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Invited commentary

Serum coenzyme Q10 levels as a predictor of dementia in a Japanese general population

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ABSTRACT

Mitochondrial impairment and increased oxidative stress are considered to be involved in the pathogenesis of neurodegenerative diseases, such as Alzheimer's disease. Coenzyme Q10 (CoQ10) is a component of the electron transport chain localized on the inner membrane of the mitochondria. In addition to its bioenergetic activity required for ATP synthesis, CoQ10 also has antioxidant activity in mitochondrial and lipid membranes, which protects against the reactive oxidative species generated during oxidative phosphorylation. Several previous studies had reported no significant differences in serum CoQ10 levels between patients with and without dementia, such as Alzheimer's disease. However, in this issue of *Atherosclerosis*, Yamagishi et al. demonstrate for the first time that a lower serum CoQ10 level is associated with a greater risk of dementia in a Japanese general population. These findings suggest that assessing serum CoQ10 levels could be useful for predicting the development of dementia, rather than as a biomarker for the presence of dementia.

Mitochondria play an essential role in energy production within cells, and energy is generated through oxidative phosphorylation in the form of adenosine triphosphate (ATP). Mitochondrial impairment and increased oxidative stress are considered to be involved in the pathogenesis of neurodegenerative diseases, such as Alzheimer's disease, which is the most common form of dementia in the elderly [1,2]. Increased oxidative stress was shown to be present in the brains of patients with Alzheimer's disease and to induce the accumulation of amyloid-beta protein [3,4]. Of note, amyloid-beta protein can impair mitochondrial function and induce oxidative stress. Coenzyme Q10 (CoQ10), also known as ubiquinone, is a component of the electron transport chain, which is located at the inner membrane of the mitochondria and plays a major role in ATP synthesis [5,6]. In addition to this bioenergetic activity required for ATP synthesis, CoQ10 also has antioxidant activity in both mitochondrial and lipid membranes, which protects them against the reactive oxidative species generated during oxidative phosphorylation. Several studies have already investigated the associations between dementia, such as Alzheimer's disease, and serum CoQ10 or antioxidant levels [7–9]. However, in this issue of *Atherosclerosis*, Yamagishi et al. [10] demonstrate for the first time that a lower level of serum CoQ10 and a lower ratio of CoQ10/total cholesterol are associated with a greater risk of disabling dementia in a general population.

Regarding serum CoQ10 levels in patients with dementia, de Bustos et al. [8] investigated serum CoQ10 levels in 44 patients with Alzheimer's disease, 17 patients with vascular dementia and 21 controls. However, no significant differences were found in CoQ10 levels among the 3 groups. Since CoQ10 levels correlate with total cholesterol levels [11], the ratio of CoQ10/cholesterol was also calculated. However, total cholesterol levels and the ratio of CoQ10/cholesterol did not differ among the 3 groups. Moreover, a population-based cross-sectional study by von Armin et al. [7] measured serum CoQ levels, as well as antioxidants (vitamin C, E, and beta-carotene) levels, in 74 mildly demented subjects and 158 controls. Vitamin C and beta-carotene levels were significantly lower in the demented subjects than in controls, but there were no differences in CoQ10 and vitamin E levels between the 2 groups. Giavarotti et al. [9] also investigated plasma oxidative stress biomarkers, including CoQ10, in 23 patients with Alzheimer's disease and 42 cognitively intact subjects. Vitamin E levels were lower in patients with Alzheimer's disease, but there were no differences in CoQ10, vitamin C or beta-carotene levels between the 2 groups. Although Polidori et al. [12] reported that both vitamin C and E levels were lower in 86 patients with dementia than in 55 controls, the association between dementia and antioxidant levels, such as vitamin C and E, is still controversial. Regarding Lewy body disease which is the second most frequent cause of dementia in the elderly,

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Molina et al. [13] reported that serum CoQ10 levels were lower in 18 patients with Lewy body disease than in 20 controls, but there was no significant difference in the CoQ10/cholesterol ratio between the 2 groups. Hence, the results of these previous studies suggest that serum CoQ10 levels are unlikely to differ between patients with and without the presence of dementia, such as Alzheimer's disease. However, as de Bustos et al. [8] and Soderberg et al. [14] commented, normal serum CoQ10 levels cannot rule out the possibility that there may be regional alterations of CoQ10 in some areas of the brain.

In this issue of *Atherosclerosis*, Yamagishi et al. [10] report their population-based prospective cohort study of approximately 6000 Japanese subjects aged 45–70 years at baseline (1984–1994) who were followed for at least 5 years. CoQ10 levels at baseline were measured in 65 subjects who developed disabling dementia with dementia-related behavioral disturbance or cognitive impairment during the follow-up compared with 130 age- and gender-matched controls. They demonstrated an inverse association between serum CoQ10 levels at baseline and the risk of incident disabling dementia, independent of various risk factors. Moreover, they reported that there was an inverse association between the ratio of CoQ10/total cholesterol and the risk of dementia. These results suggest that serum CoQ10 levels can be a predictor for dementia, but not a biomarker for the presence of dementia, in a Japanese general population. It should be kept in mind that it is currently unclear whether these results can be generalized for other ethnic populations. Moreover, as the authors commented, they did not classify dementia into Alzheimer's disease and vascular dementia. Instead, they reported that CoQ10 levels tended to be more strongly associated with dementia in subjects without a history of stroke than in those with a history of stoke. However, because the number of demented subjects was limited, further studies in a larger population are needed to confirm the differences regarding CoQ10 levels between dementia with and without a history of stroke.

Several experimental studies have shown the neuroprotective effects of CoQ10. Choi et al. [15] reported that CoQ10 protected neurons against amyloid-beta-induced neurotoxicity, mainly by inhibiting oxidative stress, in the rat cortex. Using transgenic mice overexpressing amyloid protein presenilin-1, Yang et al. [16] also showed treatment with CoQ10 to attenuate amyloid-beta overproduction and intracellular deposits associated with reduced oxidative stress in the cortex. Moreover, Dumont et al. [17] showed that CoQ10 treatment reduced oxidative stress and amyloid pathology and then improved cognitive behavior in the Tg19959 mouse model of Alzheimer's disease. Using transgenic mice with the P301S tau mutation, which causes fronto-temporal dementia, Elipenahil et al. [18] also demonstrated that CoQ10 treatment improved the survival and behavioral deficits associated with upregulated mitochondrial enzymes and reduced oxidative stress. Therefore, these findings suggest that CoQ10 plays a protective role as an endogenous antioxidant against the development or progression of dementia, especially Alzheimer's disease. However, in humans, a randomized clinical trial with 400 mg of CoQ10 three times/day for 16 weeks in 78 patients with mild to moderate Alzheimer's disease did not show any significant beneficial effects on cerebrospinal fluid biomarkers for Alzheimer's disease, such as amyloid-beta and tau levels [19]. Therefore, as Yamagishi et al. [10] commented in this issue of *Atherosclerosis*, CoQ10 may have a more prominent impact on prevention, rather than on treatment, of dementia, and serum CoQ10 levels may be a useful predictor of the development of dementia, rather than a biomarker for the presence of dementia. Both assessing serum CoQ10 levels and evaluating the effects of CoQ10 treatment are worthy of further studies to determine the predictive values of serum CoQ10 levels with regard to the development of dementia and to assess the preventative effects of CoQ10 treatment in a larger population.

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