



HAWAII DEMENTIA PREVENTION TRIAL: A RANDOMIZED TRIAL EVALUATING A MULTIFACETED NUTRITIONAL INTERVENTION TO SLOW COGNITIVE DECLINE IN MILD COGNITIVE IMPAIRMENT PATIENTS

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ABSTRACT

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Introduction: Alzheimer's disease (AD) has no effective treatment, nor does its “precursor” mild cognitive impairment (MCI). Methods: This is a nine-month, randomized, open, pilot trial. We are using four dietary changes and twelve supplements to slow progression of dementia in patients with MCI. Patients were randomly assigned to the diet-plus-supplement intervention group (1) or to the supplement intervention group (2). Supplementary cobalamin, folate, and S-adenosylmethionine (SAM) may reduce secretase/amyloid production. Antioxidants coenzyme Q10, ascorbates, gamma-tocopherol, and extracts of ginkgo biloba and centella asiatica were used. Zinc, copper, manganese, and selenium support endogenous antioxidant enzymes. Dietary interventions include berries, walnuts, decreasing dietary advanced glycation endproduct intake, and limiting saturated fatty acids to seven percent of calories. Results: In this small pilot study, it was surprising that participants in the supplement-only group improved more than in the supplement-plus-diet group. The Mini Mental State Examination (MMSE) was administered at baseline and every 3 months. While 9.6% of MCI patients normally degenerate to dementia each year, over nine months, participants in the supplement-only group had an average improvement in the MMSE of 10 points (out of 30 points). At the end of the intervention, average score was 29 out of 30 points, indicating a normal cognitive state. In the food-plus-supplement group no degeneration was seen, although improvement was also not seen.

Conclusions: This multifaceted nutritional intervention had a positive impact by slowing the progression of dementia and reducing the risk of Alzheimer's disease. A larger, multicenter trial is needed to confirm these results.

1. INTRODUCTION

There has been an alarmingly sharp increase in deaths from Alzheimer's disease (AD) between 1979 and today, with further increases forecast. According to the latest United States Centers for Disease Control figures, per 10,000 in the population, deaths from Alzheimer's disease increased from 3 in 1979 to 268 in 2013 (reported in 2016) [1]. Although cholinesterase inhibiting drugs and N-methyl-D-aspartate receptor antagonist drugs may temporarily improve memory, they may not be able to stop beta-amyloid plaque buildup or slow nerve membrane disruption and brain neuron death [2].

This intervention trial tested the ability of a multi-faceted nutritional intervention to slow beta-amyloid plaque buildup and to slow nerve membrane disruption and brain neuron death. The hypothesis was that these interventions would slow the progression of mild cognitive impairment (MCI) into AD.

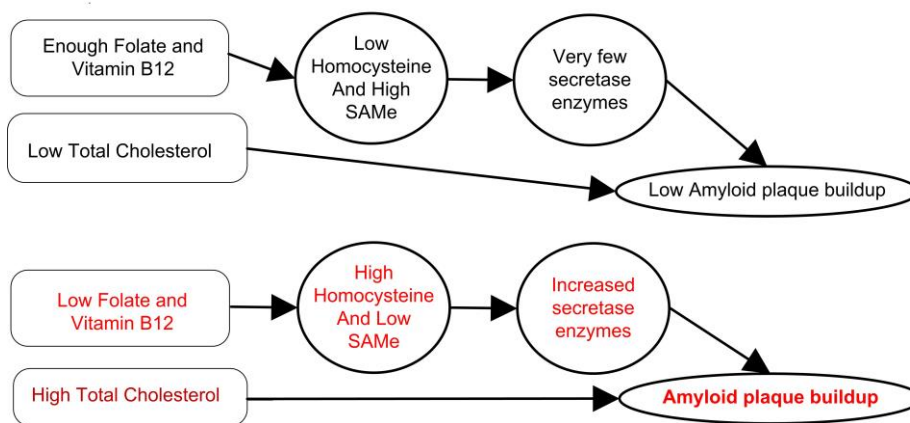
1.1. Slowing Amyloid Plaque Production: Folate, Cobalamin, Homocysteine, and SAM

Beta-secretase and gamma-secretase are two enzymes expressed in brain neurons that can abnormally cleave amyloid precursor protein (APP) into amyloid peptides [3]. These amyloid peptides can be toxic and can contribute to the formation of amyloid plaques, a signature feature of Alzheimer's disease. If we can reduce beta- and gamma-secretase biosynthesis, then there may be less abnormal cleavage of the APP [4]. Less abnormal cleavage of the APP can lead to less amyloid plaque buildup from amyloid peptides. There are no drugs available to slow the formation of the secretase enzymes. Pharmaceutical attempts to slow the production of gamma- and beta-secretase enzymes have not been successful. However, there is evidence that expression of these two enzymes can be decreased by supplying folate and cobalamin to assist the transformation of homocysteine into S-adenosylmethionine (SAM). SAM has the ability to quench, through methylation, the production of beta- and gamma-secretase.

When adequate folate and cobalamin are present, homocysteine can be converted to SAM [5]. SAM, through methylation of DNA, quenches the expression of the presenilin-1 gene, thus reducing beta-secretase biosynthesis [6]. Also, reduced homocysteine increases DNA methyltransferases, which reinforces DNA methylation, leading to decreased beta-secretase biosynthesis [7].

We would expect to find lower than normal levels of SAM in AD patients, and this has been found. The severely low levels of SAM that have been found in the cerebrospinal fluid and in all brain regions tested in AD patients may partially explain the abnormal cleavage of APP and high levels of amyloid-beta production in these patients [8].

When folate and cobalamin are not taken in adequate amounts, less homocysteine is converted to SAM. This can result in elevated homocysteine levels. Elevated homocysteine in plasma has been found to be a risk factor for the onset of AD [9]. In fact, high levels of homocysteine were found to quadruple the risk of dementia and AD [10]. Patients with confirmed AD were four times as likely to have elevated homocysteine [11]. Interestingly, higher homocysteine levels in the brain are also associated with the accumulation of phosphorylated tau, one of the signature features of AD [12].



Low levels of folate might reduce the biosynthesis of SAM from homocysteine, leading to increased rates of AD. Low levels of folate were found to triple the risk of vascular dementia and AD [10]. Patients with AD were three times as likely to have low folate levels [11]. In order to ensure adequate conversion of homocysteine to SAM, we supplied participants with an oral dosage of folic acid of 600 micrograms (mcg) daily. The daily tolerable upper intake level for folic acid is 1000 mcg.

Patients with confirmed AD were four times as likely to have low cobalamin compared to people without AD [11]. Low levels of cobalamin might limit production of SAM, leading to more production of beta- and gamma-secretase enzymes. In order to limit production of amyloid plaques, we supplied a daily dosage of 240 mcg of methylcobalamin for participants. Since absorption is often one percent of the dose, Quadros [13] 240 mcg can supply the required 2.4 mcg recommended daily allowance for cobalamin. There is no upper limit set for this non-toxic B-vitamin.

In addition to supplying folic acid and cobalamin to boost SAM production, we supplied exogenous SAM in an oral dosage of 200 milligrams (mg) daily, given in the morning. This supplemental SAM may be able to further limit the production of amyloid plaques by limiting the abnormal cleavage of the APP.

1.2. Advanced Glycation Endproducts

In advanced AD, up to half of the original brain neurons may be lost. The damage and death of these neurons may be related to excess oxidation with inadequate antioxidants—both exogenous and endogenous. The high percentage of very long-chain and highly unsaturated fatty acids in brain cell membranes increases their vulnerability to oxidation. Advanced glycation endproducts (AGEs) may increase oxidation and death of brain neurons. In addition, AGEs may increase inflammation in the brain.

AGEs can be formed when proteins and sugars react. AGEs can be formed during cooking or storage of food and can be absorbed from the diet. AGEs can also be created in the bloodstream during hyperglycemia. AGEs are deformed proteins that have been polymerized and cross-linked. AGEs are proteins that are difficult for our bodies to break up and eliminate. AGE formation may represent an early, if not initial, event in the progression of AD by increasing oxidation, inflammation, and neuronal death in the brain [14]. Serum concentration of AGEs is associated with increased cognitive decline in elderly individuals [15].

AGEs were three times as high in the brains of AD patients compared to non-AD brains [16]. AGEs were found in both amyloid plaques and tau tangles [16]. AGEs can generate an estimated 50 times as many free radicals when compared to normal proteins [17]. When AGEs accumulate in amyloid plaques in the brain, they can cause increased lipid peroxidation of both cellular membranes and mitochondrial membranes [18]. Cell death from oxidation of cellular membranes may be one of the mechanisms of pathology in AD.

AGEs, although proteins or peptides, can be taken into the bloodstream from food. However, only the shorter

AGE peptides are absorbed, and studies show that they are indeed absorbed into the blood [19]. Ten to thirty percent of the ingested AGEs may be absorbed. AGE levels in the blood have been shown to double after a meal high in foods containing AGEs. When AGEs cross the blood-brain barrier with the RAGE receptor (receptor for advanced glycation endproducts), they may trigger inflammation in the brain [20].

To reduce AGE intake, guidelines for this intervention trial discouraged cooked by broiling, barbequing, or frying of meat, poultry, or fish. Aged cheeses are also eliminated from intervention diets. Compliance has been an issue with these food preparation changes.

1.3. Antioxidants to Slow Progression of Dementia

Certain antioxidants have been found to exert protective effects on the easily-oxidized docosahexaenoic acid (DHA) and arachidonic acid in neuronal membrane phospholipids. Antioxidants are also crucial for protecting mitochondrial membranes. Neuronal death is a key factor in AD and antioxidants can reduce membrane damage leading to neuronal apoptosis [21].

1.4. Vitamin E

Vitamin E is a lipid-soluble vitamin with antioxidant properties that may decrease free radical mediated damage in neuronal cell membranes [22]. Many, but not all, observational studies have suggested a protective effect of vitamin E for the prevention of cognitive decline and AD [23]. One study looking at levels of vitamin E in blood found that the participants in the lowest tertile of vitamin E blood levels had more than twice the chance of cognitive impairment and dementia (OR of 2.2 and 2.6, respectively) compared to higher levels [24]. An Italian study found that those in the lowest tertile of plasma delta-tocopherol had an odds ratio of 3.87 for dementia compared to the highest tertile [25]. Another study showed that vitamin E in food lowered the risk of developing AD by two thirds (67%) [26]. A recent study found that those with either MCI or AD had 85% lower odds of being in the highest tertile of plasma total vitamin E [27].

Vitamin E supplements used in studies are often synthetic all-racemic alpha-tocopherol, a mixture of eight isomers, only one of which is alpha-tocopherol [28]. Four of these synthetic isomers are inactive and three are less active than rrr-alpha-tocopherol. Vitamin E supplements used in studies may also not include gamma- and delta-tocopherol. Mixtures of the various tocopherol forms, rather than alpha-tocopherol alone, may be important in the vitamin E protective association with Alzheimer disease [29]. Vitamin E that included all tocopherols was effective in cutting dementia risk in half (HR 0.46) [21]. Another study found that gamma-tocopherol was found to be more effective in scavenging free radicals than alpha-tocopherol [30]. A recent study of postmortem brains showed an association of less amyloid-beta and lower neurofibrillary tangle severity in brains with higher gamma-tocopherol, but not alpha-tocopherol content [31].

Intervention patients were encouraged to eat one ounce each of English walnuts and sunflower seeds daily to supply gamma- and alpha-tocopherol (respectively). A blend of tocopherols was part of the supplement program, providing 500 mg gamma-tocopherol, 150 mg delta-tocopherol, 60 mg rrr-alpha-tocopherol, and 11 mg beta-tocopherol daily. Vitamin C is an antioxidant and is necessary so that vitamin E can continue its antioxidant action [32]. Participants received 800 mg of ascorbated vitamin C daily split into two doses.

1.5. Berries and Anthocyanidins

Blueberries, strawberries, and red grapes contain antioxidant and anti-inflammatory flavonoids, other polyphenols, and also antioxidant carotenoids [33]. The polyphenol anthocyanins in these berries and grapes have been shown to be helpful in slowing the aging of the brain [34]. In the Nurses' Health Study, anthocyanins were found to cross the blood-brain barrier and localize in the hippocampus. Those who ate more berries delayed dementia for an average of 2 years [35]. Concord grape juice contains polyphenol compounds which have

antioxidant and anti-inflammatory properties [36]. Dieticians instructed intervention participants to include one cup of these antioxidant fruits daily. Alternatively, participants were allowed to drink a cup of Concord grape juice.

1.6. Endogenous Antioxidant Enzymes: Co-Factor Minerals

The endogenous antioxidant superoxide dismutase requires the necessary mineral co-factors copper, zinc, and manganese [37]. Another endogenous antioxidant, glutathione peroxidase, requires selenium to perform its antioxidant functions. Selenium was found to be significantly lower in AD patients [38]. These four minerals were included in the supplements for intervention participants.

1.7. Coenzyme Q10

Coenzyme Q10 (CoQ10) is the only endogenous fat-soluble antioxidant in humans. It is on the inner leaflet of the mitochondrial membrane where CoQ10 is most essential, scavenging free radicals produced by the aerobic production of energy [39]. CoQ10 is also necessary for aerobic energy production in its role in complex I of the electron transfer chain [40]. CoQ10 may be helpful in reducing the oxidative damage that precedes clinical and pathological AD symptoms. CoQ10 can reduce amyloid-beta deposition, neurofibrillary tangle formation, metabolic dysfunction, and cognitive decline [41]. CoQ10 is potentially useful for attenuating amyloid pathology in Alzheimer's disease [42]. Intervention supplements included 200 mg CoQ10 daily.

1.8. Saturated Fatty Acids, Cholesterol, and AD

Atherogenic disease can start between the ages of two and eight [43]. Atherosclerosis is promoted principally by the intake of three saturated fatty acids (lauric, myristic, and palmitic acids) found in animal fats [44]. In AD there is often a component of vascular disease that can lead to concomitant vascular dementia [45]. Higher levels of saturated fat in the diet were found to greatly increase the risk of dementia [46]. Dietary animal fats were found to double the risk of AD [47].

In a large Danish study spanning many decades, it was found that people with elevated blood cholesterol at midlife were three times as likely to get AD as were those with lower cholesterol [48]. Conversely, high levels of high-density lipoproteins (HDL) cut the risk of AD in half [49].

When there are low levels of HDL and high levels of low-density lipoproteins (LDL), beta- and gamma-secretase enzymes are over-produced. Thus, more amyloid plaques may be created [50]. Higher cholesterol levels were also associated with increased production of the amyloid precursor protein, also potentially increasing amyloid-beta [51].

To reduce amyloid plaque production and to reduce vascular dementia in AD, participants were required to restrict their saturated fatty acids to seven percent of their caloric intake.

2. MEDICAL PLANTS TO TREAT AD

This intervention trial included two medical plants that have been shown to be helpful in AD.

2.1. Ginkgo Biloba

Ginkgo biloba has been found in a meta-study of double-blind, placebo-controlled trials to be helpful in delaying the onset of AD and in treating AD [52]. Evidence suggests that ginkgo biloba protects hippocampal neurons against cell death induced by beta-amyloid [53]. In a 24-week, randomized, placebo-controlled, double-blind study in patients with mild to moderate AD, ginkgo biloba improved memory as well as donepezil did [54]. The ginkgo biloba group showed a low dropout rate, which indicates that ginkgo biloba is well tolerated.

Improvement from ginkgo biloba may continue from 3 to 12 months. One study that looked at combined cholinesterase inhibitors and ginkgo biloba treatment showed MMSE scores improving 1 point in 6 months and 2

points in 12 months, while cholinesterase inhibitors alone showed a decreased score of about 1.4 points [54]. Ginkgo biloba is contraindicated for people on blood thinners, such as warfarin. Screening for this trial rejected patients on blood thinners. Daily dosage for ginkgo biloba extract was 160 mg.

2.2. *Centella Asiatica*

A recent study found that centella asiatica lowered beta-amyloid plaque in the hippocampus [55]. This study also showed that centella asiatica functions as an antioxidant to reduce free radical damage in membranes. Another study showed that centella asiatica boosted two enzymes that reduce free radical damage: glutathione peroxidase and catalase [56]. A six-month study in healthy middle-aged patients showed that centella asiatica capsules improved the average score of the MMSE from 25 to 28, a 10% improvement [57]. A placebo-controlled, 60-day study showed that centella asiatica reduced the age-related decline in cognitive function in healthy middle-aged and elderly adults [58]. Centella asiatica side effects in this study seemed positive as it was noted to lower blood pressure and improve sleep. Our trial used 300 mg centella asiatica extract daily.

3. METHODOLOGY

Inclusion Criteria:

- Male and female subjects older than 64 years old
- Subjects must have completed neurological evaluations by a board certified neurologist
- Subjects must have an established diagnosis of MCI by formal neuropsychological testing
- Subjects must have a previous MRI (Magnetic Resonance Imaging) or CT (computed tomography) to exclude other neurological conditions
- Subjects and caregivers must be willing and able to participate in the intervention

Exclusion Criteria:

- Subjects with dementia or other memory impairment not due to MCI such as dementia with Lewy bodies, frontotemporal dementia, substance-induced dementia, or normal pressure hydrocephalus; subjects with a diagnosis of Down syndrome.
- Subjects with a previous magnetic resonance imaging (MRI) or computed tomography (CT) scan performed showing a space-occupying lesion (e.g., tumor), or other major structural brain diseases.
- Subjects with a history of stroke, transient ischemic attack, or embolism.
- Subjects with a history of clinically relevant traumatic brain injury with neurological sequelae.
- Subjects with a history of a deep venous thrombosis within the 5 years prior to the screening visit.
- Subjects with delirium, unless resolved with no symptoms for at least 30 days prior to the screening visit.
- Subjects taking warfarin or other blood thinning medications.
- Subjects taking selective serotonin reuptake inhibitors, MAO-A inhibitors, or St. John's wort.
- Subjects with chronic liver or kidney disease will be excluded.

Trial Site, Participants:

Prevention and Clinical Trial Unit, Hawaii Alzheimer's Disease Center at Hawaii Pacific Neuroscience Center, Kailua and Honolulu, Hawaii. Two participants were in the supplement-only group and one in the supplement-plus-diet group.

Summary of Interventions:

Daily Supplements:

- Folic acid, 600 micrograms (mcg).

- Methylcobalamin, 240 mcg.
- SAM, 200 mg (from 400 mg of S-Adenosyl L-Methionine tosylatedisulfate), given in the morning.
- Copper (1 mg), zinc (20 mg), selenium (100 mcg), and manganese (4 mg) to assure minimum daily requirements.
- Ascorbate 800 mg.
- Tocopherols: 500 mg gamma-tocopherol, 150 mg delta-tocopherol, 60 mg of rrr-alpha-tocopherol, and 11 mg beta-tocopherol daily.
- CoQ10, 200 mg.
- Ginkgo biloba extract, 160 mg.
- Centella asiatica extract, 300 mg.

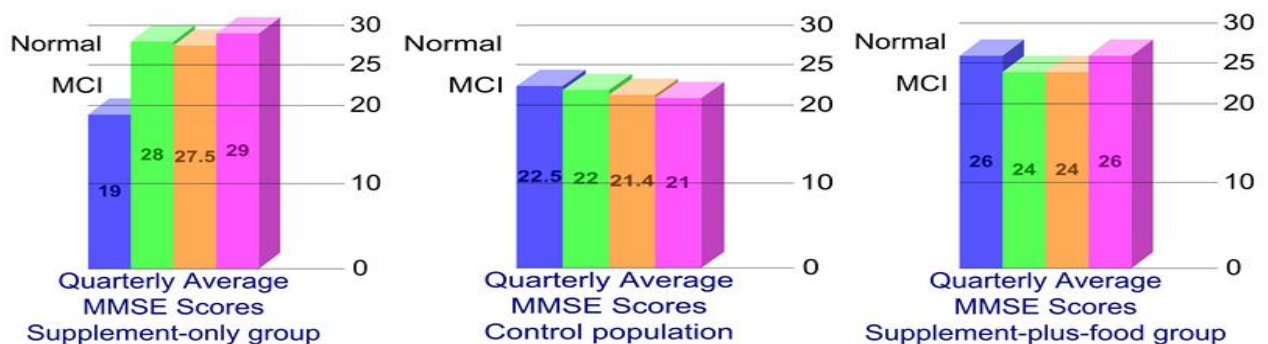
Dietary Protocol:

Reduce AGE intake: intake of broiled, barbequed, or fried meat, poultry, or fish was discouraged. Aged cheeses were also eliminated from intervention diets. One ounce of ground English walnuts and one ounce of ground sunflower seeds, taken daily when possible. Blueberries, strawberries, or red grapes, one cup or more, or one cup Concord grape juice taken daily. Saturated fatty acids were restricted to seven percent of caloric intake.

Registered dietitians taught dietary-intervention participants to implement the dietary changes from a standard script, and gave them a cookbook containing recipes to help them stay on the diet. The subjects in the 2 treatment groups received daily phone calls for the first 2 weeks to check on dietary supplement and dietary protocol compliance. After the initial 2 weeks, the subjects received phone calls every week.

4. RESULTS

Average MMSE scores in the supplement-only group at baseline were 19—just slightly lower than the lower limit for MCI, which is 20-25. This may have indicated a slight drop in cognition since diagnosis of MCI and prior to the study commencement. At the end of nine months the average score was 29, indicating a normal cognitive state. This was an increase in 10 points out of 30. The MMSE score did not change much in the supplement-plus-food group. This may indicate some protection from normal, predicted cognitive degeneration. The average progression of MCI to dementia is highly variable. In a meta-analysis of 41 studies, the average yearly clinical rate of progression from MCI to dementia was found to be 9.6% [59].



5. RESULTS & DISCUSSION

The trial was limited by the small number of participants. Enrollment was made more difficult because of the inclusion/exclusion requirements, coupled with finding participants willing to change their diet. Many elder participants were already taking multiple medications and objected to taking 7 more tablets or capsules daily.

The combination of nutritional strategies may have been responsible for the improvement in clinical memory and cognition scores.

6. CONCLUSION

This multifaceted nutritional intervention had a positive impact slowing the progression of dementia and reducing the risk of Alzheimer's disease. Supplements designed to reduce oxidation and brain cell death may be effective in slowing the progression of AD. Supplements and dietary changes that limit the production of amyloid plaques may also slow progression of AD. A larger, multicenter trial is needed to confirm these results.

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