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ORIGINAL ARTICLE

Vitamin E and Alzheimer's disease: the mediating role of cellular aging

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Abstract

Background Vitamin E represents a potent antioxidant and anti-inflammatory system, playing a role in Alzheimer's disease (AD). Different plasma concentrations of the forms of vitamin E are observed in AD compared to cognitively healthy subjects.

Aim Since these modifications may modulate the markers of oxidative stress and cellular aging, we aim to explore the relationship between vitamin E forms and leukocyte telomere length (LTL) in AD.

Methods 53 AD subjects and 40 cognitively healthy controls (CTs) were enrolled. The vitamin E forms (α-, β-, γ- and δ-tocopherol, α-, β-, γ- and δ-tocotrienol), the ratio of α-tocopherylquinone/α-tocopherol and 5-nitro-γ-tocopherol/γ-tocopherol (markers of oxidative/nitrosative damage) and LTL were measured.

Results and discussion Regression model was used to explore the associations of vitamin E forms and LTL with AD. The interaction of LTL in the association between vitamin E forms and AD was tested. AD subjects showed significantly lower concentrations of α-, β-, γ- and δ-tocopherol, α- and δ-tocotrienol, total tocopherols, total tocotrienols and total vitamin E compared to CTs. AD subjects showed higher values of nitrosative/oxidative damage. The adjusted analyses confirmed a significant relationship of AD with plasma concentrations of α- and β-tocopherols, δ-tocotrienol, total tocopherols, total tocotrienol, total vitamin E and oxidative/nitrosative damage. However, nitrosative damage was significantly associated with AD only in subjects with higher LTL and not in those expressing marked cellular aging.

Conclusions Our study confirms the role of vitamin E in AD pathology and indicates that nitrosative damage influences the association with AD only in subjects characterized by longer LTL.

Keywords Alzheimer's disease · Vitamin E · Telomere length · Oxidative stress · Nitrosative stress

Introduction

Alzheimer's disease (AD) has become a worldwide health priority. About 47 million people today are living with AD around the world and this number is probably going to triple, up to 132 million cases, by 2050 [1]. Its pathophysiological mechanisms are still partly unknown and not adequately contextualized within the aging process. Currently, no cure for AD has been available and preventive strategies are still under debate.

A robust theoretical framework of neurodegeneration describes oxidative and/or nitrosative modifications of biological molecules as responsible for the damage of neuronal components. Such abnormalities might accompany and enhance the typical changes due to the physiological aging process.

Healthy lifestyle, based on physical activity and correct diet, seems the most powerful strategy for reducing age-related cognitive decline and potentially preventing AD. For example, a considerable consumption of nutrients with antioxidant properties reduces the rate of cognitive decline and the risk of developing dementia [2].

Vitamin E is the main lipid-soluble, chain-breaking, non-enzymatic antioxidant acting in the human body. It is represented by a family of eight natural forms that include four

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tocopherols and four tocotrienols divided into the α, β, γ and δ forms. These eight compounds have additional biological properties unrelated to the antioxidant one, being regulators of gene expression and signal transduction. For example, they also act as modulators of inflammation and cellular function via interaction with specific membrane domains [3].

Telomeres are tandem repeats that cap the end of linear chromosomes to protect them from degradation and prevent chromosome fusion. Telomeres are exposed to a progressive shortening at each cellular division, potentially causing DNA damage, replicative senescence and/or apoptosis. With aging and cellular proliferation, the leukocyte telomere length (LTL) seems to decline, thus becoming a possible marker of biological age [4]. Telomeres are also involved in neurodegeneration, and LTL has been described to be associated with cognitive decline in community dwelling older persons as well as in AD patients [4, 5]. Nevertheless, the contribution of LTL in AD pathogenesis is still unclear and under debate, since some studies showed that LTL is shorter in patients with AD [6, 7], but others have not found differences in LTL between AD and cognitively healthy subjects [8, 9].

To date, there are conflicting findings on the relationship between the different forms of vitamin E and LTL and these forms with the pathological mechanisms of AD. However, it can be hypothesized that vitamin E may exert protective effects on the LTL and slow down the cellular aging thanks to its antioxidant/anti-inflammatory properties [10, 11].

The aim of the present study is to explore vitamin E forms in AD according to markers of cellular aging and oxidative/nitrosative stress.

Materials and methods

Study design

All participants were recruited from 2014 to 2017 as outpatients referred to the Geriatric Unit of the Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico (Milan, Italy). Among all subjects examined at the geriatric unit during this period, 53 well-characterized patients with overt AD and 40 sex- and age-matched cognitively healthy subjects (CTs) with bio-banked biological samples were selected. For all participants, information about their medical history, physical examination (i.e., Hand Grip Strength test, body mass index—BMI), neurocognitive assessment (i.e., Mini Mental State Examination—MMSE, Clock Drawing Test—CDT), neuropsychological tests—NPS (i.e., Trail Making Test, verbal fluency test, digit span forward and backward tests, verbal learning tests, Token Test, Rey's figure copy and delayed recall, Raven Coloured Progressive Matrices), depression evaluation (Geriatric Depression Scale—GDS) and risk factor (smoking attitude) were collected.

The diagnosis of AD was made according to the criteria by Dubois et al. [12]. AD diagnosis was supported by brain imaging (MRI and FDG-PET) and by the assessment of β-amyloid, tau and p-tau levels.

Inclusion criteria for CTs were: an MMSE score ≥ 27, NPS test negative for dementia, no neurological or psychiatric disorders, no current medical complications or treatments that could interfere with cognitive function.

None of the participants was on vitamin E supplementation. To minimize the risk of inflammatory processes, the enrolled subjects did not show any clinical signs of inflammation and had normal plasma transferrin, albumin and C-reactive protein concentrations.

The local ethical committee approved the study, and informed consent was obtained from either patients or legal representatives.

Vitamin E levels

At the recruitment, blood samples from all subjects were collected between 8 and 9 a.m., following at least 6 h of fasting. The levels of the different vitamin E forms were measured in plasma as previously described [13]. Briefly, plasma tocopherols, tocotrienols, α-tocopherylquinone, and 5-nitro-γ-tocopherol levels were measured with reverse-phase high performance liquid chromatography (HPLC) using an electrochemical CoulArray system (ESA, Chelmsford, MA, USA) [13]. Moreover, to obtain an overview on vitamin E status, variables combining all the tocopherols (α- + β- + γ- + δ-tocopherol), tocotrienols (α- + β- + γ- + δ-tocotrienol) and vitamin E forms (all tocopherols + all tocotrienols) were also computed and analyzed. As lipoprotein metabolism influences the vitamin E distribution to all tissues of the human body, vitamin E concentrations were adjusted for total cholesterol levels [14]. The ratios of α-tocopherylquinone/α-tocopherol and 5-nitro-γ-tocopherol/γ-tocopherol were additionally used as indices of α- and γ-tocopherol consumption related to oxidative and nitrosative damage, respectively. Since α-tocopherylquinone and 5-nitro-γ-tocopherol are influenced by the smoking attitude [15, 16], we adjusted our data by this potential confounding factor.

Telomere length

LTL was assessed by means of a quantitative PCR method [17]. A comparative quantitation approach was used to define the relative ratio (T/S ratio) of telomere (T) repeat copy number to a single copy gene (S) copy number. The primer pairs, their concentration and the thermal cycling profiles were as described [17], except that the number of

amplification cycles increased to 30 and 40 for the T and S reactions, respectively. In each well, 10 ng of template DNA and 24.15 µl SYBER GREEN iQ supermix (Bio-Rad, Hercules, CA, USA) were added. The linear range of T and S assay was determined by generating a standard curve using a serially diluted DNA (from 35.4 to 4.4 ng in twofold dilutions). All q-PCR assays were performed on an ABI 7500 system (Applied Biosystems, Foster City, CA, USA). LTL was expressed as T/S ratio.

Statistical analyses

SPSS statistical package (SPSS version 25, Chicago, IL, USA) was used to conduct the statistical analyses. All the studied variables were normally distributed. Data were expressed as mean values ± standard deviation (SD). Chi square or *t* test models were used to assess the main demographic, clinical and biochemical differences between groups.

Unadjusted and adjusted logistic regression models were used to explore the relationship between the molecules of interest and the diagnosis of AD. To facilitate the comparability of the findings across biomarkers, these were rescaled per their SD increase. The interaction of LTL, α-tocopherylquinone/α-tocopherol and 5-nitro-γ-tocopherol/γ-tocopherol with vitamin E forms in the association of AD was also tested. A p value < 0.05 was considered as threshold for statistical significance.

Results

Clinical characteristics of the subjects

Table 1 displays the principal clinical characteristics of the study population. As expected, AD subjects had significantly lower MMSE and CDT scores compared to CTs.

Levels of vitamin E forms and telomere length

AD subjects showed significantly lower plasmatic concentrations of α-, β-, γ- and δ-tocopherol, α- and δ-tocotrienol, total tocopherols, total tocotrienols and total vitamin E compared to CTs (Table 2). In particular, the forms that seems to be more reduced in AD patients are α-, γ-tocopherol and δ-tocotrienol, with a percentage reduction of 20.4%, 14.0% and 61.5% than CTs, respectively.

Vitamin E oxidative/nitrosative damage indices showed that AD patients also had significantly higher values of α-tocopherylquinone/α-tocopherol and 5-nitro-γ-tocopherol/γ-tocopherol.

Table 1 Principal clinical characteristics of healthy subjects (CTs) and Alzheimer's disease (AD) patients

	CTs (n°40)	AD (n°53)	p
Age (years)	78.9 ± 5.5	78.6 ± 4.7	0.771
Gender, % female	57.5%	73.6%	0.123
MMSE score	28.9 ± 1.2	20.5 ± 5.5	**< 0.001**
CDT score	4.6 ± 0.7	2.5 ± 2.1	**< 0.001**
Hand Grip score	35 ± 19.8	29 ± 23.5	0.674
GDS score	9.3 ± 5.8	7.9 ± 5.7	0.586
BMI (kg/m^2)	25.2 ± 2.6	24.0 ± 3.6	0.268
Smoking, % (% ex)	10% (40%)	7.7% (21.2%)	0.105

Significant p values (< 0.05) are in bold

MMSE Mini-Mental State Examination, *CDT* Clock Drawing Test, *GDS* Geriatric Depression Scale, *BMI* body mass index

LTL was shorter in AD compared to CTs (0.62, SD 0.27 vs 0.71, SD 0.30), but the difference was not statistically significant.

Correlation between vitamin E forms and telomere length

Pearson's correlation analyses showed that LTL was significantly correlated with γ-tocopherol ($r = 0.205$, $p = 0.050$), total tocopherols ($r = 0.262$, $p = 0.011$) and total vitamin E ($r = 0.261$, $p = 0.012$). Only a trend was observed for α-tocopherol ($r = 0.199$, $p = 0.061$) and δ-tocotrienol ($r = 0.262$, $p = 0.062$).

Association between vitamin E forms and telomere length with Alzheimer's disease

Table 2 shows the results from unadjusted and adjusted (for age, gender and smoking attitude) regression models testing the molecules of interest (per their SD) in the association with the diagnosis of AD. In particular, the adjusted analyses confirmed that δ-tocotrienol, α-tocopherol, α-tocopherylquinone/α-tocopherol, 5-nitro-γ-tocopherol/γ-tocopherol, γ-tocopherol, total vitamin E, total tocopherols, β-tocopherol, total tocotrienols, δ-tocopherol and α-tocotrienol were associated with AD (in descending strength of association; Table 3).

Nitrosative damage and telomere length in Alzheimer's disease

Exploratory analyses testing the interactions between the molecules of interest and LTL in the association with AD were all not significant, except for the nitrosative damage variable (p for interaction term = 0.041). The relative regression model was then stratified according to the

Table 2 Plasmatic levels of vitamin E forms, oxidative/nitrosative damage indices and LTL in healthy subjects (CTs) and patients with Alzheimer's disease (AD)

	CTs ($n=40$)	AD ($n=53$)	p
α-Tocopherol	6.55 ± 1.40	5.21 ± 1.21	**< 0.001**
β-Tocopherol	0.51 ± 0.12	0.46 ± 0.09	**0.009**
γ-Tocopherol	0.43 ± 0.10	0.37 ± 0.08	**0.002**
δ-Tocopherol	0.058 ± 0.013	0.053 ± 0.010	**0.044**
α-Tocotrienol	69.72 ± 21.82	60.96 ± 14.50	**0.021**
β-Tocotrienol	27.64 ± 5.70	27.94 ± 7.05	0.833
γ-Tocotrienol	13.38 ± 4.70	14.30 ± 3.77	0.302
δ-Tocotrienol	9.72 ± 2.40	3.74 ± 2.79	**< 0.001**
Total tocopherols	7.55 ± 1.55	6.54 ± 1.77	**0.005**
Total tocotrienols	120.47 ± 29.22	106.94 ± 19.94	**0.009**
Total vitamin E	7.67 ± 1.57	6.64 ± 1.78	**0.005**
α-tocopherylquinone/α-tocopherol	1.63 ± 0.26	1.88 ± 0.31	**< 0.001**
5-Nitro-γ-tocopherol/γ-tocopherol	11.26 ± 1.81	12.87 ± 2.62	**0.001**
LTL	0.71 ± 0.30	0.62 ± 0.27	0.171

Significant p values (< 0.05) are in bold

Levels of tocopherols and total vitamin E are expressed as μmol per mmol cholesterol. Tocotrienols are expressed as nmol per mmol cholesterol. The ratios α-tocopherylquinone/α-tocopherol and 5-nitro-γ-tocopherol/γ-tocopherol are expressed as nmol/μmol. Data are expressed as mean value ± standard deviation

LTL leukocyte telomere length

Table 3 Unadjusted and adjusted logistic regression analyses for AD outcome per SD increase in plasma vitamin E forms and LTL

	Unadjusted		Adjusted	
	Regression coefficient (SE)	p	Regression coefficient (SE)	p
α-Tocopherol	− 1.167 (0.296)	**< 0.001**	− 1.105 (0.300)	**< 0.001**
β-Tocopherol	− 0.618 (0.250)	**0.011**	− 0.617 (0.264)	**0.019**
γ-Tocopherol	− 0.728 (0.247)	**0.003**	− 0.688 (0.251)	**0.006**
δ-Tocopherol	− 0.470 (0.231)	**0.042**	− 0.463 (0.232)	**0.045**
α-Tocotrienol	− 0.507 (0.233)	**0.034**	− 0.480 (0.239)	**0.045**
β-Tocotrienol	0.047 (0.212)	0.831	0.048 (0.222)	0.830
γ-Tocotrienol	0.223 (0.214)	0.301	0.329 (0.228)	0.150
δ-Tocotrienol	− 2.490 (0.454)	**< 0.001**	− 2.721 (0.548)	**< 0.001**
Total tocopherols	− 0.623 (0.234)	**0.008**	− 0.601 (0.242)	**0.013**
Total tocotrienols	− 0.595 (0.245)	**0.023**	− 0.547 (0.248)	**0.027**
Total vitamin E	− 0.627 (0.234)	**0.007**	− 0.605 (0.242)	**0.013**
α-tocopherylquinone/α-tocopherol	1.016 (0.284)	**< 0.001**	1.018 (0.296)	**0.001**
5-Nitro-γ-tocopherol/γ-tocopherol	0.766 (0.253)	**0.002**	0.819 (0.271)	**0.002**
LTL	− 0.305 (0.220)	0.174	− 0.823 (0.820)	0.315

Significant p values (< 0.05) are in bold

The regression coefficients are adjusted for age, gender and smoking attitude

Results are expressed per SD increase of each single biomarker. SDs: α-tocopherol 1.453, β-tocopherol 0.108, γ-tocopherol 0.094, δ-tocopherol 0.011, α-tocotrienol 18.427, β-tocotrienol 6.469, γ-tocotrienol 4.189, δ-tocotrienol 3.966, total tocopherols 1.745, total tocotrienols 25.136, total vitamin E 1.758, α-tocopherylquinone/α-tocopherol 0.317, 5-nitro-γ-tocopherol/γ-tocopherol 2.427, LTL 0.283

LTL leukocyte telomere length

median LTL (i.e., 0.67). It was found that the association between 5-nitro-γ-tocopherol/γ-tocopherol and AD was statistically significant in those with higher LTL values ($\beta = 1.626$, SE = 0.608, $p = 0.008$), but absent ($\beta = 0.172$,

SE = 0.386, $p = 0.656$) in those characterized by more enhanced cellular aging.

Discussion

In our cohort of well-characterized subjects with AD, almost all the forms of vitamin E were significantly reduced in AD compared to CTs. These results support the hypothesis that low concentrations of vitamin E may represent a risk factor for AD in older patients [3]. In particular, α- and β-tocopherol, δ-tocotrienol, total tocopherols, total tocotrienols and total vitamin E seem particularly involved in the risk profiling of AD. Interestingly, cellular aging (as defined by LTL) seems to play a role in the relationship between nitrosative damage and AD, where high levels of 5-nitro-γ-tocopherol/γ-tocopherol were predictive of AD only in individuals with preserved telomere length.

Nowadays, most of the studies focus on the antioxidant and anti-inflammatory properties of α-tocopherol and only few studies have taken into consideration all the eight vitamin E forms related to cognitive decline and/or AD. The regulatory mechanisms of plasma vitamin E are partially unknown as well as the effects deriving from vitamin E supplementation [18]. Since each vitamin E form is functionally and biologically unique, the need to study the forms of tocopherols and tocotrienols may be important to understand the impact of their specific biological effects on the determination of clinical conditions [18, 19]. In fact, specific deficiencies of vitamin E forms or alterations of the related oxidative/nitrosative stress indexes may allow to better differentiate risk profiles and personalize interventions.

Recent studies indicate that α-, γ- and δ-tocopherol have antioxidant and anti-inflammatory properties potentially able to exert positive (and potentially complementary) effects in the pathogenesis of chronic diseases [20]. In this context, for example, supplementation with mixed tocopherols seems to have a greater effect than supplementation with α-tocopherol alone [21]. Moreover, δ-tocotrienol is a strong modulator of inflammation, in particular by affecting TNF-α concentrations [3].

Despite that we have not observed differences in LTL in AD patients compared to CTs, in our secondary analyses, we found a significant association between nitrosative damage and AD only in subjects with LTL greater than median values. In other words, it seems like the excessive nitrosylation of γ-tocopherol represents a risk factor for AD only in those individuals with preserved telomere length (i.e., biologically younger). Reactive nitrogen species substantially contribute to free radical-mediated damage in AD [22, 23]. Evidences underpin the role of nitrogen species in the propagation of cellular injury leading to damage, observed in brain aging and neurodegeneration [23]. The impact of free radical damage on LTL maintenance is not well understood and in vitro studies predicted that radical stress could either promote or repress telomerase-mediated lengthening [24], as well as induce the production of aberrant and fragile telomeric structures [25, 26].

Our data indicate that nitrosative damage influences the risk of developing AD in subjects characterized by peripheral cells with longer LTL. One explanation of this result could be that this damage has more impact in subjects in which LTL and cellular homeostasis are still maintained. On the other hand, radical stress could promote telomerase-mediated lengthening of the telomere, as previously proposed [24].

The main limitation of our study resides in the number of participants. It is possible that our analyses might have been affected by limited statistical power. At the same time, we cannot exclude that other mechanisms causing telomere shortening and not considered in the present analyses might explain our findings.

In conclusion, this study confirms a general association between vitamin E and AD. At the same time, we were able to identify subtle differences across vitamin E forms, potentially paving the way for a more detailed approach in the field. The role played by cellular aging in the mediation between antioxidant status and AD pathology should be carefully considered. Further studies are needed to confirm and expand our results.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Ethical approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards.

Informed consent Informed consent was obtained from all individual participants included in the study.

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