modifiable factors associated with improved recovery from hip fracture is of critical importance.

Nutritional status is one such factor with substantial implications for hip fracture recovery. Postfracture malnutrition has been associated with a wide variety of adverse outcomes, including increased risk of mortality [7], longer hospital stays [8], and impaired recovery of physical function [9]. Between 50% and 68% of hip fracture patients suffer from some form of postfracture malnutrition [8,10,11], with the most consistently identified areas of malnutrition being insufficient protein and total energy intakes. Consequently, postfracture nutritional interventions have focused almost exclusively on increasing protein and total energy intakes. These studies have shown mixed results in reducing mortality and improving recovery [10,12,13], and more comprehensive nutritional interventions may be necessary to improve hip fracture outcomes. Inclusion of key micronutrients may confer additional benefits, as the intake of calcium, selenium, iron, and other micronutrients has been shown to be inadequate after hip fracture [8]. However, concentrations of many other important micronutrients remain unexplored after hip fracture, including vitamin E.

Vitamin E is the collective name for the tocopherols and tocotrienols, 8 structurally related compounds with antioxidant properties [14]. α -Tocopherol is the most biologically active and abundant form of vitamin E in the body [15]. As a potent lipid-soluble antioxidant, α -tocopherol protects cell membranes from lipid peroxidation, a process in which free radicals damage the cell membrane and compromise cellular function and communication [15]. This antioxidant activity is one mechanism that has been proposed for the associations noted between both high intake and serum concentrations of α -tocopherol and lower risk of cardiovascular disease [16], cancer [17], Alzheimer's disease [18], and other chronic illnesses [19]. Although not yet studied as extensively as α -tocopherol, an increasing amount of research has focused on the γ -tocopherol form of vitamin E. In recent observational studies, high concentrations of γ -tocopherol were more strongly associated with reduced risk of colorectal and prostate cancers than α -tocopherol [20,21]. Higher concentrations of γ -tocopherol have also been associated with lower risk of cardiovascular

disease [22]. These associations may be due to the powerful anti-inflammatory effects of γ -tocopherol, which has been shown to inhibit tumor necrosis factor α , nitrogen oxides, and the cyclooxygenase 2 enzyme [23].

These strong antioxidant and anti-inflammatory properties suggest that vitamin E may play a particularly important role in hip fracture recovery. The persistent generation of reactive oxygen species [24] and inflammatory cytokines [25] shown to occur after bone fractures may be ameliorated by the presence of vitamin E. Both high intake and serum concentrations of α -tocopherol have been shown to be associated with reduced risk of many common sequelae of hip fracture, including decreased physical function [26], incident frailty [27], sarcopenia [28], bone loss [29], and cognitive decline [30]. High serum concentrations of γ -tocopherol have also been associated with lower risk of muscle weakness among older adults [31]. High serum vitamin E concentrations appear to offer protection against many of the sequelae of the hip fracture injury that contribute to protracted recovery and lasting impairments. Furthermore, hip fracture might deplete serum vitamin E even in the absence of the deleterious dietary changes shown to occur after fracture. Serum concentrations of α -tocopherol have been found to be nearly completely depleted after instances of bodily trauma [32] and major surgical procedures [33]. Hip fracture is a traumatic injury that is most often surgically repaired, and all participants in Baltimore Hip Studies cohort 4 (BHS4) had the hip fracture surgically repaired before baseline vitamin E assessment. Thus, it is postulated that vitamin E levels are likely to be depleted in hip fracture patients.

In light of the previous findings about vitamin E among older adults and the possibility of its depletion after fracture, the primary aim of this study was to examine how serum α -tocopherol and γ -tocopherol concentrations change throughout the year after hip fracture. We hypothesized that both α -tocopherol and γ -tocopherol would be lowest at the baseline visit and increase at each subsequent visit throughout the year after hip fracture. These serum α -tocopherol and γ -tocopherol concentrations have been previously correlated with dietary intake of vitamin E [26,34,35], and our findings may have dietary implications in hip fracture recovery. Consequently, we also sought to identify subpopulations of hip fracture patients at particularly high risk for low vitamin E concentrations throughout the year after fracture and to examine whether hip fracture patients have lower serum tocopherol concentrations at the time of fracture than community-dwelling older adults with no history of hip fracture. We hypothesized that the hip fracture sample would have lower serum vitamin E concentrations than nonfracture controls after adjustment for age, body mass index (BMI), difficulty preparing meals, and other important covariates.

2. Methods and materials

2.1. Study subjects

The hip fracture sample consisted of participants from the fourth cohort of the Baltimore Hip Studies (BHS4); a randomized clinical trial designed to assess the effects of an exercise intervention in comparison with usual care in reducing bone and muscle loss after hip fracture, described in detail elsewhere [36]. BHS4 enrolled 180 community-dwelling older women who had a hip fracture from 1 of 3 hospitals in the metropolitan area of Baltimore, Md, between 1998 and 2004. Eligibility criteria included surgical repair of the hip fracture,

the ability to walk independently before fracture, no medical conditions contraindicated with exercise, and a score 20 or higher on the mini-mental state examination (MMSE) [37]. Eligible patients who agreed to participate were randomly assigned to a supervised home exercise intervention or usual care. Assessments consisting of an interview, functional measurements, and blood draw were conducted by research nurses at baseline (15 days postfracture) and 2, 6, and 12 months postfracture. Vitamin E measurements were obtained from 148 unique BHS4 participants in whom a blood sample was successfully drawn at 1 or more study visit. The study was approved by the Institutional Review Boards of the University of Maryland and individual study hospitals, and participants provided informed consent.

The comparison samples (non-hip fracture controls) were composed of participants from the Women's Health and Aging Study I (WHAS), Invecchiare in Chianti Study (InCHIANTI), and National Health and Nutrition Examination Surveys (NHANES). WHAS consisted of 1002 moderately to severely disabled community-dwelling women 65 years or older living in the Baltimore metropolitan area enrolled between 1992 and 1995 [38]. InCHIANTI studied community-dwelling older adults in the Chianti area of Tuscany, Italy. Baseline data were collected from 1453 participants in 1998 [39]. Each NHANES, conducted by the National Center for Health Statistics of the Centers for Disease Control, was a 2-year, cross-sectional survey of approximately 10 000 community-dwelling participants [40]. The 3 NHANES (1999–2000, 2001–2002, and 2003–2004) most closely corresponding to the period of study for BHS4 were used.

Because vitamin E concentrations have been shown to vary by demographics [34], cognitive status [41], and other factors [34], the comparison samples were restricted on these and other covariates to be as similar as possible to the hip fracture sample aside from history of hip fracture. History of hip fracture was the first restriction criterion, as this was the primary variable of inferential comparison in this analysis. All comparison samples were restricted to conform to the eligibility criteria for BHS4 including: community-dwelling women 65 years or older and absence of medical conditions such as cancer and Parkinson disease. NHANES did not administer the MMSE, so we were unable to restrict all samples to an MMSE score of 20 or higher. Instead, all samples were restricted to participants without cognitive impairment. This corresponds to either an MMSE score of 24 or higher [42] or Wechsler Digit-Symbol Substitution task [43] score of 30 or higher [44]. Participants with scores below these cut points were excluded from the analysis. All samples were also restricted to white race and to those who were not morbidly obese ($\text{BMI} < 35 \text{ kg/m}^2$) because nearly 95% of BHS4 participants were white and none had BMI greater than 35 kg/m^2 . Lastly, we restricted the analysis to participants who had a serum vitamin E measurement.

After restriction on these criteria, the final sample for the comparison analysis was 1161, consisting of 81 participants from BHS4, 290 from WHAS, 307 from InCHIANTI, and 483 from NHANES.

2.2. Vitamin E measurement

Blood samples were obtained by venipuncture, and serum vitamin E concentrations were measured from frozen samples by reverse-phase, high-pressure liquid chromatography in all

4 comparison studies. BHS4, InCHIANTI, and NHANES assessed both α -tocopherol and γ -tocopherol, whereas WHAS measured α -tocopherol alone. The BHS4, InCHIANTI, and WHAS samples were analyzed in the laboratory of Dr Richard Semba at Johns Hopkins University (Baltimore, Md), and the NHANES samples were analyzed by The National Center for Environmental Health (Atlanta, Ga) and Craft Technologies (Wilson, NC).

2.3. Potential predictive factors of vitamin E and covariates

The relationships between the factors of interest and vitamin E concentrations were assessed throughout the year after hip fracture. The following groups of factors were measured in the BHS4 cohort either at baseline alone or at baseline and at the 2, 6, and 12 months of postfracture visits (ie, on a time-varying basis).

Physical factors included time-varying disability, as measured by instrumental activities of daily living (IADLs) [45] and lower extremity physical activities of daily living (LPADLs) [6]; time-varying physical activity measured using the Yale Physical Activity Survey (YPAS) [46]; time-varying physical function measured using the Short Form 36 Physical Functioning Domain (SFPPF) [47]; time-varying comorbidity measured using the Charlson Comorbidity Index [48]; baseline BMI; and baseline history of osteoarthritis obtained from medical records. Psychosocial factors included time-varying depressive symptoms measured using the Geriatric Depression Scale (GDS) [49] and baseline MMSE score. Demographic factors, assessed at baseline, included age at time of fracture and years of education. Lastly, lifestyle factors included time-varying current cigarette smoking status, baseline meal preparation difficulties, and time-varying usage of lipid-lowering medications (statins and fibrates).

We also examined the relationship between time from hip fracture to baseline blood draw and serum tocopherol concentrations to determine whether vitamin E was lower among those whose blood was drawn closer to the fracture. There is evidence to suggest that high intake and serum concentrations of α -tocopherol might deplete serum γ -tocopherol [50], and we determined whether such an inverse relationship in serum concentrations occurs after hip fracture.

The comparison of vitamin E concentrations between study populations was adjusted for potential confounding factors. These included age, BMI, education (high school or more vs less than high school), cigarette smoking, and meal preparation difficulties. The relationship between α -tocopherol and γ -tocopherol was also assessed.

2.4. Statistical analyses

Descriptive analyses were performed to characterize vitamin E concentrations and the predictors of interest throughout the year after hip fracture as well as in each of the comparison samples. Individual trajectories of BHS4 participants were plotted to graphically illustrate changes in vitamin E concentrations within individuals in the hip fracture cohort over time.

Linear regression and generalized estimating equations (GEE) were used to assess the extent to which serum vitamin E concentrations changed during the year after hip fracture and to

determine factors associated with these serum concentrations. Two sets of models were constructed for both α -tocopherol and γ -tocopherol. The first set used linear regression to model vitamin E around the time of fracture (baseline concentrations) and included baseline values of the factors described previously. Baseline values of IADLs, LPADLs, YPAS, SPPF, and meal preparation difficulties referred to the 2-week period before hip fracture. The second set of analyses used GEE to model vitamin E during recovery from hip fracture (2, 6, and 12 months of postfracture concentrations) and included time-varying factors during this recovery period and time of visit. Vitamin E concentrations were expected to be correlated within individuals over time, and GEE were used to account for this within-subject correlation.

Linear regression was used to compare the baseline vitamin E concentrations in BHS4 to those in NHANES, InCHIANTI, and WHAS while simultaneously adjusting for the covariates described previously. The α -tocopherol concentrations in BHS4 were compared with those in NHANES, InCHIANTI, and WHAS, whereas the γ -tocopherol concentrations in BHS4 were compared with those in NHANES and InCHIANTI.

NHANES did not collect MMSE, IADL, or depressive symptom data among older adults; and these covariates were not included in the main α -tocopherol and γ -tocopherol comparison models. To determine whether differences in these covariates might explain potential differences in vitamin E concentrations from BHS4, sensitivity analyses were conducted excluding NHANES data and including these covariates. These models compared α -tocopherol concentrations in BHS4 with those in InCHIANTI and WHAS and γ -tocopherol concentrations in BHS4 with those in InCHIANTI.

$P \leq .05$ was considered statistically significant, and $P > .05$ and $P \leq .10$ were considered marginally statistically significant. All analyses were performed using SAS version 9.1 (SAS Institute, Inc, Cary, NC).

3. Results

Table 1 presents descriptive characteristics of the hip fracture sample throughout the year after fracture. The hip fracture sample consisted of 148 women with mean age 82.3 ± 7.0 years, mean 12.2 ± 3.7 years of education, and mean MMSE 26.8 ± 2.6 . Self-reported disability, physical activity, physical function, and meal preparation difficulties were markedly worsened at 2 months postfracture vs baseline (the 2-week period before the fracture) but generally displayed a monotonic increase throughout the recovery period (2–12 months). Mean serum α -tocopherol in the hip fracture sample was lowest at baseline, increased by 2 months, and remained relatively constant throughout the remainder of the study. Conversely, serum γ -tocopherol was highest at baseline, decreased slightly by 2 months, and was fairly constant throughout the other study visits.

Despite the relatively stable mean concentrations of both forms of vitamin E from 2 to 12 months postfracture, there were large fluctuations in vitamin E concentrations within individuals and substantial heterogeneity in the pattern of change in concentrations between individuals throughout the year after fracture. The fluctuations and heterogeneity of change

are reflected in the large SDs and wide range of changes in vitamin E concentrations from baseline to 2 months, 2 to 6 months, and 6 to 12 months that are provided in Table 2.

Table 3 shows the associations between the factors of interest and vitamin E concentrations. α -Tocopherol and γ -tocopherol were negatively associated with each other at baseline ($P = .009$) and throughout recovery ($P = .1$). Longer time from fracture to baseline blood draw was associated with higher baseline α -tocopherol ($P = .005$). Higher MMSE scores were associated with higher α -tocopherol concentrations at baseline ($P = .0002$) and throughout recovery ($P = .05$). Higher BMI was marginally associated with higher γ -tocopherol concentrations at baseline ($P = .08$) and throughout recovery ($P = .09$). Several factors were negatively associated with both α -tocopherol and γ -tocopherol concentrations at baseline, including LPADLs (α -tocopherol, $P = .003$; γ -tocopherol, $P < .0001$) and current smoking status (α -tocopherol, $P = .02$; γ -tocopherol, $P = .01$). However, difficulty preparing meals was negatively associated with α -tocopherol ($P = .08$) and positively associated with γ -tocopherol ($P = .02$) during recovery.

The comparison samples are described in Table 4. Mean α -tocopherol and γ -tocopherol concentrations were highest in the BHS4 cohort. The fracture and nonfracture samples were generally similar with respect to most covariates, with the exception of education, smoking status, and meal preparation difficulties. Fewer InCHIANTI participants had at least a high school education, a greater percentage of WHAS participants had depressive symptoms, more NHANES participants were current smokers, and fewer InCHIANTI and NHANES participants experienced difficulties preparing meals.

Table 5 displays the adjusted comparisons of serum vitamin E concentrations between the study samples. After adjustment for age, education, BMI, current smoking status, and difficulty preparing meals, baseline α -tocopherol concentrations in the BHS4 cohort were the highest of the 4 comparison samples. Both InCHIANTI and WHAS had significantly lower average α -tocopherol concentrations (-12.3 and $-18.8 \mu\text{mol/L}$, respectively; $P < .0001$), whereas NHANES did not significantly differ (-1.44 ; $P = .4$) from BHS4. Baseline γ -tocopherol concentrations in the BHS4 cohort were also the highest among the comparison samples. γ -Tocopherol concentrations in both InCHIANTI and NHANES were significantly lower (-3.42 and $-6.82 \mu\text{mol/L}$, respectively; $P < .0001$) than those in BHS4 after adjustment for covariates.

4. Discussion

This study found that serum vitamin E concentrations change considerably throughout the year after hip fracture. Unadjusted mean α -tocopherol concentrations were lowest around the time of fracture and increased to a relatively stable level by 2 months. Conversely, mean γ -tocopherol concentrations were highest around the time of fracture, although the difference at subsequent time points was smaller. Although the most substantial changes in mean α -tocopherol and γ -tocopherol concentrations occurred between baseline and 2 months, vitamin E concentrations fluctuated within individuals throughout the entire year after fracture, especially for γ -tocopherol. These within-individual changes in vitamin E concentrations suggest that, despite some evidence that eating patterns remain relatively

constant over time among older adults in general, there may be great variability in dietary intake over time among older women recovering from hip fracture. However, there may be other factors unrelated to diet that could influence the fluctuation in vitamin E concentrations. Future studies that assess dietary intake after hip fracture are necessary to more conclusively determine why these fluctuations over time and heterogeneity in patterns of change in vitamin E concentrations occur.

A number of meaningful predictors of postfracture vitamin E concentrations were identified. Time from fracture to baseline blood draw was the strongest predictor of baseline α -tocopherol concentrations, which were lower when blood was drawn sooner. One explanation for this result is that the trauma of the hip fracture experience (which includes broken bone, damaged muscle, and surgical trauma) may deplete circulating levels of vitamin E. Such an explanation would corroborate previous literature that found that traumatic events greatly deplete serum levels of α -tocopherol.

An inverse relationship was also found between the α -tocopherol and γ -tocopherol forms of vitamin E both at baseline and throughout hip fracture recovery. This relationship may be explained by prior research showing that high dosages of α -tocopherol deplete γ -tocopherol concentrations [50]. Depletion of γ -tocopherol has been offered as a potential explanation for the discrepancy between the health-protective effects of α -tocopherol in observational studies and null findings of most vitamin E interventions, which exclusively supplemented high dosages of α -tocopherol [51].

A number of other factors, including age, cognitive status, physical functioning, and BMI, were found to be positively associated with either α -tocopherol or γ -tocopherol. Even among this highly cognitively functioning cohort of hip fracture patients, cognitive status was the strongest predictor of α -tocopherol during recovery from fracture. Few factors were associated with both forms of vitamin E, and the disparate sets of predictive factors further highlight the differences between α -tocopherol and γ -tocopherol. Current smoking status and difficulty preparing meals were the only factors associated with both α -tocopherol and γ -tocopherol. Collectively, the predictive factors might describe a relatively healthy and highly functioning hip fracture patient. Such an individual would likely be better equipped to shop for groceries, prepare healthy meals, and others, thereby resulting in higher vitamin E concentrations.

Consequently, it was an unexpected finding that baseline vitamin E concentrations in the hip fracture cohort were the highest of the comparison samples after adjustment for covariates. Hip fracture is a traumatic injury associated with persistent decline in physical function. Thus, it was hypothesized that the BHS4 cohort would have the lowest concentrations of the comparison samples, especially given that the comparison was made using the baseline measurements where vitamin E was lowest. Among the comparison samples, the greatest disparity in vitamin E concentrations occurred between BHS4 and WHAS. Vitamin E concentrations were hypothesized to be the most similar in these samples, as both studies were conducted in Baltimore and regional differences in diet seemed unlikely. It is doubtful that measurement differences account for this discrepancy, as vitamin E analyses were conducted in the same laboratory in BHS4, WHAS, and InCHIANTI.

However, there are several plausible explanations for these surprising findings. The first of which is that the BHS4 sample was a relatively highly functioning cohort (only 20% of screened hip fracture patients met the BHS4 inclusion criteria) that may not be representative of typical hip fracture patients. Typically less robust patients with hip fracture may experience greater difficulties shopping and preparing meals that could result in lower vitamin E concentrations. However, it is unlikely that this is the primary cause of the higher vitamin E concentrations in the hip fracture sample, as BHS4 and WHAS experienced similar IADLs and difficulties preparing meals yet had vastly different α -tocopherol concentrations. A second potential explanation is that there were differences in serum lipid concentrations between the hip fracture sample and the comparison samples. One of the limitations of this analysis is that BHS4 did not collect serum lipid data. Serum lipids transport vitamin E throughout circulation and are strong predictors of both α -tocopherol and γ -tocopherol. We found that higher serum levels of low-density lipoprotein, high-density lipoprotein, and triglycerides were positively associated with α -tocopherol and γ -tocopherol in the InCHIANTI, WHAS, and NHANES samples (results not shown). It is expected that higher serum lipids would also be associated with higher vitamin E concentrations among hip fracture patients. Inclusion of lipids in the predictive models of vitamin E concentrations among the comparison samples showed that low-density lipoprotein and triglycerides were mild confounders of the relationships between age, education, and α -tocopherol, weakening these associations by 10% to 20%. Such confounding is unlikely to substantially change our conclusions, as neither age nor education was meaningfully associated with α -tocopherol among hip fracture patients; and serum lipids did not appear to confound the associations with any other predictors of α -tocopherol and γ -tocopherol.

Perhaps, the most likely explanation for the discrepancy in adjusted α -tocopherol concentrations is the differing prevalence of vitamin E supplementation across the comparison samples. An analysis of the comparison samples revealed that vitamin E supplementation was very low (<1%) in both InCHIANTI and WHAS and considerably higher (>10%) in NHANES. This is an important consideration as vitamin E supplementation has been shown to greatly increase serum concentrations of α -tocopherol. InCHIANTI and WHAS had the lowest mean serum vitamin E concentrations and no participants with α -tocopherol concentrations greater than 60 $\mu\text{mol/L}$, a very high level most likely obtained through supplementation. Conversely, mean α -tocopherol concentrations in NHANES were similar to those in BHS4; and there was a similar prevalence of α -tocopherol concentrations greater than 60 $\mu\text{mol/L}$ in NHANES and BHS4 (10% and 8%, respectively). Although BHS4 did not assess vitamin E supplementation, a high percentage of the hip fracture sample consumed other dietary supplements (>70% took vitamin D and nearly 50% took calcium); and it is likely that vitamin E supplementation was also higher in BHS4 than InCHIANTI and WHAS where dietary supplementation was uncommon. The reasons for the higher γ -tocopherol concentrations among the hip fracture cohort are less clear. High BMI and less disability were the primary predictors of higher γ -tocopherol concentrations among the hip fracture cohort, and adjustments were made for these covariates, the comparison with nonfracture controls. Differences in supplemental intake are

also an unlikely cause of the disparity, as most vitamin E supplements contain only the α -tocopherol form and may actually deplete γ -tocopherol.

Although the explanation for the higher vitamin E concentrations identified among hip fracture patients as compared with similar nonfracture controls is currently unclear, this was the first study to assess changes in vitamin E concentrations over time in a cohort of hip fracture patients. This study was also one of the first longitudinal analyses of vitamin E in any cohort of older adults, as most previous studies have been limited by vitamin E measurements at a single time point. Associations with outcomes in prior work have generally been studied either cross-sectionally or years later, presumably under the assumption that dietary patterns remain fairly constant among older adults. One of the strengths of this analysis was the availability of serum vitamin E data at multiple time points during the year after fracture. These data enabled us to track changes over time, which, given the relatively short half-lives of vitamin E, were suggestive of widely fluctuating dietary patterns during recovery from fracture. This study was also novel in that it was the first to conduct adjusted comparisons of concentrations of any dietary antioxidant between different study samples of older adults. The comparison populations used in this analysis were derived from large studies with rich data allowing for adjustment on a number of important covariates. Most of the samples studied contained both α -tocopherol and γ -tocopherol, and this study will add to the growing body of literature including the γ -tocopherol form of vitamin E.

Although the high concentrations of both α -tocopherol and γ -tocopherol among hip fracture patients uncovered in this study do not suggest a relative deficiency of vitamin E after fracture as was hypothesized, further study exploring the reasons for these high concentrations is warranted, as serum vitamin E is an important predictor of disability among older adults. Future efforts should include hip fracture patients with a more typical burden of disability, address dietary intake patterns after fracture to allow for direct correlation between intake and serum concentrations that was not possible in this study, and measure serum lipids to assess whether these factors play a determinative role in the high concentrations identified throughout the year after hip fracture. In the interim, our results suggest that vitamin E concentrations should be monitored among hip fracture patients experiencing difficulty preparing meals as well as those exhibiting poor cognitive and physical function.

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Abbreviations

BHS4	Baltimore Hip Studies cohort 4
BMI	body mass index
GDS	Geriatric Depression Scale

GEE	generalized estimating equations
IADLs	instrumental activities of daily living
InCHIANTI	Invecchiare in Chianti Study
LPADLs	lower extremity physical activities of daily living
MMSE	mini-mental state examination
NHANES	National Health and Nutrition Examination Survey
SFPP	Short Form 36 Physical Functioning Domain
WHAS	Women's Health and Aging Study I
YPAS	Yale Physical Activity Survey

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Table 1

BHS4 participant characteristics

Characteristic	Baseline	2 mo	6 mo	12 mo
	Mean (SD), n	Mean (SD), n	Mean (SD), n	Mean (SD), n
Age at fracture (y)	82.0 (6.9), 148	–	–	–
Education (y)	12.2 (3.7), 146	–	–	–
Charlson Comorbidity Index (no. of comorbidities)	1.1 (1.3), 148	–	–	–
BMI (kg/m ²)	23.9 (4.2), 143	–	–	–
MMSE ^a score	26.8 (2.6), 148	–	–	–
IADLs ^a (no. of limitations) ^b	1.1 (1.3), 143	2.8 (1.4), 116	2.0 (1.5), 126	1.9 (1.6), 124
LPADLs ^a (no. of limitations) ^b	1.9 (2.0), 148	6.5 (2.8), 132	4.5 (2.8), 134	4.1 (2.8), 132
GDS ^a score	2.4 (2.6), 147	3.4 (2.8), 130	2.9 (2.6), 134	3.3 (2.9), 132
Total activity time of YPAS ^a (h) ^b	25.0 (18.1), 147	13.5 (13.0), 131	19.7 (13.4), 133	18.8 (13.6), 133
SFPF ^a (points) ^b	65.7 (26.0), 148	30.1 (21.0), 132	45.0 (25.6), 134	49.8 (28.6), 133
α -Tocopherol (μ mol/L)	44.0 (11.9), 96	51.8 (16.6), 96	50.5 (15.9), 108	50.6 (15.1), 92
γ -Tocopherol (μ mol/L)	8.3 (4.2), 96	7.7 (3.6), 96	8.1 (4.1), 108	7.6 (3.9), 92
		Yes, n (%)		
History of osteoarthritis	148 (39.2%)	–	–	–
Current smoker	148 (6.0%)	132 (5.3%)	134 (5.2%)	133 (3.8%)
Lipid-lowering medications	147 (12.9%)	145 (8.3%)	142 (8.5%)	141 (11.3%)
Difficulty preparing meals ^b	148 (18.2%)	132 (59.1%)	134 (40.3%)	133 (39.9%)

^a Higher MMSE, GDS, YPAS, and SFPF scores indicate better function; lower IADLs and LPADLs indicate better function.

^b Baseline values refer to 2-week period before hip fracture.

Table 2

Change in vitamin E concentrations during year after hip fracture

Variable	<u>Change from baseline to 2 mo</u>	<u>Change from 2 to 6 mo</u>	<u>Change from 6 to 12 mo</u>
	Mean (SD), range	Mean (SD), range	Mean (SD), range
α -Tocopherol ($\mu\text{mol/L}$)	6.1 (7.7), -11.9 to 25.9	-1.9 (8.9), -44.0 to 16.2	0.7 (10.2), -21.6 to 50.6
γ -Tocopherol ($\mu\text{mol/L}$)	0.3 (3.3), -6.7 to 17.3	0.1 (2.6), -7.1 to 6.0	-0.2 (2.5), -10.7 to 9.1

Table 3

Adjusted associations between factors and vitamin E concentrations

Predictor	β Coefficient for α-tocopherol ^a (95% CI) (P)		β Coefficient for γ-tocopherol ^b (95% CI) (P)	
	Baseline	Recovery	Baseline	Recovery
α -Tocopherol (μ mol/L)	–	–	–0.062 (–0.11 to –0.016) (.009)	–0.029 (–0.068 to 0.01) (.1)
γ -Tocopherol (μ mol/L)	–0.34 (–0.60 to –0.09) (.009)	–0.52 (–1.19 to 0.17) (.1)	–	–
Time to baseline blood draw (d)	0.50 (0.15–0.85) (.005)	–	0.055 (–0.097 to 0.21) (.5)	–
Age (y)	–0.023 (–0.20 to 0.15) (.8)	–0.51 (–0.23 to 0.55) (.4)	0.10 (0.027–0.17) (.008)	0.026 (–0.088 to 0.14) (.7)
BMI (kg/m ²)	–0.025 (–0.30 to 0.25) (.9)	–0.27 (–0.87 to 0.33) (.4)	0.11 (–0.014 to 0.22) (.08)	0.13 (–0.019 to 0.28) (.09)
MMSE score	1.02 (0.49–1.56) (.0002)	1.09 (–0.022 to 2.21) (.05)	0.14 (–0.09 to 0.37) (.2)	–0.098 (–0.37 to 0.18) (.5)
LPADLs (no. of limitations) ^c	–1.17 (–1.92 to –0.41) (.003)	–0.25 (–1.64 to 1.15) (.7)	–0.74 (–1.06 to –0.43) (<.0001)	–0.22 (–0.52 to 0.075) (.1)
IADLs (no. of limitations) ^c	–0.30 (–1.71 to 1.10) (.7)	0.85 (–1.21 to 2.91) (.4)	–0.51 (–1.10 to 0.088) (.09)	–0.54 (–1.06 to –0.021) (.04)
SFPP (points) ^c	–0.021 (–0.086 to 0.044) (.5)	0.02 (–0.10 to 0.14) (.7)	–0.073 (–0.10 to –0.047) (<.0001)	–0.031 (–0.072 to 0.011) (.1)
Current smoker (yes vs no)	–5.37 (–9.92 to –0.82) (.02)	11.0 (–3.05 to 25.0) (.1)	–2.53 (–4.47 to –0.59) (.01)	2.00 (–2.51 to 6.52) (.4)
Difficulty preparing meals (yes vs no)	–1.76 (–6.50 to 2.98) (.47)	–4.96 (–10.59 to 0.67) (.08)	1.41 (–0.61 to 3.43) (.2)	1.71 (0.27–3.16) (.02)

Bold text signifies $P < .05$. CI indicates confidence interval.^a Adjusted mean difference in α -tocopherol per unit of factor.^b Adjusted mean difference in γ -tocopherol per unit of factor.^c Baseline values refer to 2-week period before hip fracture.

Table 4

Comparison population participant characteristics

Variable	BHS4	InCHIANTI	WHAS	NHANES
	Mean (SD), n	Mean (SD), n	Mean (SD), n	Mean (SD), n
α -Tocopherol ($\mu\text{mol/L}$)	44.4 (11.3), 81	31.8 (8.5), 303	24.8 (10.2), 290	44.0 (18.4), 483
γ -Tocopherol ($\mu\text{mol/L}$)	8.2 (4.3), 81	1.6 (0.7), 303	–	4.9 (3.5), 483
Age (y)	80.1 (6.6), 81	73.7 (6.6), 307	77.6 (7.4), 277	75.0 (6.3), 483
BMI (kg/m^2)	24.3 (3.9), 79	27.6 (4.5), 295	28.5 (6.1), 271	27.4 (5.6), 459
IADLs (no. of limitations)	0.8 (1.2), 79	0.4 (1.2), 307	0.9 (1.2), 290	–
MMSE score	27.5 (1.8), 81	26.6 (1.8), 307	27.8 (1.9), 290	–
<i>Yes, n (%)</i>				
High school education or more	81 (75.3%)	307 (9.8%)	290 (42.8%)	483 (78.3%)
Depressive symptoms (GDS 6 or CES-D 16)	81 (13.6%)	307 (19.9%)	290 (28.3%)	–
Current smoker	81 (7.4%)	307 (10.1%)	290 (12.1%)	186 (19.4%)
Difficulty preparing meals	81 (13.6%)	307 (4.2%)	290 (12.4%)	483 (4.6%)

Table 5

Adjusted vitamin E population comparisons

Study sample	β Coefficient ^a (95% CI) (P)	
	α -Tocopherol	γ -Tocopherol
BHS4	– (reference sample)	– (reference sample)
NHANES	–1.44 (–4.71 to 1.82) (.4)	–3.42 (–4.17 to –2.67) (<.0001)
InCHIANTI	–12.3 (–15.7 to –8.94) (<.0001)	–6.82 (–7.65 to –5.99) (<.0001)
WHAS	–18.8 (–21.9 to –15.7) (<.0001)	–

Model was adjusted for age, education, BMI, current smoking status, and difficulty preparing meals.

^a β Coefficient represents adjusted mean difference in tocopherol between BHS4 and comparison studies.