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Increased dietary vitamin K intake is associated with less severe subjective memory complaint among older adults

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ABSTRACT

Objectives: Increased dietary intake of vitamin K, a fat-soluble nutrient involved in brain health and function, has been associated with better cognitive performance in older adults. Our objective was to determine whether the dietary vitamin K intake was associated with the presence and severity of subjective memory complaint among older adults.

Study design: Observational, cross-sectional cohort study.

Main outcome measures: One hundred sixty older adults taking no vitamin K antagonist were included. The daily dietary vitamin K intake was assessed using a 50-item food frequency questionnaire. The subjective memory complaint was assessed at the same time using the Memory Complaint Questionnaire (MAC-Q; score 0–30, best). Serious subjective memory complaint was defined as MAC-Q score ≤ 15 . Age, gender, body mass index, education level, number of comorbidities, history of stroke, objective cognitive disorders, functional autonomy, mood, serum concentrations of vitamin B12, TSH, albumin, and estimated glomerular filtration rate were used as potential confounders.

Results: Compared to participants without serious subjective memory complaint, those with serious subjective memory complaint ($n = 110$) had a lower mean dietary vitamin K intake ($298.0 \pm 191.8 \mu\text{g/day}$ versus $393.8 \pm 215.2 \mu\text{g/day}$, $P = 0.005$). Increased log dietary vitamin K intake was positively associated with the MAC-Q score used as a quantitative variable (fully adjusted $\beta = 0.79$, $P = 0.031$), and inversely with serious subjective memory complaint (fully adjusted OR = 0.34, $P = 0.017$).

Conclusions: Increased dietary vitamin K intake was associated with fewer and less severe subjective memory complaint in older adults taking no vitamin K antagonists. These findings provide epidemiological data supporting future vitamin K replacement trials.

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1. Introduction

Beyond its classical role in blood coagulation [1], vitamin K emerges as a fat-soluble nutrient involved in the physiology of the central nervous system (CNS) [2–4]. In particular, vitamin K

regulates the synthesis of sphingolipids, a major constituent of the myelin sheath and neuronal membranes, also involved in neuronal proliferation, differentiation, senescence, transformation and cell–cell interaction [3,4]. Vitamin K also controls for the biological activation of vitamin K-dependent proteins (VKDPs) implicated in neuron physiology and survival [3,4]. In one study, decreased serum concentrations of phyloquinone (i.e., vitamin K₁) were associated with diminished episodic memory performance in a group of healthy individuals [5], and patients with Alzheimer's disease (AD) have been shown to exhibit lower serum concentrations of

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phylloquinone when compared to cognitively healthy controls [6]. These findings seem especially relevant in clinical practice as it is plausible that high intakes of vitamin K may contribute, along with other dietary and lifestyle factors, to the prevention of cognitive decline. In fact, lower vitamin K intakes have been observed in community-dwelling elders at an early stage of AD [10,11]. AD is a chronic, progressive neurodegenerative brain disease affecting 26 million people worldwide [7], which natural evolution is characterized by increasingly severe cognitive disorders affecting functional autonomy combined with a subjective memory complaint (SMC), which occurs much before the first objective signs [8,9]. Although the links between the dietary vitamin K intakes and objective cognitive impairments have already been described [10,11], the relationship between dietary vitamin K and SMC has not been examined yet. This could lead to interesting perspectives for clarifying and preventing cognitive decline in older adults, even before the onset of the first objective signs of dementia. The objective of the present study was to determine whether the dietary vitamin K intake was associated with the presence and severity of SMC among older adults.

2. Methods

2.1. Participants

We studied patients aged 65 and older consecutively recruited in the CLIP (Cognition and Lipophilic vitamins) study from February to April 2014. The CLIP study is an observational, cross-sectional cohort study designed to examine the relationships between neurocognition and lipophilic vitamins among patients hospitalized or seen in consultation in the geriatric acute care unit of the University Hospital of Angers, France [12]. After giving their informed consent for research, included participants received a full medical examination consisting of structured questionnaires, a standardized clinical examination and a blood test. For the present analysis, participants were excluded when usually taking vitamin K antagonists (VKAs; i.e., warfarin, acenocoumarol, or fluindione) since VKAs deplete the active form of vitamin K. The regular use of VKAs was systematically noted from the primary care physicians' prescriptions and sought by questioning the patients and their relatives. All study subjects gave informed consent to participate in this research. The study was conducted in accordance with the ethical standards set forth in the Helsinki Declaration (1983). The entire study protocol was approved by the local Ethical Committee.

2.2. Explanatory variable: dietary vitamin K intake

The dietary vitamin K intake was estimated from a semi-quantitative food frequency questionnaire (FFQ) [13]. FFQs are considered the only practical and affordable method to assess dietary usual intake in relation to development of various diseases in large epidemiological studies [13]. The 50-item FFQ used here was specifically designed to determine the daily dietary vitamin K intake during the previous 12 months. It comprises 50 food items identified as important contributors to phylloquinone intake (e.g., spinach, iceberg lettuce, collards, and broccoli) and items with very high phylloquinone content ($\geq 500 \mu\text{g}/\text{usual portion}$). The FFQ was interviewer-administered in 30 min by questioning the patients and/or their relatives when applicable. Estimated vitamin K intake was calculated for each food item by multiplying the amount of phylloquinone for that food item by the selected frequency and serving size (calculated as 0.5 for smaller than, and 1.5 for larger than the suggested portion), and all values were added to provide an estimate in $\mu\text{g}/\text{day}$ of each participant's daily vitamin K intake.

The vitamin K FFQ shows good relative agreement with 5-day food records ($\kappa = 0.60$, $P < 0.001$) [13].

2.3. Dependent variables: subjective memory complaint

The SMC was rated using the Memory Complaint Questionnaire (MAC-Q) [14], in the absence of delirium identified with the Confusion Assessment Method [15]. The six-item MAC-Q requires participants to compare current memory function to memory function at earlier ages in daily scenarios. Five questions address daily activities compared to 5 years ago; and one final question addresses the general feeling on overall memory function compared to 10 years ago. For each question, five possible answers range from "much better now" (scored 5) to "much worse now" (scored 1), with a total score out of 30 (best). Serious SMC was defined as MAC-Q score ≤ 15 ($/30$), as previously published [12]. The MAC-Q is easy to perform, has been validated against lengthy questionnaires, and demonstrates good internal consistency together with satisfactory test-retest reliability [14].

2.4. Covariables

Age, gender, body mass index (BMI), education level, number of comorbidities, history of stroke, objective cognitive disorders, functional autonomy, mood, serum concentrations of vitamin B12, thyroid-stimulating hormone (TSH), albumin, and estimated glomerular filtration rate (i.e., creatinine clearance, eGFR) were used as potential confounders. The BMI was calculated as: $[\text{weight (kg)}/\text{height}^2(\text{m}^2)]$. Weight was measured with a beam balance scale, and height with a height gauge. Evaluation of education level was based on self-report. High education level was defined as graduate studies. Evaluation of comorbidities (i.e., diseases lasting at least 3 months and running a course with minimal change, whatever the etiology) was based on self-report and medical record [16]. History of stroke was sought by questioning the patients, the family physicians and the patients' files. Stroke was defined according to the World Health Organization criteria as rapidly developed signs of focal or global disturbance of cerebral function lasting longer than 24 h, with no apparent nonvascular cause [17]. In case of clinical suspicion, computed tomography or magnetic resonance imaging scan was necessary to confirm the diagnosis and to distinguish among ischemic stroke and intracranial hemorrhage. Objective cognitive disorders were defined as Mini-Mental State Examination score < 24 in the absence of delirium [18]. Functional autonomy was assessed with the 4-item Instrumental Activities of Daily Living (IADL) score (range 0–4, worst) [19]. Mood was rated with the 4-item Geriatric Depression Scale (GDS) score (range 0–4, worst) [20]. Finally, the serum concentrations of vitamin B12, TSH, albumin and creatinine were measured using automated standard laboratory methods at the University Hospital of Angers, France, and eGFR was calculated using the Cockcroft-Gault formula ($[(140 - \text{age years}) \times \text{weight}_{\text{kg}}/\text{creatinine}_{\mu\text{mol/L}}] \times 1.04$ for females, and $\times 1.25$ for males).

2.5. Statistical analysis

The participants' characteristics were summarized using means and standard deviations or frequencies and percentages, as appropriate. Statistics were performed on logarithmically transformed values for the dietary vitamin K intake to improve the symmetry of the non-Gaussian distribution. Firstly, comparisons between participants separated into two groups according to serious SMC (i.e., MAC-Q score ≤ 15) were performed using Student's *t*-test or the Chi-square test, as appropriate. Secondly, the mean difference of dietary vitamin K intake was calculated between participants with serious SMC and those without. Thirdly, univariate and multiple (i.e., fully

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