

The Prevention of Memory Loss and Progression to Alzheimer's Disease with B Vitamins, Antioxidants and Essential Fatty Acids: A Review of the Evidence

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Abstract *Memory loss and increased risk of Alzheimer's disease (AD) is strongly associated with low levels of B₁₂ and folic acid, fish consumption and raised plasma homocysteine (Hcy). Placebo controlled trials have shown protection from memory loss and/or reduced brain shrinkage in older people with raised Hcy levels given high dose supplements of vitamin B₁₂, folic acid, B₆ or docosahexaenoic acid. In those with early stage AD there is some evidence of a reduction in cognitive decline in those given high dose B vitamins. There is inconclusive evidence regarding the combined supplementation of high dose vitamin C, together with vitamin E. The need for early screening for cognitive decline and raised Hcy is essential given the growing body of evidence that Hcy lowering nutrients arrest cognitive decline and accelerated brain shrinkage.*

Introduction

Alzheimer's disease (AD) is characterized by a progressive loss of cognitive functions including memory, language, judgment, praxis and orientation and is diagnosed on the basis of shrinking in the thickness of the medial temporal lobe, which is considered to be the primary pathology that generates the associated symptoms.¹ The detectable, preclinical phase of AD presents as mild cognitive impairment (MCI).^{2,3}

Episodic memory impairment is the most common initial symptom of MCI.⁴ Poor performance in verbal or visuospatial memory recall, processing speed, attention and executive function tasks requiring planning or judgement and semantic fluency are common predictors of Alzheimer's risk.⁵⁻⁷ (These aspects of memory and cognitive function are included in Food for the Brain's Cognitive Function Test available free on-line at: www.cognitivefunctiontest.org).

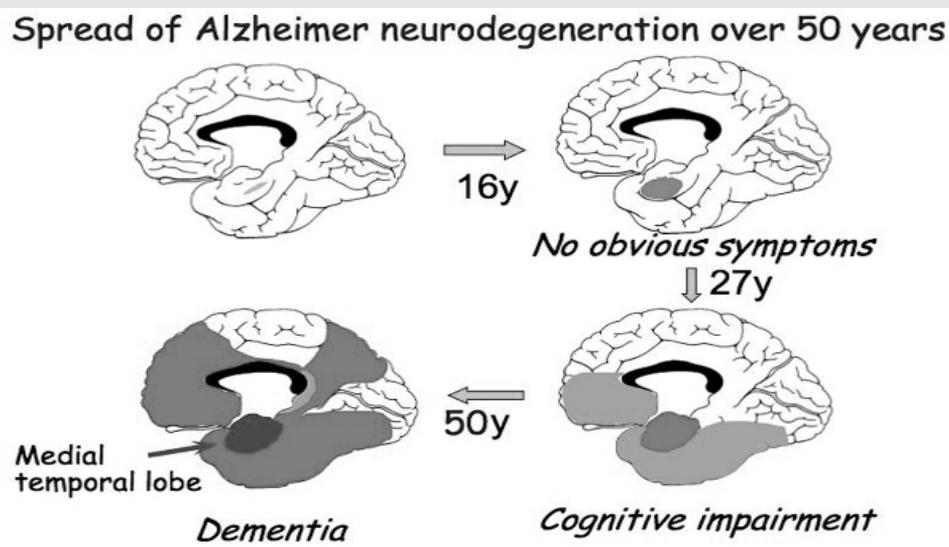
The process of memory decline and brain

shrinkage associated with AD is thought to occur over a 30 to 40 year period, hence identifying the need for screening ideally from age 50 (see **Figure 1**, p.54).

High Homocysteine, and Low Folic Acid and Cobalamin Status as Markers

Both high plasma homocysteine (Hcy) levels and low folic and (cobalamin) B₁₂ levels in blood correlate with increasing risk for AD according to a systematic review.⁸ A review in 2008 concluded: "Seventy-seven cross-sectional studies on more than 34,000 subjects and 33 prospective studies on more than 12,000 subjects have shown associations between cognitive deficit or dementia and Hcy and/or B vitamins."⁹ Hcy levels also predict and correlate with rate of cognitive decline,¹⁰ as does B₁₂ status.^{11,12}

There is, therefore, ample evidence to propose that lowering Hcy by giving appropriate supplemental levels of Hcy lowering nutrients,

Figure 1. Spread of Alzheimer neurodegeneration over 50 years.

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including B₆, B₁₂ and folic acid, would reduce risk. At what point in the process are cognitive decline reversible, and what dosage of nutrients confers maximum protection?

Clinical Trials of B Vitamins in Relation to Prevention of Memory Decline

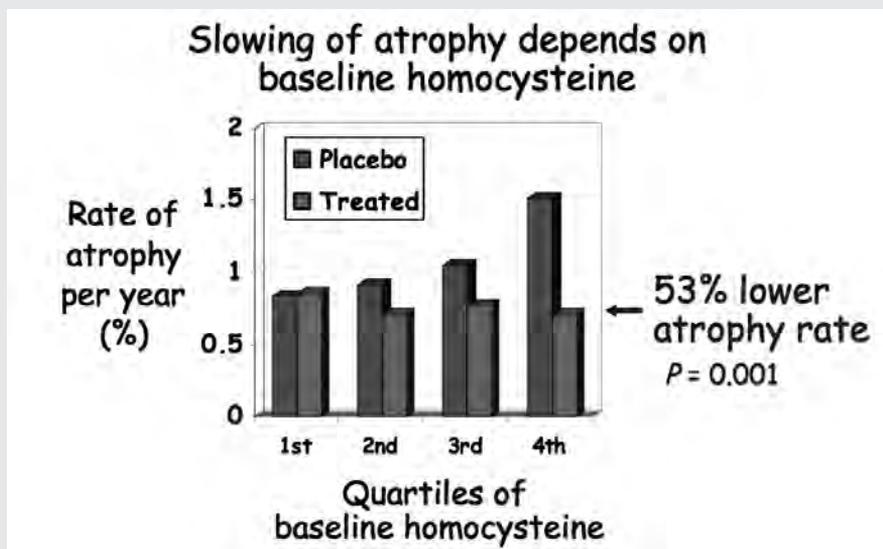
Durga et al provided older adults (>50 years) without MCI, but with raised Hcy (>13 µmol/L), supplemental folic acid (0.8 mg/d) or placebo for three years.¹³ The results demonstrated a highly significant improvement in memory, information processing speed and sensorimotor speed in the treatment group.

AD Smith et al. investigated the effects of giving B vitamins versus placebo in a randomized controlled trial to those with MCI, measuring brain shrinkage with an MRI scan, as well as cognitive function.¹⁴ In this study a Hcy above 9.5 µmol/L correlated with accelerated brain shrinkage and cognitive decline. Those given folic acid (0.8 mg/d), vitamin B₁₂ (0.5 mg/d) and B₆ (20 mg/d) had a significant reduction in the rate of brain shrinkage (p=0.001; **Figure 2**, p.55). Treated patients with baseline Hcy levels > 13 µmol/L had rates of atrophy that were 53% lower than

other patients in the treatment group. Greater rates of atrophy were associated with lower final cognitive test scores.

De Jager evaluated changes in cognition in patients with MCI from the previous study, given B vitamins or placebo. These results, pending publication, indicate a greater decrease in cognitive function with higher baseline Hcy, with effectively no significant further decline in those taking the B vitamins. In patients with a baseline of Hcy above 11 µmol/L, the difference in cognitive decline between the placebo and supplemental group was significant.¹⁵

Aisen et al. gave Hcy-lowering B vitamins to those already diagnosed as suffering from mild to moderate AD.¹⁶ Patients were not selected on the basis of Hcy values (mean Hcy was 9.1 µmol/L at baseline), and brain scans were not conducted. The patients received folic acid (5 mg/d), B₁₂ (1 mg/d), and B₆ (25 mg/d) over a period of 18 months). No overall difference occurred in rate of cognitive decline in those on the supplements versus placebo. However, when the patients were divided into those with high and low cognitive test scores at the start, those who had milder AD did significantly respond; those taking the B vitamins

Figure 2. Slowing of atrophy depends on baseline homocysteine

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hardly got worse over 15 months, while those on the placebo showed a steady decline. Over the 18 months Hcy dropped from an average of 9.1 $\mu\text{mol/L}$ to 6.8 $\mu\text{mol/L}$.

Kwok et al. studied 140 subjects with mild to moderate AD or vascular dementia given either methyl B₁₂ (1 mg/day) and folic acid (5 mg/day) or placebo for 24 months.¹⁷ They found a significantly smaller decline in the Mattis Dementia Rating Scale (construction domain) in the supplemented subjects with a baseline Hcy > 13 $\mu\text{mol/L}$ ($p=0.003$).

Ford et al. gave 299 older hypertensive men without cognitive impairment either B₁₂ (0.4 mg), folic acid (2 mg), B₆ (25 mg) or placebo over two years.¹⁸ No change was found in the cognitive subscale of the Alzheimer's Disease Assessment Scale (ADAS-cog). However this test is not sufficiently sensitive to changes outside of the scope of MCI and dementia. Also, homocysteine levels were not measured.

These studies suggest that Hcy-lowering B vitamins can, at least, arrest cognitive decline and possibly improve it in people over age 50, with or without cognitive decline, but with a raised Hcy level (>9.5 $\mu\text{mol/L}$), and may arrest or slow down cognitive decline in those with

mild AD, but not in moderate to severe AD. However, it is conceivable that AD patients with raised Hcy may respond differently.

Further research is needed to determine if these improvements prevent the development of AD, and to determine what combination and intake of Hcy lowering nutrients have the most significant clinical effect. This is also the conclusion of a recent review.¹⁹

The effect of lowering Hcy could potentially have many positive effects on brain function. Hcy is itself a toxic amino acid capable of inducing neurotoxicity those NMDA receptor activation and oxidative stress through increasing NOS. It also damages blood vessels potentially impairing oxygen and nutrient flow to the brain, associated with vascular dementia. Raised Hcy also reflects faulty methylation. Methylation is required for the formation of neurotransmitters and phospholipids. Lowering Hcy is also associated with reducing oxidative stress.

The Role of N-Acetyl Cysteine, Glutathione, and MethylB₁₂

Methylation requires the synthesis of S-adenosyl methionine (SAM) from Hcy, a pathway that is B₁₂ and folic acid dependent. SAM

synthesis is impaired by oxidative stress, while B₁₂ is also vulnerable to oxidative deactivation. Oxidative stress increases the requirement for SAM but decreases its synthesis. In the liver, Hcy can also be metabolized via the transsulfuration pathway to synthesize the essential intracellular antioxidant, glutathione. Theoretically, by providing glutathione, or its precursor N-acetyl cysteine (NAC), together with methyl B₁₂, SAM can be spared and Hcy lowered.

A small number of general practitioners have been implementing a B vitamin based Hcy management approach, including NAC and reported good outcomes. A series of case reports have been published.²⁰ Quoting the author: "Patients presenting with mild cognitive impairment frequently have raised blood Hcy levels; I routinely measure this in all such cases. There is now good evidence for lowering elevated levels with high dose B-vitamins. I also prescribe the antioxidant NAC to further lower Hcy. In my experience, I have found significant clinical improvement from this approach."

Hcy can also be processed in the liver by the betaine-homocysteine methyl transferase (BHMT) pathway, requiring trimethylglycine (TMG) and zinc. The addition of NAC, TMG and zinc to the usual combination of B₁₂ (ideally as methyl B₁₂), folic acid and B₆ has yet to be tested in a clinical trial and may yield further reductions in Hcy with associated clinical improvements.

Vitamins C and E

A cross-sectional and prospective study of 4,740 Cache County Utah elderly residents found the combination of vitamin E and C to be associated with reduced AD prevalence of 78% and incidence of 63%. A trend toward lower AD risk was also evident in users of vitamin E together with multivitamins containing vitamin C, but there was no evidence of a protective effect with use of vitamin E or vitamin C supplements alone, with multivitamins alone, or with vitamin B-complex supplements. Lowest risk was reported in those supplementing at least 1,000 mg/day of vitamin C with at least 1,000 IU/day of vitamin E.²¹ In a double-blind study, subjects with MCI were randomly assigned to receive 2,000 IU/day of vitamin E, 10

mg/day of donepezil, or placebo for three years. There were no significant differences in the rate of progression to AD between the vitamin E and placebo groups at any point.²² These results suggest that there might be more therapeutic gains when treating patients that have yet to develop either MCI or AD. These results also suggest that both vitamins E and C are likely to be more beneficial than using vitamin E alone.

Fish Consumption and Omega-3 Essential Fatty Acid Supplementation

Eating fish once a week reduces risk of developing AD by 60%, according to a study by Morris et al.²³ They followed 815 people, aged 65 to 94 years, for 7 years and found that the dietary intake of fish was strongly linked to AD risk. They found that the strongest link was the amount of docosahexaenoic acid (DHA) in the diet; the higher the DHA intake the lower their risk of developing AD. The lowest amount of DHA per day that offered some protection was 100 mg. Eicosahexaenoic acid (EPA) intake did not reach significance; however, the highest intake of EPA consumed was 30 mg a day.

In a RCT, 900 mg of DHA was taken daily for 24 weeks with reported improvements in learning and memory function among those with age-related cognitive decline.²⁴ In a further trial by the same research group, 2,000 mg/day of algal DHA or placebo to 402 subjects with mild to moderate AD for 18 months resulted in no cognitive improvement.²⁵

Clinical Recommendations

AD is an advanced disease process, requiring many years of progression before it is clinically diagnosed. Using nutritional supplements late in the disease process may yield limited benefits. However, the low cost and potential benefits of nutritional supplements make them attractive therapeutically. On the basis of the evidence, there is good logic to pursue specific clinical recommendations, especially among patients without any evidence of cognitive impairment. Patients 50 years or older should have their cognitive function tested. Hcy should also be tested in patients exhibiting signs of reduced cognitive function. Supplement Hcy-lowering nutrients daily if the Hcy result is above 9.5

μmol/L. These include:

- folic acid: 400–800 mcg
- B₁₂: 500–1,000 mcg (preferably, methyl B₁₂)
- B₆: 20–40 mg

There is good logic in using these additional daily nutrients:

- zinc: 10–15 mg
- TMG: 1,000–2,000 mg
- NAC: 500–1,000 mg
- omega-3 essential fatty acids (fish source): 500–1,000 mg DHA

While there might be some logic in supplementing with vitamin E (1,000 IU/day) and vitamin C (>1,000 mg/day) among elderly individuals without MCI or AD, further research is needed.

Contraindications

Folic acid supplementation, especially in those with low vitamin B₁₂ status, may increase colorectal and other cancer risk in older people.²⁶ This issue remains unresolved since a recent large-scale study by the American Cancer Society involving almost 100,000 people reported a reduced, not increased risk of colorectal cancer with increasing folate intake.²⁷ Until more definitive conclusions can be made, daily doses exceeding 400 mcg should be used with caution, especially in countries that have implemented food fortification with folic acid. It is also unknown if this cautionary recommendation applies to those supplementing with a combination of Hcy-lowering nutrients as a result of raised Hcy levels.

Dietary Guidelines

There is an increasing body of evidence linking metabolic syndrome, insulin resistance and diabetes with risk for dementia/AD. Following a low glycemic load diet, high in oily fish, nuts, seeds and beans, with plenty of antioxidant rich fruits and vegetables, is likely to be protective. Limit or avoid coffee, which is known to raise Hcy levels. Whether or not coffee intake increases or reduces risk for AD is currently inconclusive.

Competing Interests

The author receives royalties of nutritional supplement formulae in the UK and South Africa.

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