

# The Relations Between the Vitamins and Alzheimer Dementia

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## 1. Introduction

The number of people suffering from dementia might triple over the next 50 years, measures for treatment and prevention of dementia are crucial. As vitamins are involved in many biochemical processes, they are essential for good health. They can possibly take role more probably in the prevention and treatment of dementia. For this reason, the relations between the vitamins and dementia, especially Alzheimer Dementia (AD) have been studied for many years.

Until the 1900s, vitamins were obtained solely through food intake, and changes in diet can alter the types and amounts of vitamins ingested. Vitamins have been produced as commodity chemicals and made widely available as inexpensive pills for several decades, allowing supplementation of dietary intake.

There are many observational studies indicating associations of vitamin deficiencies with cognitive dysfunction. Most of the studies in the subject are cross sectional studies. Nevertheless, these type of studies can not prove whether a nutritional deficit is the cause or the result of an impaired cognitive status. Longitudinal prospective observational studies and interventional studies are more suitable to releave causal relationships. Interventional studies with long follow up periods are preferred, since short follow up time can not be enough to evaluate the effects. There are some individual studies reporting promising, positive results about vitamin supplementation in prevention and treatment of dementia.

Vitamin A, C and E have antioxidant activity, which have been investigated for its prevention from neuronal death and improving neuronal function through maintaining mitochondrial homeostasis. Vitamin E may modulate signal transduction pathways and participate in the synthesis pathways of neurotransmitters. Several epidemiological studies have indicated a relationship between blood concentrations of antioxidant micronutrients and cognitive impairment. Though not sufficient, there are some prospective longitudinal and interventional studies indicating the useful effects of antioxidant vitamins in prevention and treatment of dementia.

Deficiencies of several B vitamins, including thiamine (B1), riboflavin (B2), niacin (B3), pyridoxine (B6), folate (B9) and cobalamin (B12) have been reported to be associated with cognitive dysfunction in many studies. In some studies, pathophysiological models have been formulated, including the association of B vitamin deficiencies with metabolic disturbances in the structural constituents of cerebral tissue, such as phospholipids and

myelin, as well as in signaling molecules, such as neurotransmitters. More recently, the association between the deficiency of B vitamins, particularly folate and cobalamin, and cognitive impairment has been investigated in relation to hyperhomocysteinemia. It was shown that plasma homocysteine is a better correlate of cognitive function than the serum folate or cobalamin concentrations themselves. Homocysteine is a well established risk factor for vascular disease, but some epidemiological and cross sectional studies have also suggested that it may play a role in cognitive performance and pathophysiology of dementia in older people, possibly as the metabolic link between micro-vascular disease and Alzheimer dementia. Some prospective longitudinal and interventional studies have reported the useful effects of some B vitamins, though there existed contradictory results also. Furthermore, there was a large heterogeneity among present vitamin B interventional studies with cognitive assessments in terms of dosage, routes of intervention (for vitamin B12), age and cognitive function assessments. It seems that it will be worthwhile to perform new larger studies, especially considering the results of the studies reporting recovering effect of folate supplementation on cognition.

The most recent reported vitamins related to cognitive functioning are vitamin D and vitamin K. Vitamin D has been reported to be critical to healthy brain development and function. Vitamin D in sufficient amounts seemed to protect brain cells and reduce inflammation according to some biological evidence. Some epidemiological and cross-sectional studies showed the association of vitamin D deficiency with Alzheimer disease and dementia. To disclose if there is a causal relationship between them, prospective longitudinal studies are needed in the subject. Vitamin K is also required for normal brain development and function. Some authors proposed a possible role of vitamin K deficiency in the pathogenesis of Alzheimer disease. It is obviously useful to do experimental animal and case controlled human studies in the first step to clarify the role of vitamin K in the pathogenesis of dementia.

In this section, we will try to discuss the relations of AD with the antioxidant vitamins, B vitamins and lastly vitamin D and K with the help of cross-sectional or longitudinal prospective observational studies, and interventional studies. Nevertheless, the subject has many aspects. As vitamin deficiencies can cause cognitive impairment, cognitive impairment can also determine changes in dietary habits and consequently cause vitamin deficiencies. Vitamin intake through food or supplementation forms can have different effects. There is also a possibility that vitamins have useful effects in different subgroups of people, based on age, nutritional status or vitamin level. Multivitamin supplementation may be more useful. Detailed investigations about these aspects will be informative.

## **2. Antioxidant vitamins**

### **2.1 Pathophysiological mechanisms**

Brain tissue is particularly vulnerable to free-radical damage because of its low level of endogenous antioxidants (Reiter, 1995). Neuropathological studies documented typical lesions from exposure to free radicals in the brains of patients with AD (Behl, 1997; Christen, 2000; Pratico & Delanty, 2000; Varadarajan et al., 2000). Lipid peroxidation seems to be especially susceptible to oxidative stress (Knopman, 1998; Pitchumoni et al., 1998; Sinclair et al., 1998). Increasing evidence also implicates neuronal membrane associated oxidative stress (for example, consequent to deposition of amyloid  $\beta$ -peptide ( $A\beta$ )) and alteration of membrane lipid metabolism (and consequent accumulation of ceramides and cholesterol) as

pathogenetic factors of synaptic dysfunction and neuronal degeneration (Cutler et al., 2004; Hyun et al., 2010; L.J. Miller & Chacko, 2004). Antioxidant treatment improved neuronal function through maintaining mitochondrial homeostasis. In a canine model of human aging, it was shown that aged canine mitochondria showed significant increases in reactive oxygen species production and a reduction in NADH-linked respiration. Mitochondrial function was improved selectively in aged dogs treated with antioxidant diet (Head et al., 2009).

Vitamin A levels in brain decline with age and lower still in individuals with AD (Goodman, 2006). A metabolic product of vitamin A, retinoic acid, is known to slow cell death and offer protection from A $\beta$  (Sahin et al., 2005). In addition to its antioxidant activity, vitamin E may modulate signal transduction pathways and participate in the synthesis pathways of neurotransmitters (Azzi et al., 1992; Martin et al., 1997; Meydani et al., 1997). Plasma vitamin C level was decreased in AD in addition to vitamin A and E (Foy et al., 1999). Vitamin C enhances the effect of medications used to treat dementia allowing the drugs to pass more easily into the brain and therefore to cause a greater effect. As a conflicting result, in the analysis of the association between the level of serum antioxidants and memory performance in an elderly, multiethnic sample of 4809 subjects; Perkins et al (Perkins et al., 1999) found a decreased serum level of vitamin E consistently associated with memory deficit after adjustment for age, education, income and vascular risk factors. Serum levels of other antioxidants (vitamins A and C,  $\beta$ -carotene and selenium) did not correlate with memory performance.

## 2.2 Studies

SENECA study reported a positive, although weak, correlation between plasma concentrations of lycopene,  $\alpha$ -carotene,  $\beta$ -carotene, total carotenes,  $\beta$ -cryptoxanthin,  $\alpha$ -tocopherol and Mini Mental State Examination (MMSE) scores (Haller et al., 1996). In the elderly population studied by Ortega et al., dietary intake of vitamin C,  $\beta$ -carotene and vitamin E were associated with a better cognitive function (Ortega et al., 2002). Perrig et al. (Perrig et al., 1997) showed that higher plasma ascorbic acid and  $\beta$ -carotene concentrations were associated with better memory performance in older people, both cross-sectionally and longitudinally over a 22 year period. In another cohort study performed on 455 elderly people with a duration of 7 year, high  $\beta$ -carotene levels were associated with less cognitive decline in APOE4 carriers but not in APOE4 negatives (Hu et al., 2006). Rats given dietary supplements of fruit and vegetable extracts for 8 months, beginning at 6 months of age, slowed age-related declines in neuronal and cognitive functions (Joseph et al., 1998). More importantly, these rats were able to reverse age-related deficits in several neuronal and behavioral parameters when administration was started at 19 months of age (Joseph et al., 1999). In another study investigating the effects of acute, short and long term pre-training administration of ascorbic acid on passive avoidance learning and memory in rats, it was concluded that short- and long-term supplementation with ascorbic acid (vitamin C) had facilitatory effects on acquisition and retrieval processes of passive avoidance learning and memory in rats (Shadidi et al., 2008).

Vitamin C supplements were shown to protect against cognitive decline in a 4 year follow up study (Paleologos et al., 1998). In Rotterdam Study (Engelhart et al., 2002), the cohort study of dietary antioxidants with a duration of 6 years, high intakes of vitamin C and E were found to be associated with lower risk of AD. In a recent study on 5395 participants

older than 54 years of age and free of dementia with a mean follow up period of 9.6 years, it was shown that participants in the highest tertile of vitamin E intake were 25% less likely to develop dementia compared with those in the lowest tertile of the intake. Dietary intake levels of vitamin C, beta carotene, and flavonoids were not related with dementia risk after multivariate adjustments. Results were similar when risk for AD was specifically assessed (Devore et al., 2010). In CHAP cohort study, on 815 elderly residents free of AD at baseline with a follow up period of 3.9 years, it was found that dietary vitamin E was associated with decreased risk for AD, while intakes of vitamin C,  $\beta$ -carotene and vitamin E from supplements were not associated at all (M.C. Morris et al., 2002). In another study investigating the effects of high dietary intake of vitamin E on prevention from AD, it was found that  $\alpha$ -tocopherol alone may not be as protective as the combined tocopherols (M.C. Morris et al., 2005a). In addition, the risk of AD was inversely related to the intake of  $\alpha$ ,  $\gamma$  and  $\delta$  but not  $\beta$  tocopherol. It was found that higher levels of dietary vitamin E lowered the risk of AD and slowed cognitive decline over the six-year course of the investigation.

In Cache County study, performed on 3227 subjects older than 64 years of age with a follow-up period of 3 years, vitamin E and C supplements in combination were associated with reduction in AD incidence, but not in users of those supplements alone (Zandii et al., 2004). Likewise, in another cohort study with a 5 year follow-up period, conducted on 894 elderly subjects, combined use of vitamins E and C supplements were associated with less cognitive decline (Maxwell et al., 2005); while in another study performed on 2969 elderly participants without cognitive impairment at baseline, the use of supplemental vitamin E and C, alone or in combination, did not reduce risk of AD or overall dementia over 5.5 years of follow-up period (Gray et al., 2008). In spite of the successful results of dietary intake of vitamin E on the prevention, supplemental use of it alone (2000 IU/day) was not shown to have an effect on progression of minimal cognitive impairment to AD and on mean cognitive change in randomised controlled studies respectively (Kang et al., 2006; Petersen et al., 2005). In a randomised controlled study performed on 341 patients with moderate AD, the patients treated with selegiline,  $\alpha$ -tocopherol supplement or combination of them had longer time to institutionalization (Sano et al., 1997). However, no significant benefit was shown in cognitive tests.

About the role of vitamin E in treatment, there is a safety problem other than analyzing its effectiveness. Recent meta-analyses of randomized trials involving vitamin E in cardiac patients and other patient groups suggest a slightly higher mortality risk associated with vitamin E treatment (Bjelokovic et al., 2007; E.R. Miller et al., 2005; Vivekananthan et al., 2003). One meta-analysis (E.R. Miller, 2005) concluded that the mortality rate associated with vitamin E treatment increased in a nonlinear dose-dependent manner, with the relative risk beginning to rise above 1 at doses  $\geq 400$  IU/day. In a study about this subject performed on 847 probable or mixed AD patients with a follow up period up to 15 years, there was no evidence that treatment with high doses of vitamin E (2000 IU/day) had an adverse effect on survival. In fact, patients whose regimens included vitamin E tended to survive longer than those taking no drug or a choline esterase inhibitor alone. It is noteworthy that the survival benefit to those taking vitamin E did not become apparent until after 4 or more years of follow up. In light of the potential for beneficial effects on vitamin E and mixed clinical trial evidence, these results emphasize the need for additional research on vitamin E supplementation in AD using a dose range that extends above 400 IU per day.

### 2.3 Comments

In conclusion, there are positive results about the use of antioxidant vitamins on mostly prevention of AD and mostly through diet. There is not sufficient evidence about their use in the treatment. In recent years, it seems that the researches on vitamin E and C have dominated. This can be due to the relation of these vitamins to the structure and physiology of brain and, more consistent finding of association between serum levels of vitamin E and memory performance in the studies. However, vitamin A is also a good candidate for more future studies.

The intake of vitamins through diet or supplementation forms and the number or quantity of different vitamins and presence of other ingredients in the supplementation forms can change the effect. For example, in the manufactured capsules of vitamin E, only  $\alpha$ -tocopherol is present. But at real, vitamin E is composed of 4 different tocopherol forms and 4 corresponding tocotrienols. This may cause ineffectiveness of vitamin E supplementation found in some studies. Also, the interaction of antioxidant vitamins with other antioxidants like flavonoids and other chemicals present in fruits and vegetables can provide benefit in the dietary intake of vitamins.

## 3. B vitamins

### 3.1 Pathophysiological mechanisms

Deficiencies of several B vitamins, including thiamine (B1), riboflavin (B2), niacin (B3), pyridoxine (B6), folate (B9) and cobalamin (B12), have been related with cognitive dysfunction in many observational study (Riedel et al., 1998). In some studies, pathophysiological models have been formulated, including the association of B vitamin deficiencies with metabolic disturbances in the structural constituents of cerebral tissue, such as phospholipids and myelin, as well as in signaling molecules, such as neurotransmitters (Rampersaud et al., 2003). In particular, thiamine deficiency has been associated with lactic acid accumulation, reduction in oxygen uptake, decrease in transketolase activity, and an impairment in cholinergic activity, leading to the loss of memory and other cognitive functions (Micheau et al., 1985). Cobalamin is essential for neuronal generation and its deficiency can cause degeneration of the nervous system (Herrmann & Obeid, 2007). Various cobalamines were shown to have intracellular antioxidant activity in vitro. The compounds inhibited intracellular peroxide production, maintained intracellular glutathione levels, and prevented apoptotic and necrotic cell death (Birch et al., 2009). Folic acid plays an important role in neuroplasticity and in the maintenance of neuronal integrity (Kronenberg et al., 2009). It enhances the plasma concentrations of docosahexaenoic acid (DHA) and eicosapentaenoic acid (EPA). EPA, DHA, and arachidonic acid are of benefit in dementia by up-regulating gene expression concerned with neurogenesis, neurotransmission and connectivity, improving endothelial nitric oxide (eNO) generation, enhancing brain acetylcholine levels, suppressing the production of proinflammatory cytokines and precursing to anti-inflammatory compounds that protect neurons from cytotoxic action of various noxious stimuli, oxidative stress and neuronal apoptosis (Das, 2008).

Recently, the association between the deficiency of B vitamins, particularly folate and cobalamin, and cognitive impairment has been investigated in relation to hyperhomocysteinemia (hHcy). Several epidemiological studies have also suggested that hHcy may play a role in the cognitive performance (Prins ND, 2002) and pathophysiology of

dementia in older people (Bell et al, 1992; Nilsson et al., 1996; Wahlin et al., 1996), possibly as the metabolic link between micro-vascular disease and old-age dementia (M.S. Morris et al., 2001; Parnetti et al., 1997). Feeding mice with a B-vitamin deficient diet for 10 weeks induced hHcy, significantly impaired learning and memory, and caused a significant rarefaction of hippocampal microvasculature unrelated to gliosis and neurodegeneration (Troen et al., 2008).

Homocystein (Hcy) is an aminoacid entirely derived from the body's intermediary metabolism (Fekkes et al., 1998; Pietrzik & Bronstrup, 1997), which can be converted to either methionine or cysteine. Both folate and cobalamin participate in the methylation of Hcy to methionine and in the remethylation and synthesis of S-adenosylmethionine (Bottiglieri, 1996; Parnetti et al., 1997). The other metabolic pathway, which converts Hcy to cysteine requires the active form of vitamin B6 (pyridoxal phosphate) (Pietrzik & Bronstrup, 1997). The most common cause of hHcy is accepted to be a deficiency of folate or cobalamin (Selhub, 2000). Almost two-thirds of the prevalence of hHcy is attributable to low vitamin B status or intake (Selhub J, 2008). Although the catabolic rate of Hcy results from the interaction between genetic make-up and B vitamin status, it is generally accepted that elevated plasma Hcy concentrations are a sensitive marker for folate and cobalamin tissue deficiency (Bottiglieri, 1996; Joosten et al., 1993; Lokk, 2003; McCaddon et al., 1998; Nilsson et al., 1996; Nilsson et al., 1999; Parnetti et al., 1997).

Folate and vitamin B12 are essential cofactors for the methionine/Hcy cycle in the brain. These vitamins mediate the remethylation of Hcy, which affects the production of the universal methyl donor, S-adenosylmethionine, in the brain among other organs. Hypomethylation, caused by low B-vitamin and hHcy, is linked to key pathomechanisms of dementia (Obeid et al., 2007). Also, Hcy is recognised to be proatherogenic and protrombotic (Hassan et al., 2004) and accepted to be an independent risk for developing occlusive arterial diseases (Refsum et al., 1998; Ueland & Refsum, 1989). hHcy exerts an inhibitory effect on adult mouse brain neurogenesis (Rabaneda et al., 2008). Low folate status and elevated Hcy increase the generation of reactive oxygen species and contribute to excitotoxicity and mitochondrial dysfunction which may lead to apoptosis (Kronenberg et al., 2009). hHcy is also proposed to be one of the effects of the oxidation of vitamin B12, as a result of oxidative stress (McCaddon et al., 2002). Furthermore, experimental studies in cell cultures have shown that Hcy is neurotoxic, possibly by activating N-methyl-D-aspartate receptors (Lipton et al., 1997) or DNA damage and consequent apoptosis (Kruman et al., 2000). In a population based study on 1779 subjects, hHcy has been reported to be an independent risk factor for dementia and cognitive impairment without dementia (Haan et al., 2007).

Depending on the used marker, 3-60 % of the elderly are classified as vitamin B12 deficient and about 29 % as folate deficient. Predominantly, the high prevalence of poor cobalamin status is caused by the increasing prevalence of atrophic gastritis type B, which occurs with a frequency of approximately 20-50% in elderly subjects (Wolters et al., 2004). Another cause of atrophic gastritis is long term treatment with proton pump inhibitors (Kuipers et al., 1995,1996; Lundell et al., 2006). Atrophic gastritis results in declining gastric acid and pepsinogen secretion, and hence decreasing intestinal digestion and absorption of both B vitamins. Such patients with atrophic gastritis require parenteral supplements. Folic acid intake among elderly subjects is generally well below the recommended dietary reference values (Wolters et al., 2004). So, folic acid deficiency is primarily caused by dietary deficiency. Meanwhile, vitamin B12 deficiency is due to two main causes, food cobalamin malabsorption and pernicious anemia (Andres et al., 2004).

### 3.2 Studies

Many epidemiological, cross-sectional and case control studies reported the association of dementia with low blood levels of vitamin B12 and folate or hHcy. However, these studies are unable to exclude the possibility that such associations of hHcy or vitamin B deficiencies are rather a result than a cause of the disease.

Kivipelto M et al (Kivipelto et al., 2009), in their prospective study found that persons with high Hcy had more than twice as high a risk of developing AD than persons with low Hcy, even after adjusting for confounding or mediating factors, suggesting that Hcy is involved in the development of dementia and AD. Vitamin B12 itself seemed not to be directly involved, because holo-transcobalamin showed no association with dementia. In some cohort studies, hHcy was found to be correlated with decline in constructional praxis and recall memory (Tucker et al., 2005) and increased risk for dementia (Dufoil et al., 2003; Haan et al., 2007; Ravaglia et al., 2005; Seshadri et al., 2002; McCaddon et al., 2001), while in some others it was not correlated with cognitive decline (Clarke et al., 2007; Kalmijn et al., 1999; Luchsinger et al., 2004; Mooijaart et al., 2005; Teunissen et al., 2003). In the cohort studies, low plasma level of folate was found to be associated with decline in constructional praxis and lower cognitive function regardless of Hcy respectively (de Lau et al., 2007; Tucker et al., 2005). In another cohort study performed on 370 non demented persons older than 74 years of age, persons with low serum level of vitamin B12 or folate had the risk of developing AD (Wang et al., 2001). In addition to low folate and high Hcy plasma levels, low plasma concentration of vitamin B12 was also associated with decline of constructional praxis in a 3 year cohort study (Tucker et al., 2005).

Cohort studies of dietary intake of B vitamins in healthy elderly persons revealed conflicting results. In one of them, dietary intake was found to be not related with the risk of developing AD (MC Morris, 2006a). In another, the highest quartile of total folate intake was related to lower risk of AD (Luchsinger et al., 2007), while the other reported that rate of cognitive decline among persons in the top folate intake was more than twice that of those in the lowest fifth of intake (MC Morris et al., 2005b).

Despite potential benefits of vitamin B supplementation for lowering Hcy, the positive contribution of this supplementation to cognitive function among demented and non-demented persons remains debatable. There was a large heterogeneity among present vitamin B interventional studies with cognitive assessments in terms of dosage, routes of intervention (for vitamin B12), age and cognitive function assessments.

It has been proven that folate supplementation reduces plasma Hcy levels. This was observed by Jacques et al. in the Framingham Offspring Study cohort, after the folate fortification of grain in the Unites States started in January 1998 (Jacques et al., 1999). Nevertheless, the relationship between dietary folic acid intakes and plasma Hcy concentrations seems to be characterized by a threshold effect (Selhub, 1993): above a certain dosage of folate supplementation, there is no additional effect on lowering circulating Hcy. It is not clear where this threshold stands: a metanalysis of 12 randomized controlled trials assessed that the minimum dosage of folate capable of determining a maximum reduction (about %25) of circulating Hcy was 0.5 mg/day. More recent randomized trials determined this threshold at 0.8 mg/day (Wald et al., 2001) or 0.4 mg/day (van Oort et al., 2003). The differences are possibly explained by population selection biases (van Oort et al., 2003).

Some randomised controlled trials, including persons with normal cognitive function, cognitive impairment and dementia, evaluated the effect of folate supplementation on cognitive function. Among cognitively impaired subjects (n=30) with low folate serum

levels, Fioravanti et al (Fioravanti et al., 1998) observed a significant improvement of some scores of the Randt Memory Test in the folate treated group compared with the placebo group after 60 days of treatment. In another trial using a mixed factorial design in normal subjects (n=211), the authors observed that folate-treated older women's cognitive test scores (Rey Auditory-Verbal Learning Test) improved (Bryan et al., 2002). Controversially, in another small study including 7 subjects with dementia reported no statistically significant differences between the supplemented group and the control group, and noted a negative trend in specific test scores of the supplemented group (Sommer et al., 2003). Because of the small number of subjects, study results need to be interpreted cautiously. Finally, the 3-year randomised controlled FACIT trial included 818 older subjects (older than 60 years) with augmented plasma total Hcy and normal serum vitamin B12 levels. The effect of folic acid supplementation on cognition was the secondary end point. The 3-year change in memory, information processing speed and sensorimotor speed were significantly improved in the folic acid group in comparison to the placebo group (Durga et al., 2007). Folic acid potentiated the effect of memantine on spatial learning and neuronal protection in an AD transgenic model (Chen et al., 2010).

Some other randomised controlled studies assessed the effect of vitamin B12 intervention on cognitive functions in humans. There is a large heterogeneity among trials regarding the cognitive status of participants, the doses and administration routes of vitamin B12, the duration of supplementation and the applied cognitive function assessment instruments. Sample sizes ranged from 18 to 78 subjects receiving vitamin B12, and the duration of supplementation ranged from 4 weeks to 6 months. For most cognitive tests, there was no significant improvement in vitamin B12 supplemented patients as compared with the placebo group (Eussen et al., 2006; Hvas et al., 2004; Stoot et al., 2008). However, Bryan J et al found that healthy younger, middle-aged and older women (n=211) who took vitamin B12 (or either of folate and vitamin B6 ) for 35 days showed better performance on some measures of memory performance compared to placebo (Bryan et al., 2002). Interestingly, a statistically significant worsening of cognitive tests was reported in two studies. In 195 vitamin B12 deficient subjects of normal and impaired cognition, Eussen et al (Eussen et al., 2006) observed that improvement of the cognitive test score in the placebo group was significantly more marked than that of the vitamin B12 group. Similarly, another study reported a significant worsening of the '12 words learning test' score in a vitamin B12 treated population of 140 old patients with cognitive impairment and methylmalonic acidemia, in comparison to the placebo group (Hvas et al., 2004). For reasons of heterogeneity of these controlled trials, no reasonable conclusion can be drawn regarding the effects of vitamin B12 on cognition. In addition, several uncontrolled cohort studies assessed the effects of vitamin B12 intervention on cognitive function in humans with conflicting results.

A few studies (Lewerin et al., 2005; McMahon et al., 2006; Stott et al., 2005; van Uffelen et al., 2007) reported data of combined B vitamin intervention on cognition, in subjects with normal cognition, dementia or vascular disease (17-409 participants). Trial durations ranged from 12 weeks to 2 years. One study found a significant improvement in one of eight cognitive tests (Reitan trail-making test, part B) (McMahon et al., 2006). In a recent randomized, double-blind controlled study in 271 individuals over 70 years old with mild cognitive deficit, high dose B vitamins lowering Hcy level slowed the rate of accelerated brain atrophy, which was found to be major determinant of cognitive decline in this population (Smith et al., 2010). It was reported that trials were needed to see if the same treatment will delay the development of AD (Smith et al., 2010).

### 3.3 Comments

Most studies reporting associations between cognitive function and Hcy or B vitamins have used a cross-sectional or case-control design and have been unable to exclude the possibility that such associations are a result of the disease rather than being causal. The prospective study indicating that persons with high Hcy have more than twice as high as developing AD than persons with low Hcy, even after adjusting for confounding or mediating factors, is an important one. The Hcy hypothesis of dementia has attracted considerable interest, as Hcy can be easily lowered by folic acid and vitamin B12, raising the prospect that B-vitamin supplementation could lower the risk of dementia (Clarke et al., 2008). While some trials assessing effects on cognitive function have used folic acid alone, vitamin B12 alone or a combination, few trials have included a sufficient number of participants to provide reliable evidence. Among these studies, FACIT Trial (Durga et al., 2007) is an outstanding one. This large, randomised and controlled trial on elderly participants with high plasma Hcy and normal vitamin B12 serum level have showed that folic acid supplementation improved several cognitive domains that tend to decline with advancing age. Therefore, folate supplementation may be an interesting approach to prevent cognitive decline in elderly people. New trials with larger number of participants are needed to test the importance of vitamin B intake through diet or supplementation forms in the prevention and treatment of AD.

## 4. Vitamin D

Vitamin D exhibits functional attributes that may prove neuroprotective through antioxidative mechanisms, neuronal calcium regulation, immunomodulation, enhanced nerve conduction and detoxification mechanisms. Compelling evidence supports a beneficial role for the active form of vitamin D in developing brain as well as in adult brain function. The vitamin D receptor and, biosynthetic and degredative pathways for the hydroxylation of vitamin D have been found in the rodent brain; more recently these findings have been confirmed in humans. The vitamin D receptor and catalytic enzymes are colocalized in the areas of the brain involved in complex planning, processing, and the formation of new memories. These findings potentially implicate vitamin D in neurocognitive function (Buell & Dawson-Hughes, 2008).

Treatment with  $1,25(\text{OH})_2\text{D}_3$  attenuated hippocampal atrophy and protected neuron density ( a marker for neuronal death) in aging rats (Landfield & Cadwalleder-Neal, 1998). Data in human subjects with AD revealed a reduction in VDR mRNA in specific regions of the hippocampus (CA1 and CA2) compared to controls (Sutherland et al., 1992) and a higher frequency of VDR polymorphisms were found in Alzheimer's brains than age-matched controls (Gezen-Ak et al., 2007).

Low serum levels of  $25(\text{OH})\text{D}$  have been associated with increased risk for cardiovascular diseases, diabetes mellitus, depression, dental caries, osteoporosis, and periodontal disease, all of which are either considered risk factors for dementia or have preceded incidence of dementia. There is a higher prevalence of falls and fractures in patients with AD (Buchner & Larson, 1987) and community studies have shown that residents with AD and dementia had lower serum concentrations of  $25(\text{OH})\text{D}$  (Kipen et al., 1995). While the temporal associations of these findings remains unclear, in a study in patients with AD,  $25(\text{OH})\text{D}$  concentrations were significantly elevated after year-round sun exposure. Additionally, the sun- exposed cohort had a reduced risk of falls and fractures compared to the unexposed (Sato et al., 2005).

Data from the Nutrition and Memory in Elderly study (NAME) (Scott et al., 2004) supported these findings. In subjects (n=318) who completed a full neurological and psychiatric examination, in addition to magnetic resonance imaging, it was observed that vitamin D concentrations were lower in patients with dementia than those without. Additionally, vitamin D concentrations lesser than 50 nmol/L were associated with a higher prevalence of a diagnosis of possible or probable AD. In a recent cross-sectional investigation of vitamin D, dementia and MRI measures of cerebrovascular disease among 318 participants, mean vitamin D concentrations were lower in subjects with dementia. There was a higher prevalence of dementia, large vessel infarcts and increased white matter hyperintensity volume among participants with vitamin D insufficiency. After adjustment for age, race, sex, bodymass index, and education, vitamin D insufficiency was associated with more than twice the odds of all cause dementia, AD and stroke (Buell et al., 2010). Based on increasing number of studies linking the risk factors of AD with vitamin D deficiency, Grant WB (Grant, 2009) states that there are established criteria for causality in a biological system. The important criteria include strength of association, consistency of findings, determination of the dose-response relation, an understanding of the mechanisms, and experimental verification. Grant WB (Grant, 2009) suggests that further investigation of possible direct or indirect linkages between vitamin D and dementia is needed. Studies of incidence of dementia with respect to prediagnostic serum 25(OH)D or of vitamin D supplementation are warranted. In addition, since the elderly are generally vitamin D deficient and since vitamin D has so many health benefits, those over the age of 60 years should consider having their serum 25(OH)D tested, looking for a level of at least 30 ng/ml but preferably over 40 ng/ml, and supplementing with 1000-2000 IU/day of vitamin D3 or increased time in the sun spring, summer, and fall if below those values (Grant, 2009).

## 5. Vitamin K

Vitamin K is necessary for the liver functioning. Vitamin K dependent  $\gamma$ -carboxylation of glutamate takes part in formation of the coagulation factors 2, 7, 9 and 10. More recently, it has been established that vitamin K dependent  $\gamma$ -carboxylation of glutamate occurs also in extrahepatic sites and modifies proteins with other functions. One of these sites is brain. Allison AC (Allison, 2001) proposed a possible role of vitamin K deficiency in the pathogenesis of AD and in augmenting brain damage associated with cerebrovascular disease, based on the potential actions of vitamin K in the brain and through a link to the apolipoprotein E genotype. The apolipoprotein E4 allele, an established risk factor for AD (Mattson, 2004), strongly influences plasma vitamin K levels (Kohlmeier M, 1996; Saupé J, 1993). Thus, carriers of apolipoprotein E4 allele could also those with the lowest vitamin K concentrations, an association that has not yet been investigated. Vitamin K is required for normal brain development and function. The maternal exposure to coumarin derivatives is associated with abnormalities of the central nervous system (Pauli & Haun, 1979). Vitamin K deficiency is associated with decreased sulfation in the brain. Keratan sulfate is dramatically decreased in cerebral cortex of AD patients (Lindahl, 1996). Considering keratan sulfate proteoglycan being the major protein of synaptic vesicles (Scranton et al., 1993), one manifestation of decreased sulfation can be abnormal structure and function of the major protein of synaptic vesicles (Allison, 2001). Likewise, addition of vitamin K to the chick embryo increases tyrosine phosphorylation in the brain adhesion and cytoskeletal proteins (Saxena et al., 1997), suggesting that vitamin K plays an role in the development of the

central nervous system. Another vitamin K dependent protein in the brain is Gas 6, a product of growth arrest specific gene 6. Both Gas 6 and its tyrosine kinase receptor are widely distributed throughout the central nervous system (Prieto et al., 1999). Interaction of these plays an important role in preventing neurons from apoptosis (Allen et al., 1999). Cell culture studies have shown that Gas 6 can rescue cortical neurons from A $\beta$  induced apoptosis (Yagami et al., 2002) and provided evidence that vitamin K can have a protective role against oxidative injury in developing oligodendrocytes and neurons (Denisova & Booth, 2005).

Considering that a relative deficiency of vitamin K, affecting the extrahepatic functions of the vitamin, is common in aging men and women; Allison AC (Allison, 2001) suggests that it is obviously useful to do experimental animal and case controlled human studies in the first step to clarify the role of vitamin K in the pathogenesis of dementia. In a likely study, low vitamin K intakes in 31 community-dwelling elders at an early stage of AD was detected in comparison to 31 age and sex matched cognitively intact control subjects (Presse et al., 2008).

## 6. Multi-intervention

Due to the fact that the interventional trials with antioxidants and B-vitamins did not hold the expectations, studies combining micronutrients are of particular interest. To date, a few prospective studies estimating the effect of nutrition and vitamin supplementation exist. One of these studies (Wolters et al., 2005) was performed on 220 healthy, free living women older than 60 years of age. After taking multivitamins (containing 8 vitamins and 4 minerals) for 6 months daily, no change on cognitive performance was observed as compared to placebo. The intervention period of only 6 months may be too short for improving cognitive performance in well-educated elderly women without dementia. Another study (McNeill et al., 2007) was performed on 910 healthy men and women aged 65 years and over. Four hundred and fifty six of them were on active daily treatment with 11 vitamins and 5 minerals for 12 months, while the remaining ones took placebo. Benefit was detected only on verbal fluency tests in the subgroups of participants aged over 74 years or those with increased risk of micronutrient deficiency. In a 12 month, open label trial with 14 mild AD patients, the efficacy of a multi-component formulation showed promising results regarding neuropsychiatric inventory and activities of daily living (Chan et al., 2008). This was confirmed by placebo-controlled data from 12 institutionalized patients with moderate to severe AD showing improvement in cognition, mood, and daily function (Remington et al., 2009). As a result, to draw any conclusion, larger randomized controlled studies with combined supplements are needed, especially in the context that multi-component dietary approaches such as Mediterranean diet or fruit and vegetable (or juice) consumption have been shown to be successful (Barberger-Gateau et al., 2007; Dai et al., 2006; MC Morris et al., 2006b; Scarmeas et al., 2006, 2009).

## 7. Conclusion

There is a relationship of levels of antioxidant vitamins and B vitamins to vascular dementia. Nevertheless, if this relationship is based on causality, it is not so clear after performed longitudinal and interventional studies. New trials with larger number of participants will be more clarifying. Recently, vitamin D deficiency has been found to be related with AD. Longitudinal and interventional studies, especially with long follow up

period, will be informative about its role. Additionally, vitamin K is thought to have a possible role in the pathogenesis of dementia.

The subject has multiple aspects. As vitamin deficiencies can cause cognitive impairment, cognitive impairment can also determine changes in dietary habits and consequently cause vitamin deficiencies. Vitamin intake through diet or supplementation forms can have different effects. There is also a possibility that vitamins have useful effects in different subgroups of people, based on age, nutritional status or vitamin level. Multivitamin supplementation may be more useful. The roles of vitamins in dementia are not clear yet as those of macronutrients in spite of the reports expressing the benefits of caloric restriction and intake of higher unsaturated fatty acids on cognitive functions. Presence of relationships between macronutrients and vitamins is also possible. Detailed investigations about these aspects will be informative.

## 8. References

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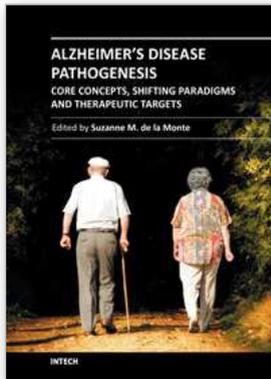
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## **Alzheimer's Disease Pathogenesis-Core Concepts, Shifting Paradigms and Therapeutic Targets**

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Alzheimer's Disease Pathogenesis: Core Concepts, Shifting Paradigms, and Therapeutic Targets, delivers the concepts embodied within its title. This exciting book presents the full array of theories about the causes of Alzheimer's, including fresh concepts that have gained ground among both professionals and the lay public. Acknowledged experts provide highly informative yet critical reviews of the factors that most likely contribute to Alzheimer's, including genetics, metabolic deficiencies, oxidative stress, and possibly environmental exposures. Evidence that Alzheimer's resembles a brain form of diabetes is discussed from different perspectives, ranging from disease mechanisms to therapeutics. This book is further energized by discussions of how neurotransmitter deficits, neuro-inflammation, and oxidative stress impair neuronal plasticity and contribute to Alzheimer's neurodegeneration. The diversity of topics presented in just the right depth will interest clinicians and researchers alike. This book inspires confidence that effective treatments could be developed based upon the expanding list of potential therapeutic targets.

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