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Perspective

Insufficient evidence for vitamin E in Alzheimer's disease

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Abstract Vitamin E has recently been suggested to slow down the progression of Alzheimer's disease. Current evidence is based on three studies in patients with Alzheimer's disease and one study in patients with mild cognitive impairment which all together included only 1756 patients. Importantly, two of these studies were negative, and the two other studies had severe methodological weaknesses that preclude more definite interpretation. Based on the notion from patients suffering from cerebrovascular diseases that vitamin E may induce serious side effects (i.e., hemorhagic stroke), vitamin E cannot be recommended for use in Alzheimer's patients.

Keywords: Alpha-tocopherol; Cognition; Dementia; Free radical scavenger

The lipophilic antioxidant vitamin E (α-tocopherol) vividly interacts with cell membranes, scavenging free radicals and thereby interrupting chain reactions resulting in neuronal injury [1]. Because of its property as free radical scavenger, neuroprotective effects of vitamin E have been postulated in cerebrovascular and neurodegenerative diseases over many years, which have been proven in experimental disease models [2]. In cerebrovascular diseases, a meta-analysis based on 9 randomized, placebo-controlled studies with ≥1-year follow-up and a total number of 118,765 subjects (59,357 on vitamin E and 59,408 on placebo) demonstrated that vitamin E delivery at variable doses (50–800 mg/day) had beneficial effects on ischemic stroke incidence (relative risk 0.90 [95% confidence interval 0.82–0.99]) [3].

Regarding Alzheimer's disease, considerably less evidence supports the therapeutic efficacy of vitamin E, as pointed out in a recent article [4] and again summarized in the present issue of *Alzheimer's Dementia: Translational Research and Clinical Interventions* [5]. Indeed, the present data evidence is basically based on four studies:

(1) The double-blind, placebo-controlled, randomized multicenter study of the American Alzheimer's Disease Cooperative Study (ADCS) group evaluated effects of vitamin E (2000 IU/day) in 341 patients with moderate Alzheimer's disease (Clinical Dementia Rating [CDR] Scale 2) over an observation period of 2 years either alone or in combination with the monoamine oxidase B inhibitor selegiline [6]. Compared with placebo, vitamin E significantly delayed the primary endpoint, which was the development of severe dementia [CDR Scale 3], nursing home referral, or death ($P = .001$). A major criticism relates to the fact that baseline Mini-Mental State Examination (MMSE) score varied statistically tendentially but considerably regarding its parameter value between the placebo group (13.3 ± 4.9) and the three other groups (11.3 ± 5.7 [vitamin E], 12.7 ± 5.0 [selegiline], and 12.9 ± 5.7 [vitamin E plus selegiline]). Baseline MMSE was highly predictive for the primary endpoint in this cohort ($P = .012$). Similar to vitamin E, selegiline also postponed the primary endpoint in this study. Considering the small cohort recruited, the size of groups was small (84–87 patients per group). Despite adjustment for baseline MMSE, the relevance of these findings is questionable. The primary endpoint did not differ between groups in nonadjusted analyses.

(2) The more recent Trial of Vitamin E and Memantine in Alzheimer's Disease was a double-blind,

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placebo-controlled, randomized multicenter study on 613 patients with mild or moderate Alzheimer's disease (MMSE score 12–26) on choline esterase inhibitors receiving vitamin E (2000 IU/day), memantine (20 mg/day), or vitamin E plus memantine (2000 IU/day/20 mg/day) [7]. Over a mean observation period of 2.77 years, the delivery of vitamin E slowed down the decline of the ADCS activities of daily living (ADCS-ADL) score (mean difference compared with placebo: 3.15 [confidence interval 0.92–5.39]). In patients receiving memantine, vitamin E notably did not affect the decline of the ADCS-ADL score (mean difference to placebo: 1.98 [−0.24 to 4.20] for memantine and 1.76 [−0.48 to 4.00] for vitamin E plus memantine), which has to be interpreted as evidence for noneffi-cacy of vitamin E treatment. Convincing rationales for the lack of therapeutic response of vitamin E under simultaneous memantine treatment is lacking, particularly as patients receiving vitamin E plus memantine performed worse than patients receiving memantine only. Larger patient samples will be required to evaluate effects of vitamin E more consistently in both groups.

(3) A double-blind, placebo-controlled, randomized, explorative monocenter study from Spain examined effects of vitamin E (800 IU/day) in 57 patients with mild, moderate, or severe Alzheimer's disease, of which only 33 patients could be included into the statistical analysis, because they continued the study over the entire observation period of 6 months [8]. In the total cohort, vitamin E did not influence the change of cognitive performance, which was evaluated by the MMSE score, the Blessed Dementia Scale, and the clock test. In a subsequent analysis of the blood oxidized glutathione (GS-SG) value, only 9 of 19 patients exhibited a decrease of blood GS-SG during vitamin E treatment (so-called responders). In the latter patients, cognitive performance did not change in response to vitamin E treatment. In the 10 patients not exhibiting a decrease of blood GS-SG (so-called nonresponders), the MMSE score worsened significantly during vitamin E treatment. The conclusions of this study are confined by its pilot character without predefined endpoints and the low protocol adherence of participants. The study was interpreted as a possible evidence for a detrimental effect of vitamin E.

(4) The double-blind, placebo-controlled, randomized multicenter study of the ADCS group on 769 patients with mild cognitive impairment (CDR Scale 0.5) evaluated effects of vitamin E (2000 IU/day) or donepezil (10 mg/day) over an observation period of 3 years [9]. Vitamin E treatment did not affect the primary endpoint, which was the development of possible or probable Alzheimer's disease (hazard ratio 1.02 [confidence interval 0.74–1.41]). Donepezil also did not influence disease progression over 3 years (0.80, 0.57–1.13).

In summary, the two favorable studies on patients with Alzheimer's disease had severe methodological weaknesses. In the first study, the baseline MMSE score varied considerably between groups [6]. In the second study, vitamin E improved disease development when administered alone but not when administered in patients receiving memantine [7]. The third study on patients with Alzheimer's disease [8] and the only study on patients suffering from mild cognitive impairment [9] were negative. The total number of patients recruited in the four studies was small (1756 patients).

In stroke, vitamin E therapy is not recommended in clinical practice despite much larger studies with less methodological weaknesses. Although vitamin E reduced ischemic stroke incidence in the previous meta-analysis [3], it increased hemorrhagic stroke risk (relative risk 1.22 [1.00–1.48]). Total stroke risk was unaffected in this meta-analysis (0.98 [0.91–1.05]). Based on the current state of knowledge, there is little evidence that vitamin E improves the course of Alzheimer's disease. On the contrary, serious concerns have to be raised that adverse effects of vitamin E unraveled in the stroke studies (i.e., increase of hemorrhagic stroke risk) may impose risks to Alzheimer's patients. Another meta-analysis showed that vitamin E increased mortality in patients suffering from cerebrovascular or cardiovascular diseases but in tendency reduced mortality in patients without cerebrovascular or cardiovascular diseases [10]. Whether Alzheimer patients, which as a matter of fact often have vascular comorbidities (namely cerebral microangiopathy), rather belong to the first or secondary category should be evaluated in larger controlled trials. Based on current evidence, vitamin E treatment cannot be recommended in Alzheimer's disease.

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