

Nutraceuticals Against Alzheimer's Disease

Shari Lieberman, Ph.D.

Professor, University of Bridgeport, School of Human Nutrition

INTRODUCTION

The aim of this paper is to discuss the role of nutraceuticals in the prevention and management of Alzheimer's disease. There is a lot of misinformation with respect to what works, what does not work, what can be combined, and whether certain nutrients or herbs can be taken alongside medication, this paper will clear up some of the confusion surrounding this topic so that anti-aging physicians can confidently utilize some of these nutrients and interventions with their patients.

ANTIOXIDANTS

Antioxidants are very important in the treatment of virtually all diseases because most chronic diseases carry with them a great deal of oxidative stress. Oxidative stress plays a major role in neurodegenerative diseases such as Alzheimer's disease (AD), Parkinson's disease (PD), Huntington's disease (HD), and amyotrophic lateral sclerosis (ALS). Oxidative stress is accelerated by the aging process and also by a lack of dietary antioxidants. So this whole myth of if you eat well you don't need to take supplements that just doesn't fly as we are exposed to so many things that accelerate oxidative stress. A large number of studies have found an association between high dietary antioxidant intake and a decreased risk of AD. And that is very important because preventing a disease is significantly easier than treating it. So prevention is key and research suggests that preventing AD is actually not that difficult. 80% of children and 68% of adults do not eat a single fruit or vegetable each day. Not one. Forget about five. They are not even eating one. So you can start to get an idea from a dietary perspective as to why AD is on the

rise. It is on the rise because of the environment, and it's also on the rise because of how and what we are eating.

Treatment with antioxidants is a promising approach for slowing disease progression. Oxidative damage actually may result from beta-amyloid induced free radicals, inflammation, altered antioxidant defenses, and mitochondrial abnormalities. There is an ongoing study with vitamin E to see if it actually slows AD progression. Klatter *et al* conducted a retrospective chart review on 130 patients with AD who were given at least 5 mg of donepezil (Aricept) and also a 1000 IU of vitamin E. A yearly Mini-Mental State Examination score data was compared to a databank of patients who did not take any vitamin E. Results showed that those taking the combination therapy declined at a significantly lower rate. Food consumption studies have had similar outcomes. There are numerous antioxidants in food, you get a plethora of them – everything from flavonoids to well known antioxidants like vitamin E and vitamin C. However, intervention studies have given us mixed results. The study mentioned above where patients were given 1000 IU of vitamin E, used a very large dose, but the problem with most intervention studies with vitamin E is that they use synthetic vitamin E. And there are a lot of problems with that. Number one, synthetic vitamin E, which is dl-alpha tocopherol, has about an eighth of the activity of natural vitamin E. The other thing is that synthetic vitamin E could interfere with the absorption of other tocopherols, such as gamma tocopherol, tocotrienol, and other components of the vitamin E spectrum. Thus the use of synthetic versus natural vitamin E is a very real prob-

lem in research. The dosing is a problem as well. If you have a study where 1,000 IU of synthetic vitamin E are given, and then 400 IU of natural vitamin E are given, and then another 2,000 international units of synthetic vitamin E are given, it is really all over the map. But in general, results suggest that dosing vitamin E in combination with other antioxidants can actually reduce the severity of brain damage. And that is because antioxidants do not operate in a vacuum, they are synergistic and have different properties – they are usually either fat soluble or water soluble, but some (e.g. Coenzyme Q10 and alpha-lipoic acid (ALA)) are to penetrate both. The mere fact that one would even try to reduce any disease with just vitamin E or just vitamin C is insane. Because any high dose antioxidant can operate as a prooxidant. That is a real problem, however that accounts for some of the findings that we are seeing in the research. If you are going to take antioxidants, you should take all the major ones together or you really should not be taking them at all.

Low concentrations of vitamin C and vitamin E have been observed in the cerebral spinal fluid of AD patients. Kontush *et al* conducted a study where 400 IU of vitamin E plus 1000 mg of vitamin C, or vitamin E and C alone, was given to AD patients for one month. Results showed that only the combined vitamin C and E together significantly decreased susceptibility of the cerebrospinal fluid and plasma lipoproteins to oxidation. Why? Because they operate together, in fact, vitamin C regenerates vitamin E in the body. So it is very important if you are going to do this kind of work to do it right and to do it properly. Antioxidants are best given before significant damage occurs. Mild damage can be reversed. Significant damage is a whole other story

and that is why the very best intervention is very early on.

Antioxidants may protect the aging brain against oxidative damage associated with the pathologic changes of AD. Zhandi *et al* studied more than 3,000 elderly residents who were at risk for AD. The researchers looked at the use of vitamin E and vitamin C supplements in combination, and found that it was associated with a significantly reduced risk of Alzheimer's disease and prevalence. The study also showed that vitamin E, vitamin C, B vitamins, or multivitamins used alone did not reduce the risk of prevalence. So there is a real association between the synergism of antioxidants used in combination.

GINGKO BILOBA

Ginkgo biloba is probably the most studied herb with respect to memory, cognition, overall brain performance, and certainly AD. Wettstein compared the efficacy of four cholinesterase inhibitors (tacrine, donepezil, ravastigmine, metrifonate) to Ginkgo (EGB 761) in AD patients. EGB 761 is a proprietary Ginkgo biloba extract made in Germany and is available in the United States. There is no guarantee that all Ginkgo biloba extracts are the same or of the same quality. So EGB 761 is a very specific Ginkgo biloba extract. The differences in the effects of the active substances and placebo were measured using ADAS (Alzheimer's Disease Assessment Scale) cognition scale, taking into account the different degrees of dementia and the dropout rate due to adverse drug reaction. The efficacy was expressed as a delay in symptom progression or the difference in response rates between placebo and active substrate. Results showed that there was no difference between the four drugs and the Ginkgo extract. What does that mean? It means that they all work equivalently. Having an over the counter dietary supplement work

as effectively as a drug is fine. It doesn't even have to work better than the drug; it can work equally to the drug. And in this particular study, the Ginkgo biloba extract was equal in efficacy to those four cholinesterase inhibitors. Only one drug, tacrine, had a very high dropout rate due to the side effects. Wettstein concluded that new prescription medications should be critically reviewed, and that these drugs and Ginkgo should be considered equally effective in treating mild to moderate Alzheimer's dementia. Thus, here we have a study that actually demonstrated that there is no difference, in terms of efficacy, between drug treatment and Ginkgo biloba treatment in patients with mild to moderate AD.

How does Ginkgo work? If you actually look at the pharmacology of many of these natural substances, more is often known about the pharmacology of natural substances than that of prescription drugs, and this is definitely the case with Ginkgo biloba. There are literally thousands of studies on Ginkgo biloba. Ginkgo biloba is not only used for dementia, but in the treatment of dementia its mode of action includes increased blood flow, protection against ischemia and mild hypoxia, effects on nerve cell energy metabolism, reducing edema, and protection of myelin. It is also a very, very powerful free radical scavenger, and it has effects on various cerebral neurotransmitter and receptor systems. So it has a very wide range of pharmacological actions, yet in comparison to some of the other drugs it has very few side effects. Furthermore, the few side effects that are associated with Ginkgo biloba are very mild. The cerebral bioavailability of Ginkgo has been demonstrated by electroencephalography – it can actually pass through the blood brain barrier. And the World Health Organization accepts and classifies Ginkgo as an anti-dementive drug. It is

registered as a drug to be used for the treatment of AD in more than 50 countries, however the United States FDA does not accept it as treatment.

There has been quite a concern about Ginkgo causing bleeding. To put this in perspective, there are only four cases of spontaneous bleeding reported in patients taking Ginkgo but who were also taking aspirin, warfarin, or ibuprofen – all of which are drugs that thin the blood. Just four reports, yet millions upon millions of people take Ginkgo biloba. Is that a huge cause of concern?

People are told not to take certain nutrients, including Ginkgo, postoperatively as they may increase the risk of postoperative bleeding. In the case of Ginkgo there really isn't any clear evidence that it increases bleeding. Bal Dit Sollier et al conducted a double-blind placebo controlled study on 32 healthy men to evaluate the effect of 14 days of treatment of Ginkgo (120, 240, or 480 mg per day) on the blood. Results showed that there were no alterations of coagulation of platelet function, and that bleeding time was not increased, even at the high dose of 480 mg. Thus, we can say that bleeding events are not related to the pharmacological properties of Ginkgo.

HUPERZINE ALPHA

Huperzine alpha or huperzine A is a very interesting plant compound that is extracted from club moss, or *Huperzia serrata*. It is a sesquiterpene alkaloid, which is a powerful and reversible inhibitor of acetylcholinesterase. Therefore it works very much like the cholinesterase inhibitor drugs that are on the market. Human and animal safety data confirm that it is safe and nontoxic. There is rapid penetration and absorption into the brain, very much like with Ginkgo biloba. Compared to tacrine and donepezil, huperzine A has a longer duration of activity and a higher therapeutic index. That

means compared to drugs that are commonly used. The cholinergic side effects are minimal and are not significant when compared to other drugs. Huperzine A also reduces neuronal death by glutamate.

Zhang et al conducted a study of 202 AD patients from 15 centers. Participants received either 400 micrograms of huperzine A each day or a placebo for 12 weeks. Results showed remarkable improvements on several scales, including the ADAS cognitive scale, the MMSE scale, the CIBIC-Plus (Clinician Interview Based Impression of Change-Plus) scale, and the activities of daily living (ADL) scale. Huperzine A was found to significantly improve cognition, behavior, activity of daily life and mood in AD patients. Furthermore, it is a safe and effective treatment.

Xu et al conducted a double-blind placebo-controlled multi-centered trial of 60 patients comparing the effect of 200 micrograms of huperzine A in capsules, to 200 micrograms of huperzine A in tablets, just to see if there was a difference in absorption and bioavailability. Results based on numerous mental and quality of life scales revealed that patients treated with both huperzine A tablets and capsules significantly and remarkably improved. In addition, free radicals in erythrocytes and plasma reduced in both groups. There was no change at all in the placebo group.

In another study of similar design conducted by Xu et al patients were given either 200 micrograms of huperzine A each day or a placebo for a period of eight weeks. All patients were evaluated with the Wechsler memory scale, the Hasegawa dementia scale, the MMSE scale, the ADL scale, and the treatment emergency symptom scale – all of which are very well established, standardized scales – in order to determine whether treat-

ment led to a difference in cognition, daily activities, mood, mental state, etcetera. A lab evaluation and a thorough blood and urine evaluation were also conducted. Results showed that there was a significant improvement in memory and behavioral and cognitive function in the huperzine A group versus the placebo group (58% versus 36%). Furthermore, no severe side effects were reported at all in the huperzine A group.

All studies of huperzine A have reported significant improvement for mild to moderate AD on several scales – memory, behavior, and cognitive function. In conclusion, huperzine A has a very, very clear indication in the treatment of AD patients. It is equal to the efficacy of some of the AD drugs that are available, and some studies suggest that it may actually be superior because it is associated with very few and very mild side effects and the duration of its effectiveness is longer than the known drugs that are on the market.

PHOSPHATIDYLSERINE

Phosphatidylserine is a very interesting compound. Phosphatidylserine is the major phospholipid in the brain and it makes up the basic structure of the cell membrane. Membrane phosphatidylserine and phospholipids play an important role in cell-to-cell communication and transfer of biochemical messages to the cell. Phosphatidylserine enhances cellular metabolism and communication, and oral supplemental effects neuronal membranes, cell metabolism and specific neurotransmitters: acetylcholine, norepinephrine, serotonin, and dopamine.

Numerous double-blind placebo-controlled studies have been carried out on phosphatidylserine and they demonstrate that it can lead to very significant improvements in early dementia, early AD, and age-related cognitive decline. The FDA has approved health claims for

phosphatidylserine for reducing dementia and age-related memory decline. Several studies demonstrate that phosphatidylserine improves memory, brain wave activity, and brain metabolism in the early stages of AD.

Engel et al conducted a double-blind placebo-controlled crossover study of 33 patients with AD. Participants were given 300 milligrams of phosphatidylserine each day or a placebo for eight weeks. Results showed that the Clinical Global Improvement score significantly improved with phosphatidylserine, but not with placebo. Furthermore, the improvement carried over to the following wash-out and treatment phases, and the EEG was improved by reducing higher power values in AD patients and shifting the EEG power more to normal. Other AD studies of phosphatidylserine have also shown improvements in several measures of cognition.

ALPHA-LIPOIC ACID

Alpha-lipoic acid (ALA) also plays a role in brain function. Oxidative stress and energy depletion are biochemical characteristics and hallmarks of AD, as is mitochondrial failure. ALA is a powerful antioxidant, which also improves glucose metabolism and utilization in the brain. Hager et al gave 600 mg ALA daily to nine patients with AD and related dementias, who were already receiving standard acetylcholinesterase inhibitors, in an open study lasting about 337 days. Results showed that those receiving the ALA had stabilization of cognitive function demonstrated by constant scores on the MMSE scale and AD assessment scales.

FISH OIL: OMEGA-3 FATTY ACIDS

There is not a single reason why someone shouldn't take a fish oil supplement. As a rule of thumb, if you open a bottle of fish oil and it smells, throw it away. It's rancid. Really good quality fish oil sup-

plements basically have no odor. So if they smell, toss them out. Don't use them.

Many studies have shown that dietary Omega-3 fatty acids improve brain function, however there is a limited amount of data as to whether they offer protection against AD. Morris et al studied 815 aged 65 to 94 years for about four years, to see if they would develop AD. Results showed that participants who ate fish just once a week or more had a 60% less risk of AD compared to those who rarely or ever ate fish. Total intake of omega-3 and DHA was associated with a reduced AD risk, thus we can conclude that dietary intake of omega-3 fatty acids and weekly fish consumption may reduce the risk of AD.

Human beings evolved consuming a diet with equal amounts of Omega-3 (n-3) and Omega-6 (n-6) essential fatty acids. Over the past 100 - 150 years, the amount of dietary n-6 has increased enormously due to increased intake of oils from corn, sunflower seeds, safflower seed, cottonseed, and soybeans. We are now eating a ratio of n-6 to n-3 of about 30:1. That is not the way we are supposed to be eating. And that is why you can get a sense of why inflammation is so rampant. When we talk about if we eat chicken or if we're eating beef, what do you think the animals are being fed? Their essential fatty acid ratio is also about 30:1. So we're in a constant state of inflammation. We take in a lot of arachidonic acid just from meat. Omega-3 fatty acids and Omega-6 fatty acids actually compete for incorporation into the cell membrane. And these changes in our diet actually set the stage for degenerative disease.

CONCLUSION

In conclusion, there are a number of things that anti-aging physicians can do to help prevent and treat AD. Patients should be encouraged to take a full-spectrum antioxidant supplement, containing all the major antioxidants – vita-

min A, vitamin C, vitamin E, and selenium. It is important to take only natural vitamin E (d-alpha tocopherol and mixed tocopherols) and natural beta-carotene. Most research focuses on patentable products. Don't dismiss a few studies that show promise. Plant compounds and natural products really have an important role in both the treatment and prevention of AD. The therapeutic dose of Ginkgo biloba for AD is 240 or 480 mg/day. Not 120 mg – that would be for prevention. The therapeutic dose of huperzine A for AD is 200 to 400 micrograms, and that of phosphatidylserine is 300 mg/day. Patients should also take 3 grams of fish oil each day. They should be encouraged to eat a diet rich in antioxidants and phytonutrients, not an Atkins type diet. Those diets will not prevent or treat AD. Those

types of diets are loaded with Omega-6. They are loaded with arachidonic acid and they are proinflammatory. Eat a diet low in sugar and refined products, foods with a low glycemic-index. Everyone 12-5 should be encouraged to exercise their brain. There are a lot of great studies showing that just exercising the brain, by reading, writing, doing a hobby, or learning a new language, reduces the risk of AD. A recent study has also shown that physical activity, just exercising, also reduces the risk of AD. Avoid aluminum cookware, and avoid mercury as much as you can. Consider toxic metal evaluation. Avoid chemicals and pollutants as much as humanly possible. AD is easy to prevent and there are a lot of things that we can do to actually slow its progression or even stop or reverse the disease process.

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ABOUT THE AUTHOR

Dr. Shari Lieberman is a nutritionist, scientist, and exercise physiologist who has been in private practice as a clinical nutritionist for more than twenty years. Dr. Lieberman is a faculty member of the University of Bridgeport (Connecticut USA) School of Human Nutrition graduate program. She is an author of numerous books including *Dare to Lose*, *The Real Vitamin and Mineral Book*, and *All About Vitamin C*. Dr. Lieberman also serves as a contributing editor to the American Medical Association's 5th Edition of *Drug Evaluations*.