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Short Communication

Vitamin E Status and Quality of Life in the Elderly: Influence of Inflammatory Processes

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Abstract

Chronic low grade inflammation is a characteristic of aging that may lead to alterations in health status and quality of life. In addition to intrinsic biological factors, recent data suggest that poor nutritional habits may largely contribute to this condition. The present study aimed at assessing mental and physical components of quality of life and at determining their relationship to vitamin E status, inflammation and tryptophan (TRP) metabolism in the elderly. Sixty-nine elderly subjects recruited from the Three-City (3C) cohort study participated in the study. Quality of life was assessed using the medical outcomes study (MOS) 36-item short-form health survey (SF-36). Biological assays included the measurement of plasma vitamin E (alpha-tocopherol), inflammatory markers, including interleukin (IL)-6 and C reactive protein (CRP), and TRP metabolism. Results showed that participants with poor physical health status, as assessed by the SF-36, exhibited lower circulating concentrations of alpha-tocopherol together with increased concentrations of inflammatory markers. Similarly, poor mental health scores on the SF-36 were associated with lower concentrations of alpha-tocopherol, but also with decreased concentrations of TRP. These findings indicate that nutritional status, notably as it relates to vitamin E, is associated with immune function and quality of life in the elderly.

Introduction

Impaired quality of life, associated with mood and physical symptoms, is frequent in the elderly. Approximately 7-40% of older persons report mental dysfunctions, especially in the form of mood and cognitive alterations, and these contribute considerably to their social and occupational dysfunction [1, 2]. With the growing elderly population, there is a risk of a recrudescence of aged-related behavioural symptoms and reduced wellbeing. Thus, the promotion of healthy lifestyles and the prevention of impaired quality of life in the elderly represent a major public health concern.

Nutritional factors have been recently involved in pathways likely to influence mood and wellbeing. This idea is supported by a growing number of data indicating the protective effects of nutritional factors, including antioxidants, on mood symptoms, cognitive decline and impaired quality of life in the elderly [3, 4]. Recent data suggest that the mechanisms by which micronutrients influence health and quality of life involve immunological processes [5]. Alpha (α)-tocopherol is the most bioavailable form of vitamin E. This natural antioxidant is lipid-soluble, and due to this property, it exerts preferentially its antioxidant activity in lipid-rich membranes, which concerns immune cells. In terms of immunomodulatory properties, α-tocopherol was shown to exert anti-inflammatory actions, including the modulation of T cells function and prostaglandin-E2 production by macrophages and the reduction pro-inflammatory cytokine synthesis from activated macrophages and monocytes [5, 6]. The current recommended dietary intake of vitamin E is 15mg per day of α-tocopherol [7]. However, this standard appears not to be reached in the aged population, a condition that may facilitate the development of immune alterations. Inflammation is a fundamental characteristic of aging. In the aged organism, the chronic, low-grade, activation of the innate immunity is associated with an over-expression of inflammatory factors, including pro-inflammatory cytokines (e.g., tumor-necrosis-factor (TNF)-α, interleukin (IL)-6), to the detriment of anti-inflammatory factors [8]. Not only involved in age-related inflammatory processes and disorders, pro-inflammatory cytokines appear also to play a role in the pathophysiology of mood and cognitive disorders, including depression [9, 10]. The alteration of tryptophan (TRP) metabolism through the induction of the enzyme indoleamine-2,3-dioxygenase (IDO) upon chronic immune activation represents a mechanism by which inflammation induces mood symptoms. IDO can be induced in a variety of immune cells, such as monocyte-derived macrophages and microglia, by inflammatory cytokines, including most notably IFN-γ [11]. This enzyme catalyzes the rate-limiting step of TRP conversion into kynurenine (KYN) and then quinolinic-acid, thereby reducing the availability of TRP for conversion into serotonin. *In vivo*, the activity of IDO is reflected by the relative concentrations of KYN and TRP, with increased KYN/TRP ratio indicating increased IDO

activity. Interestingly, older age has been associated with increased IDO activity and TRP degradation, consistent with the notion that immune activation is more prominent/sustained in the elderly [12, 13]. Altogether, these data support the hypothesis that vitamin E status may participate in aged-related alterations in health and quality of life, through effects on immune function and inflammatory pathways. The purpose of this study was to assess quality of life (mood and physical components) and to determine its relationship to vitamin E status, inflammation and TRP metabolism in a population of elderly subjects.

Subjects and Methods

Participants

Participants (N=69) were recruited from the Three-City (3C) study, an epidemiological cohort study of 9,294 aged, not institutionalized, persons living in Bordeaux, Dijon and Montpellier recruited since 1999 (PI: A. Alpérovitch, INSERM U708). The general methodology of the 3C study was published elsewhere [14]. Participants in the present study were drawn from the Bordeaux site at 7-year follow up. Subjects with known or acute signs of inflammatory disease, with dementia or taking statins or medications likely to influence immune parameters were excluded. This study was conducted according to the guidelines laid down in the Declaration of Helsinki and all procedures involving human subjects were approved by the Consultative Committee for the protection of Persons in Biomedical Research of the Kremlin-Bicêtre University Hospital (Paris). Written informed consent was obtained from all subjects.

Assessment of Quality of Life

Quality of life was assessed using the medical outcomes study (MOS) 36-item short-form health survey (SF-36) [15], a well validated self-report questionnaire which assesses the physical and mental components of quality of life through eight health concepts: physical functioning, physical role functioning, bodily pain, general health, vitality, social functioning, emotional role functioning and mental health. According to standard procedures, two summary scores ranging from 0 to100 (worst to best health) were calculated corresponding respectively to physical health and mental health. These scores were weighted, norm-based and expressed as t-scores with mean=50 (SD=10).

Biological Measurements

Fasting blood samples were collected between 8.00am and 9.30 am the same day as the assessment of quality of life. Plasma were stored at –80°C until thawed for the biological assays.

Vitamin E status – Plasma vitamin E concentrations were measured according to the method of Menke et al [16]. Briefly, after addition of 2,6-di-tert-butyl-p-cresol, vitamin E was extracted from 100µL plasma with hexane and separated by high-performance-liquid-chromatography.

Inflammatory markers -Assays included the measurement of C-reactive protein (CRP) and the pro-inflammatory cytokine, IL-6. These markers were selected on the basis of previous reports indicating their involvement in neuropsychiatric symptoms in aged populations or with metabolic disorders [17, 18]. Plasma concentrations of IL-6 were assayed by quantitative enzyme-linked-immunosorbent-assay (ELISA) techniques based on appropriate and validated sets of monoclonal antibodies (R&D Systems). CRP was measured by enzyme-immunoassay (EIA, Chemicon, Millipore, France). Inter- and intra-assay variability is reliably <10%.

TRP catabolism - Free TRP and KYN plasma concentrations were determined by high-performance-liquid-chromatography, as described elsewhere [19].

Statistical Analysis

Relationship between vitamin E status, inflammatory markers and TRP levels was estimated using the Bravais-Pearson (*R*) coefficient for continuous variables. Separate multivariate linear regression analyses entering biological parameters in separate models adjusting for age and gender were used to assess the association of vitamin E, inflammatory markers and TRP metabolism with the SF-36 physical and mental health summary scores. Finally, dichotomous analyses were performed stratifying participants into distinct subgroups on the basis of their mental and physical health status (poor versus good), as assessed by the SF-36. Good mental and physical heath statuses corresponded respectively to a summary mental health score and a summary physical health score above the median of the study population (respectively ≥73 and ≥67). Analyses of variance with age as covariate (ANCOVA) were performed to compare biological parameters across subgroups. Three participants had a missing value for one question of the SF-36. Accordingly, the missing value was replaced using the algorithm described by the authors [15]. All probabilities were two-tailed, with the level of significance set at $p<0.05$.

Results

Sixty-nine elderly subjects (46 women, 23 men) participated in the study. The mean age and body mass index (BMI) of participants were respectively 78.9 years (SD= 4.9) and 27.7 kg/m^2 (SD= 4.3). The mean physical health and mental health summary scores were respectively 61.7

(SD= 22.6) and 67.4 (SD= 18.9). Overall, there was no significant relationship between gender, BMI and quality of life scores (all $p>0.05$). Age, however, correlated significantly with both the physical and mental components of quality of life (respectively, $R= -.407$, $p<0.001$ and $R= -.363$, $p<0.01$), with greater age corresponding to lower quality of life.

As expected, IL-6 levels correlated significantly with CRP levels ($R= .377$, $p<0.01$). Interestingly, IL-6 levels also correlated with vitamin E levels; with higher IL-6 levels corresponding to lower vitamin E concentrations ($R= -.277$, $p<0.01$). CRP concentrations were negatively correlated with levels of TRP ($R= -.270$, $p<0.05$), the latter being also correlated to KYN levels ($R= .443$, $p<0.001$). In addition, there was a trend for a relationship between IL-6 and TRP concentrations ($R= -.209$, $p=0.09$). There was no significant relationship between age, BMI and any of the measured biological parameters. Nevertheless, gender was related to IL-6, TRP, KYN and vitamin E, with women displaying lower levels of IL-6, TRP and KYN and higher levels of vitamin E compared to men (all $p<0.05$). Accordingly, subsequent analyses were performed controlling for the age and gender of participants.

Separate multivariate linear regression analyses adjusting for age and gender revealed that IL-6, CRP, TRP and vitamin E were significantly associated with the physical health summary score (respectively $\beta= -.312$, $p=0.007$; $\beta= -.222$; $p=0.047$; $\beta= .299$, $p=0.011$ and $\beta= .317$, $p=0.006$), indicating that the better was physical health status the lower were the concentrations of IL-6 and CRP and the higher were the levels of TRP and vitamin E. Similar analyses associating each biological parameter to the mental health summary score indicated that mental health status was positively associated with TRP levels ($\beta= .282$, $p=0.019$) and with vitamin E ($\beta= .275$, $p=0.022$).

Thirty-five participants were found to exhibit poor/low physical health status and 34 participants exhibited good physical health status. As shown in **Table 1**, there was no significant difference in terms of gender or BMI between the two subgroups but a significant difference in age, with participants with poor/low physical health being significantly older. When controlling for age, participants with poor/low physical health status were found to exhibit significantly lower levels of vitamin E, higher concentrations of IL-6 and tended to display greater CRP levels compared to participants with high physical health status. Regarding mental health, 35 participants exhibited mental health subscores below the median of the study population, denoting poor/low mental health status. Consistent with differences found for physical health status, participants with poor/low mental health status were found to be older compared to participants with high mental health status. When controlling for age, participants with poor mental health status were found to exhibit significantly lower concentrations of vitamin E and TRP compared to participants with good mental health status.

Discussion

Results from this study clearly indicate an association between vitamin E status, immune processes and quality of life in the elderly. Participants with greater plasma concentrations of vitamin E (α-tocopherol) exhibited lower plasma levels of inflammation together with better health status, as determined by higher scores of mental and physical quality of life on the SF36 questionnaire. This finding is consistent with recent data showing an association between low serum concentrations of α-tocopherol and subsequent decline in physical function in a population-based sample of community-living elders [4]. In our study, plasma concentrations of α-tocopherol correlated with both the mental and physical components of quality of life, suggesting the involvement of vitamin E in multiple dimensions of health and wellbeing.

Our findings indicate that regulation of inflammatory processes may represent a primary pathway by which vitamin E influences health and quality of life in the elderly. Due to its antioxidant property, α-tocopherol is able to modulate immune function and regulate inflammatory responses [5, 6]. This effect is certainly not negligible in aging where inflammation is prominent and it might thus contribute to improve health and wellbeing in the aged population [6]. Recent data have shown that α-tocopherol can suppress immune-induced TRP degradation in mitogen-stimulated peripheral blood mononuclear cells *in vitro* [20]. This mechanism could explain the positive association of plasma vitamin E with health and quality of life, given the well-known role of TRP and serotonin pathways in the regulation of mood and neurovegetative functions. In our study, however, α-tocopherol did not significantly correlate with TRP concentrations. Nevertheless, similarly to α-tocopherol, TRP levels were associated with both physical health and mental health, albeit this association was more pronounced in regards to mental health. This data is consistent with the role of TRP metabolism in mood and mental processes and is in line with previous results indicating a significant relationship between immune activation, reduced serum TRP and worse quality of life scores in medically-ill patients [21]. The dichotomous analysis made to compare subgroups in regards to physical and mental health status did not allow us to measure any significant difference in KYN levels and in the ratio of KYN/TRP between subgroups. Nevertheless, the finding that decreased TRP levels were associated with increased levels of inflammatory markers is in favour of the hypothesis of increased TRP degradation upon chronic, low-grade, inflammation [11].

Lower levels of plasma α-tocopherol in the elderly may either reflect insufficient dietary vitamin E intake [22, 23] or increased formation of reactive oxygen species (ROS) by inflammatory processes, and thus degradation of antioxidants, including vitamin E. These possibilities merit

228 further investigation as they might involve different preventive strategies. In one case, a regular
229 consumption of vitamin E rich compounds, and probably other antioxidants such as carotenoids and
230 polyphenols which contribute to vitamin E regeneration, may prevent age-related alterations in
231 immune function and quality of life. In the other case, supplementation with α-tocopherol may be
232 relevant as this treatment was shown to decrease inflammatory processes and enhance immune
233 function in aged animals [(6)].

234 Altogether these results suggest that vitamin E status may influence quality of life in the
235 elderly and that chronically activated inflammatory pathways may play a role in this relationship.
236 Nevertheless, due to the correlational and cross-sectional aspects of this study, these findings cannot
237 be interpreted in terms of causality. Other limitations to the present study include the limited sample
238 size and the lack of operational control for potential confounders which may be linked to nutritional
239 and immune status as well as to mental health. Despite exclusion of participants with acute
240 inflammatory disease, we cannot rule out an effect of undiagnosed co-morbidity on nutritional and
241 immune status. Finally, because of the absence of specific dietary data documenting on TRP intake
242 at the time of the evaluation, we cannot exclude the possibility that, in addition to inflammatory
243 processes, insufficient dietary intake of TRP-rich compounds may have contributed to decreased
244 TRP concentrations in participants from this study.

245 In conclusion, the present findings document a clear association between vitamin E levels
246 and inflammatory pathways in the elderly and suggest that their interaction may influence quality of
247 life. Insufficient antioxidant intake and/or defences, as assessed by plasma vitamin E, appear to
248 correlate with signs of inflammation and participate in aged-related alterations in health and quality
249 of life.

250

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254 This study was conducted according to the guidelines laid down in the Declaration of Helsinki and
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256 protection of Persons in Biomedical Research of the Kremlin-Bicêtre University Hospital (Paris).
257 Written informed consent was obtained from all subjects.
258 Author's contribution: LC was involved in study design, statistical analysis, data interpretation and
259 manuscript writing; AM and VDP performed laboratory measurements of inflammatory markers;
260 NC was responsible for the implementation and measurement of vitamin E; FCG was involved in
261 study design; DF was involved in the measurement of tryptophan and kynurenine; PBG was the
262 local coordinator of the epidemiological study and was involved in study design, data interpretation

and manuscript editing; SL was the coordinator of inflammation measurements and was involved in study design, data interpretation and manuscript editing.

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Table 1. Vitamin E status, inflammatory markers and TRP catabolism in participants with poor/low mental or physical health versus participants with good mental or physical health

	SF36 – Physical Health		SF36 – Mental Health	
	Poor/low (N=35)	**Good (N=34)**	**Poor/low (N=35)**	**Good (N=34)**
Age	80.7 (4.9)	77.1 (4.2) **	80.4 (4.6)	77.4 (4.7) *
Sex (female/male)	24/11	22/12	25/10	21/13
Body mass index (kg/m^2) [-b-]	26.5 (4.8)	25.1 (3.9)	26.5 (4.9)	25.1 (3.8)
Vitamin E status				
Alpha- tocophérol (µmol/L)	31.3 (5.7)	36.0 (7.9) **	31.7 (6.3)	35.6 (7.7) *
Inflammatory markers				
IL-6 (pg/mL)	5.0 (5.5)	2.8 (1.8) *	4.65 (5.4)	3.16 (2.4)
CRP (mg/L)	5.0 (5.4)	2.9 (3.8) #	4.72 (4.9)	3.15 (4.5)
TRP catabolism				
TRP (µmol/L)	54.9 (10.7)	59.9 (10.9)	53.3 (10.3)	61.5 (10.2) **
KYN (µmol/L)	2.2 (0.7)	2.1 (0.6)	2.1 (0.7)	2.1 (0.5)
KYN/TRP x 1000 (mmol/mol)	40.5 (13.3)	35.1 (8.1)	40.5 (13.6)	35.2 (7.6)

Data are shown as means (SD). IL-6: interleukin-6; CRP: C reactive protein; TRP: tryptophan; KYN: kynurenine. ** $p < 0.01$; * $p < 0.05$; # $p = 0.07$ (corrected for age)

[-b-] this information was missing for 4 subjects.