Institutionen för Neurobiologi, Vårdvetenskap och Samhälle

Exploring the role of vitamin E in Alzheimer's disease

An Epidemiological and Clinical Perspective

AKADEMISK AVHANDLING
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ABSTRACT

Vitamin E, the main non-enzymatic lipophylic antioxidant in the human body, has a major role in protecting the brain from damage mediated by free radicals. The term vitamin E encompasses eight natural congeners (forms): four tocopherols and four tocotrienols, named α, β, γ, and δ. Most investigation of vitamin E in relation to dementia and Alzheimer´s disease (AD) has focused primarily only on α-tocopherol, with conflicting findings. However, increasing knowledge regarding the biological properties of vitamin E provides a strong biological rationale that other forms of vitamin E, beyond just α-tocopherol, may play a role in AD pathogenesis.
The aim of the present project is to investigate the relation of all eight natural vitamin E forms with mild cognitive impairment (MCI) and AD in older adults, by combining both an epidemiological and a clinic-based approach.

Study I. Plasma levels of all eight natural vitamin E forms, and markers of vitamin E oxidative/nitrosative damage (α-tocopherylquinone, 5-nitro-γ-tocopherol), were investigated in subjects with AD, MCI, and normal cognition (CN) in a clinical-based, multi-centre European study (AddNeuroMed Project). Compared to CN subjects, AD and MCI cases had lower plasma levels of total tocopherols, total tocotrienols and total vitamin E. Both MCI and AD cases had 85% lower odds to be in the highest tertile of plasma total tocopherols and total vitamin E, and they were, respectively, 92% and 94% less likely to be in the highest tertile of total tocotrienols than the lowest tertile. Further, both disorders were associated with increased plasma indices of vitamin E oxidative/nitrosative damage (ratios α-tocopherylquinone/α-tocopherol and 5-nitro-γ-tocopherol/γ-tocopherol).

Study II. Within the AddNeuroMed Project, analysis which integrated plasma levels of vitamin E forms with structural magnetic resonance (MRI) parameters, derived from automated regional analysis, was used to differentiate AD and MCI cases from CN individuals, and to predict MCI conversion to AD. The analysis of MRI and vitamin E data alone provided an accuracy of 83.2% and 92.8% respectively, for AD *versus* CN, and of 58.1% and 87.8% for MCI *versus* CN. The integrated analysis of plasma vitamin E and MRI data enhanced the accuracy, which were 98.2% for AD *versus* CN and 90.7% for MCI *versus* CN. This combination of data also correctly identified 85% of the MCI who converted to clinical AD at one year follow-up and 67% of the non-converters.

Study III. The association of plasma levels of eight natural vitamin E forms with the incidence of AD was examined in a Swedish population-based prospective study (Kungsholmen Project) of oldest-old individuals (age 80+), using six-year follow-up data. Subjects with higher concentrations of total tocopherols, total tocotrienols or total vitamin E had approximately a 50% reduced risk of developing AD in comparison to subjects with lower plasma levels (highest *versus* lowest tertile).

Study IV. The association of serum levels of all eight natural vitamin E forms and markers of vitamin E oxidative/nitrosative damage, with the incidence of cognitive impairment (MCI or AD) was investigated in a Finnish population-based prospective study (CAIDE) of older adults (age 65+), using eight-year follow-up data. The odds of cognitive impairment was reduced for subjects in the medium tertile of γ-tocopherol serum levels, relative to those subjects in the lowest tertile [odds ratio and 95% confidence interval: 0.27(0.10-0.78)]. Subjects with a higher serum value for the index of γ-tocopherol nitrosative damage (5-nitro-γ-tocopherol/γ-tocopherol ratio; high and middle versus lowest tertile) were about three times more likely to develop cognitive impairment.

Conclusions. α-tocopherol is the only vitamin E form currently used to define vitamin E dietary requirements, and it is the only congener tested in randomized controlled trials in subjects with AD and MCI. The results of this project provide evidence that suggests that the other natural forms of vitamin E can also be important in cognitive impairment and AD in older adults. Thus, all natural vitamin E forms should be considered when studying the association of this micronutrient with cognitive impairment and AD. These findings also suggest that some aspects of vitamin E supplementation in preventing and treating AD should be re-examined. This should include the timing of intervention, the composition of supplementation, and the assessment of plasma levels of all vitamin E forms. The latter can help identify subjects who could benefit from vitamin E supplementation, and monitor in-vivo biological response to treatment.

Key words: Alzheimer's disease, clinical-based study, mild cognitive impairment, nitrosative stress, oxidative stress, population-based study, tocopherol, tocotrienol, vitamin E, α-tocopherylquinone, 5-nitro-γ-tocopherol.

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