

MEMORY PRESERVATION DIET™ © 2005 TO REDUCE RISK AND SLOW PROGRESSION OF ALZHEIMER'S DISEASE (AD)

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Abstract: *The Memory Preservation Diet™ (MPD), developed by a multidisciplinary, multi-university team is expected to reduce risk, or delay onset, of Alzheimer's disease (AD) in adults, reduce conversion of persons with progressive Mild Cognitive Impairment (MCI) to AD, and help slow progression of disease in persons who already have symptomatic AD. The MPD is an evidence-based comprehensive diet whose 6 primary objectives are to 1) increase intake of anti-oxidants including vitamins E & C; 2) achieve a higher ratio of Omega-3 polyunsaturated fatty acids (PUFA) to Omega-6 PUFAs to approach a 1: 4 ratio 3) achieve adequate amounts of folates, S-adenosyl methionine & B-vitamins, especially B-12; 4) increase insulin sensitivity 5) increase foods that are anti-inflammatory 6) reduce LDL cholesterol, saturated and trans fats, and substitute healthier fats. Foods were chosen based on the evidence for both their individual contributions and synergistic interactions to enhance risk reduction and disease mitigation properties.*

Key words: *Nutrition, Alzheimer's disease, non-pharmacological treatment, prevention.*

INTRODUCTION AND SIGNIFICANCE

AD is an age-related chronic disease that may actually develop over several decades. As with other major chronic diseases, there are multiple interrelated factors that cause the disease and may modify its progression. AD may also be comprised of multiple similar diseases with different risk and treatment profiles. Though exact mechanisms and processes, particularly at the cellular and molecular level, are not precisely understood there is growing recognition that environmental and lifestyle factors play a critical role in influencing the development and progression of AD pathology and symptoms, as they do with other chronic diseases such as cardiovascular diseases (heart disease, stroke, etc) and diabetes [1].

The evidence also suggests that the proposed dietary program could produce stronger effects on cognition than the current pharmacological treatments for early AD. If the Memory Preservation Diet (MPD) delays progression of AD by even 6-12 months (the Japanese diet trial suggested delay of over 2 years [2]), not only will dollars be saved but also the quality of life of all involved will be improved. Given that each 5 year delay in average age of onset can cut prevalence rates in half, the financial implications are huge. At a more personal level, but one also complicated by financial considerations, persons with AD and their families are understandably eager to have safe options for slowing progression of this disease.

The Memory Preservation Diet is also protective of other conditions that older adults, AD patients, and their care partners may experience such as diabetes, heart disease, stroke and cancer. The hope of preventing and slowing progression of this very frightening disease, may spur sufficient additional motivation to take protective dietary actions for the heart, pancreas and other organs.

REVIEW OF THE EVIDENCE FOR MEMORY PRESERVATION DIET

Cardiovascular disease, stroke and AD

Vascular disease and stroke, and cardio-vascular risk factors such as diabetes [3], insulin resistance, hyperinsulinemia, high LDL cholesterol [4], high blood pressure [5], lower cerebral perfusion, inflammation [6], elevated levels of homocysteine, high Body Mass Index have all been shown to be risk factors for AD and dementia. Lack of exercise, poor nutrition and smoking also show as risk factors.

Understanding the role of vascular disease in AD was fundamentally

altered by findings from the landmark Nun Study [7], which also gave credence to the idea that AD is a chronic disease lasting many decades. Postmortem analysis revealed that some elderly nuns functioning at a cognitively normal level (both in reported daily activities as well as on yearly study evaluations) had extensive amyloid plaques and neurofibrillary tangles (NFTs) diagnostic of severe AD. However, after further examination, their brains were found to be free of significant vascular lesions in the cortical and sub-cortical areas of their brains. Researchers concluded that risk of observable dementia symptoms in the presence of AD plaques and tangles was highly correlated with the absence or presence of vascular lesions in the brain. With regard to high blood pressure, the Honolulu Asian Aging study reported that untreated high blood pressure in middle-aged men increases risk for dementia. [5] In addition, there is growing evidence that poor blood vessel function in the brain can contribute to or accelerate the neuro-degenerative processes of Alzheimer's disease. [5] Bradley found lower cerebral perfusion is related to risk and level of severity of AD and a Swedish study found supporting evidence that low diastolic as well as high systolic pressure, obesity and high LDL cholesterol are associated with an increased risk of Alzheimer disease and dementia and suggest that low diastolic pressure may increase dementia risk by affecting cerebral perfusion. The link to heart disease risk factors is becoming widely accepted as is the idea that cardio-vascular risk factors are additive in increasing risk of dementia [8].

Diabetes mellitus and AD

Currently, there is a growing interest in clarifying the roles of insulin resistance (IR), hyperinsulinemia, Type 2 Diabetes Mellitus, and insulin degrading enzyme in the pathogenesis of AD, and its associated neuronal cytoskeletal lesions and A β deposits in the brain. The Rotterdam study group concluded that the association of increased serum insulin with increased risk of cognitive impairment is a direct effect of insulin on the brain rather than mediated through an increase in cardiovascular risk factors. [3] One of the earliest researchers in this area, Craft, initially reported enhanced memory in persons with AD from insulin administration but not from administration of glucose, but later concluded that BOTH glucose and insulin levels were important, and that the evidence supports an association among Alzheimer's disease, impaired glucose metabolism, and reduced insulin sensitivity [9], and that the effects of insulin on glucose metabolism, memory and plasma amyloid precursor protein differed according to APO-E genotype. There may be a common

genetic aetiology predisposing to insulin resistance and late onset AD. De la Monte's group suggests that AD may represent a neuro-endocrine disorder, similar but distinct from diabetes mellitus, a "type 3 diabetes" or diabetes of the brain [10]. Several studies suggest insulin competes with beta-amyloid (A-beta) for IDE (insulin degrading enzyme), a mechanism relating insulin levels to AD pathology and cognitive impairment in humans. Biological studies also revealed the role of insulin in regulation of phosphorylation of tau protein and metabolism of A-beta, the main constituent of AD amyloid pathology. However another group concluded that while reduced insulin signaling in the brain may lead to changes in Akt and GSK3 beta activity and tau hyperphosphorylation, insulin resistance must interact with other mechanisms for development of Alzheimer's disease.

Inflammation and AD

Flex asserts that "Neuroinflammation is a central feature of Alzheimer's disease (AD). C-reactive protein (CRP) is a key molecule of the acute phase of inflammation that has been localized in the two characteristic lesions of AD brain, senile plaque and neurofibrillary tangles." One report notes that "chronically activated glial cells are thought to contribute to the inflammatory state that underlies one aspect of Alzheimer's etiology." The Honolulu Asian Aging Study (HAAS) findings also support the view that inflammatory markers may reflect not only peripheral disease, but also cerebral disease mechanisms related to dementia - measurable long before clinical symptoms appear. [6] Some scientists are now proposing that inflammation underlies and helps link many major chronic diseases.

Lifestyle risks and interventions for other chronic diseases and AD

In summary, with the exception of brain-particular risks such as head trauma, evidence is building that the risk profile for AD looks more and more like those for cardio-vascular diseases and diabetes, and therefore it is not surprising that evidence is also building for the role of lifestyle related risk factors.

For heart disease, stroke, and diabetes, the most powerful interventions for both prevention and treatment/secondary prevention appear to be a combination of physical exercise, weight loss and change in diet. [11, 12]

Weight Loss

While dietary content (see below) and physical exercise appear thus far to be important for both prevention and treatment of AD, the role of weight

loss in AD is not well understood and appears complex as some studies are now showing that weight loss can be a precursor of symptomatic AD and clearly is problematic in many people who already have full blown AD [13]. Also, there is growing evidence that intentional or unintentional weight loss after 65 can increase mortality, whether based on older adult population epidemiological studies such as NHANES II Mortality Study, longitudinal studies (over 40,000 people in Norwegian study), or cross sectional and prospective studies of nursing home patients or hospital discharges.

For older adults, intervention programs for slowing progression have worked well for other chronic diseases. A systematic literature review by the ATTICA study investigators concludes that the Mediterranean Diet significantly reduces coronary heart disease by 8-45% in multiple studies and is appropriate for public health purposes. [12] Exercise and diet intervention studies at Tufts Human Nutrition Research Center on Aging demonstrate that, by using proper intervention methods, frail older adults can successfully improve physical fitness and reduce chronic disease symptoms, including those of diabetes and renal disease. These studies also demonstrated that lifestyle interventions can help reduce inflammation which has been linked with oxidative stress. An Italian review article suggests that the Western diet is a primary underlying cause of both increasing prevalence of insulin resistance and AD etiology, as opposed to lower prevalence rates in countries of origin for ethnic groups whose native diet is quite different. A study comparing incidence of dementia in the US to that in India, whose people generally have a very different cuisine and generally more physical activity, found a significant difference –with an incidence rate about 1/3 that of the US. Other synergies are explored below in a section specific to nutrition and AD.

Nutrition and Alzheimer's Disease

The Memory Preservation Diet (MPD) reflects a convergence between four independent sources of research evidence: 1. nutrition-related protective/risk factors for AD; 2. risk factors identified for chronic diseases such as stroke, diabetes and vascular diseases (which themselves are thought to elevate risk for AD); 3. AD-related evidence from epidemiological studies, and 4. evidence from tissue culture studies some of which have now been confirmed by animal or human clinical studies. Thus while the MPD is based almost exclusively on evidence directly related to brain health, it is also protective for stroke, diabetes and cardio-vascular diseases. The MPD is a heart healthy diet also designed to reduce insulin resistance.

There is a rich body of evidence informing the MPD. Epidemiological and animal studies are fertile fields for suggesting the importance of diet, and specific dietary components that may reduce risk factors for AD. Epidemiological studies on dietary patterns of human adults suggest that high antioxidant, low fat diets [14] during mid-adult life may reduce risk for AD. Autopsy cases of human brain tissue (confirmed AD vs. normal controls) and epidemiological studies [15] suggest high cholesterol and high intake of saturated or trans fat (found in animal meats, full-fat dairy products, many processed products and some oils) is significantly associated with higher risk for AD and impaired cognition. Kalmijn and Morris [16,15] further showed intake of unsaturated, non-hydrogenated fats (such as those found in olive oil, canola oil and nuts) and more specifically, dietary intake of Omega-3 fatty acids (weekly consumption of fish [17]) may be protective against AD. Other epidemiological studies also provide evidence for these and other protective factors including vitamin B-12 and other B vitamins, [18] folic acid, vitamin E, combination of vitamin E and C [19], and specific foods, such as fish and seafood. [17]

Many of the dietary factors suggested by epidemiological studies as protective or risk enhancing have thus far been validated by in vitro tissue studies and in vivo animal and clinical studies as exemplified below. In vitro measurements of actual antioxidant and other nutrient relevant content of human brain tissue and one case control study of vitamin concentrations in blood of persons with and without AD [20] confirmed the various epidemiological studies that found high homocysteine levels and lower intake of vitamins E, C and B-vitamins to be associated with higher risk of AD. Dozens of animal studies using either AD transgenic or aged animals suggest that diet, using nutrients indicated by epidemiological studies as risk factors, can be a powerful treatment to reduce both amyloid plaques and cognitive deficits. These animal studies demonstrate independent contributions of antioxidants, [21] DHA Omega-3's, [22] folates [23] to prevent/reverse cognitive decline and/or inhibit beta-amyloid formation, oligomerization, or deposition. Another study found hypercholesterolemia promoted beta-amyloid accumulation. Many protective dietary factors seem to delay onset and reverse cognitive problems in aged or transgenic animals, suggesting diet could be a powerful prevention and treatment option. For instance, a nutritionally complete senior canine food enriched with vitamins E and C, alpha-lipoic acid, L-carnitine, fruits and vegetables improved cognitive function in aged canines. [24] These studies also demonstrate that a single nutrient can have multiple relevant affects. For example, Martin's studies demonstrate Omega-3 fatty acids enhance action of vitamins E and C and diminish oxidative stress in hamsters [25], and reduce inflammation in humans. [26]

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Chinese Medicine texts have also weighed in on many of these same foods including nuts (rich sources of vitamin E, Omega-3 & Omega-6 polyunsaturated fatty acids and many nutrients). Martha Clare Morris also recommends nuts as a source of both vitamin E (natural with mixed tocopherols) and a variety of other nutrients and vitamin such as selenium, magnesium, calcium, polyunsaturated fatty acids, including Omega-3 fatty acids. Almonds are a particularly excellent source of vitamin E, and have now been shown to reduce beta-amyloid and improve memory and learning in AD transgenic mice. Walnuts and pecans are excellent sources of Omega-3's. Nuts are included in Harvard Health Newsletter's 2005 dietary recommendations for heart health and prevention or treatment of diabetes.

ADDITIONAL EVIDENCE RELATED TO 6 OBJECTIVES OF THE MPD

Antioxidants

A MRI spectroscopic analysis of AD mouse brain expressing mutant APP (which develop toxic excess of A-beta plaques) revealed a dramatically altered neurochemical profile compared to wild type mice. Among other findings, a Boston group found that glutathione, the brain's primary endogenous antioxidant, was decreased by 36% in the cerebral cortex of APP mice. Glutathione's low levels suggest oxidative stress may play a role in the development of the altered metabolic profile observed. Other studies had shown glutathione cycle impairment is a key event in A-beta induced cell toxicity and reduced levels are correlated with cognitive impairment. Many studies have suggested free radical production is increased in brains of individuals with Alzheimer's disease. Abnormalities of antioxidative mechanisms in Alzheimer brain tissue were reported. The increased oxidative stress may affect brain function in Alzheimer's disease by several mechanisms, including mitochondrial dysfunction, disturbed energy homeostasis, excitotoxicity, apoptosis, microglia activation [25] and advanced glycation. Oxidative stress may also promote protein fibrillization that is crucial for A β neurotoxicity. A β -induced oxidative stress increases acetylcholinesterase activity perhaps contributing to cholinergic deficits observed in AD.

Animal studies found that higher amounts of various antioxidants from a variety of sources reduce age and pathology related cognitive decline e.g. blueberries in transgenic AD mice, [21] and in aged rats, [21] apple juice in transgenic AD mice, and spinach diet in aged rats. [21] Additional research showed that a variety of other high antioxidant berry fruit extracts

(including boysenberry, cranberry, black currant, strawberry, dried plums, and purple grape), appeared to protect against toxic effects of A-beta, [21] and confirmed that fruit polyphenolics actually cross the blood brain barrier, and localize in specific areas of the brain involved in learning and memory. Further, several antioxidant compounds including vitamin E, curcumin, [27] melatonin and other compounds block toxicity of A-beta in vitro in AD mice models. Thus the evidence is accumulating that dietary antioxidants should slow brain aging and beneficially influence pathways to AD pathology.

Vitamin E Controversy

The meta-analysis [28] suggesting possible risk from vitamin E treatment in persons with cardiovascular risk has met with an uneven response in the scientific community. Moreover the two large studies in the meta-analysis involving Alzheimer's disease patients showed NO ADVERSE effects from vitamin E supplementation of quite high level amounts (2000 IU) and in fact showed improvements in morbidity (and no effect on mortality rates) in contrast to some of the other studies. The authors of the meta-analysis speculate that it is the FORM of vitamin E used in most of the studies (alpha form, especially synthetic) that might be problematic perhaps creating an imbalance with respect to other tocopherols e.g. gamma and delta. There is also clinical trial evidence that vitamin E may have positive effects on persons with AD. [29]

The Memory Diet incorporates Martin and Martha Clare Morris's reports [30] that natural vitamin E, especially from foods, with mixed tocopherols and tocotrienols, is the best sources of vitamin E and may be the only really protective form. Morris reports that both gamma tocopherol and alpha tocopherol have independent protective effects against AD and cognitive decline in older adults. Other studies have shown that food sources offer higher bio-availability of vitamin E than supplements. In addition nuts and seeds and certain vegetables in the diet offer a natural whole food source of vitamin E with mixed tocopherols and tocotrienols.

Vegetables vs. Fruit and AD

Using two very different populations, two epidemiological prospective studies, both controlling for other factors, suggest that high consumption of vegetables, particularly green leafy vegetables, is much more important than consumption of fruits to reduce risk of AD. Yet another epidemiological study showed that persons who drank at least 3 glasses of vegetable or fruit

juices had _ the risk of AD compared to those who did not, probably because manufacturers of juices use the entire fruit or vegetable, including skin and seeds, where the nutrients are concentrated. Animal studies such as those with apple juice and transgenic AD mice demonstrate that the appropriate dose (too much is counter productive) not only prevents cognitive decline in aging TG mice, but also affects multiple mechanisms thought to be related to AD etiology: suppresses Presenilin 1 (PS-1), a precursor to A-beta; reduces glutathione production; preserves acetylcholine levels; and alleviates A-beta toxicity. Additional research suggests that mechanisms in addition to antioxidant and anti-inflammatory activities might be involved in the beneficial effects of fruit or vegetable extracts. The most important of these is their ability to increase cellular signaling and neuronal communication. [21] Other studies offer evidence that fruit polyphenolics improve neuronal plasticity in hippocampus and that cognitive improvements afforded by polyphenolic-rich fruits such as blueberries appear, in part, to be mediated by their effects on hippocampal plasticity.

Our working hypothesis is that generally one cannot eat too many vegetables since they are loaded with a variety of potent nutrients, fibers, few calories and most also have little to no sugar content. One must beware, however, of the high sodium content in most vegetable juices.

Eating too many fruits may expose one to excess fructose and sugars triggering insulin problems. Because of their higher caloric content, too much fruit can reduce consumption of the variety of foods needed for a healthy balanced diet. Thus we recommend nutrient intense sources of fruits such as berries and 1 or 2 cups of 100% fruit juice, together with a variety of other healthy fruits during the day, limiting total intake to equivalent of 3 to 4 whole fruits per day.

Tea

Camellia sinensis (CS), and in particular green tea (unfermented CS), has been found to have ingredients relevant to AD. Teas pure form contains catechins and phenolic acids (responsible for tea's antioxidant effectiveness) which were found more powerful than the antioxidant vitamins C, E and _-carotene in an in vitro lipoprotein oxidation model. A key ingredient found in green tea, but not black tea, inhibits beta-secretase, which plays a role in the production of beta-amyloid and senile plaques in AD [31]. Both black and green teas inhibit acetylcholinesterase, as well as butyrylcholinesterase, both found in senile plaques in AD. (This same mechanism is used by one of the current AD drugs, rivastigmine.) Coffee had none of these properties.

Green tea also powerfully increases insulin sensitivity.

Tea is included in the MPD diet also to reduce other beverages that are problematic such as soda and coffee, and to offer a healthy choice that is popular with many older adults. It is inexpensive and has been shown to have no adverse effects, even in large quantities. The ATTICA study found coffee intake over 2 cups to be problematic, aggravating low level inflammation, a risk factor for heart disease and dementia.

Fats and brain health; Omega-3's and relevance of balance of healthy fats

Fats in the diet dramatically affect various aspects of health and brain function. Fat constitutes 60% of the dry weight of the brain. It is used in the production of several hormone-like compounds called prostaglandins that help regulate blood pressure, heart rate, blood vessel constriction, blood clotting and the nervous system and immune functions. Dietary fat also transports fat-soluble vitamins like vitamins A, D, E and K, from the food into the body, and in the body but not the brain, is an important source of energy.

Dr. Martin's team's review study of the role of fatty acids in the brain, including charts of polyunsaturated fatty acids (PUFA) content and ratios of fish and vegetable oils, sets the stage for that part of our diet recommendations. They suggest brain tissue membrane composition reflects dietary sources and that an optimal balance of Omega-6 and Omega-3 fatty acids is necessary to maintain brain cell membrane and vascular health, and protect against oxidative stress and cognitive decline. [32] For instance Morris et al [17] reported that dietary intake of Omega-3 fatty acids from both vegetable and animal sources, and weekly consumption of fish (rich in docosahexaenoic acid (DHA) may reduce the risk of incident AD. Otsuka/Ueki's case control study reported that diets of AD and vascular dementia patients were excessive in intake of Omega-6 PUFA and deficient in intake of Omega-3 PUFA, compared to matched controls who did not have dementia. The American and most Western diets are very deficient in Omega 3's and over abundant in Omega-6's; instead of the ideal ratio for the human body and brain of 1:4, these diets are in the range of 1:20 to 1:75.

Membrane fluidity, which is a critical factor for a membrane's function, depends on its lipidic composition. PUFAs present in the membrane as part of phospholipids increase the membrane fluidity because, by bending some chains, double bonds in PUFAs prevent them from compacting themselves perfectly. Omega-3 fatty acids, especially DHA and EPA, are highly concentrated in the brain, comprising about 22% of the fatty acid

composition of brain phospholipids & brain cell membranes. As a primary determinant of cell membrane fluidity and nerve cell communication, Omega-3's are critically important for cognitive and behavioral function as well as normal growth and development. Hashimoto's group in Japan (using DHA in fish oil) and Cole's group at UCLA [22] (using DHA in marine algae) showed that AD transgenic mice exhibited rapid cognitive decline when deprived of DHA and other Omega-3's in their diet. Cole's group further demonstrated that the decline was associated with significant loss of synapses and dendritic material. Cole's group also showed reversal of effects of DHA deprivation by adding DHA back to the diet of DHA deficient TG 2576 mice; DHA allowed the mice to recover and form new synapses. Both Hashimoto and Cole conclude that DHA protects dramatically against cognitive decline and synaptic deterioration in AD transgenic mice, and thus might also do this in humans.

Omega-3's have been shown to work with presenilins to control AKT, A-beta and prevent phosphorylation of tau. DHA regulates neuronal functions by modulating membrane properties such as neurotransmitter release, ion channel and enzyme regulation, and receptor-mediated transcription of genes involved in critical neuronal functions, such as memory.

A higher ratio of dietary Omega-3 to Omega-6 fatty acids than is currently consumed in our population is also recommended for heart health, and can be achieved by increasing consumption of fish and alpha-linolenic acid (Omega-3) in canola, soy and flaxseed oils. Large prospective trials show that people who experience the least coronary heart disease (CHD) have a diet that is rich in fish, PUFAs, whole-grain cereals, fruits and vegetables and low-fat dairy foods, and low in saturates from dairy fat, meat fat and fried foods. The FDA has now allowed heart health claims for Omega-3's including DHA. Studies of the efficacy of fish in the diet to slow progression (secondary prevention) of heart disease and prevent mortalities gives further reason to emphasize fish in the proposed Memory Preservation Diet. The GISSI Prevenzione Trial reported changes in mortality rates due to increasing intake of fish could be seen in as little as 90 days, an efficacy superior to pravastatin and at the same level as simvastatin or aspirin. They reported only beta-blocking agents are superior, but long-chain Omega-3 fatty acids from fish display their beneficial effects even in patients already treated with beta-blockers.

Omega-3 fatty acids are also important for reducing risk of depression. Since depression itself is a risk factor for Alzheimer's disease this is a yet another instance of a nutrient serving as upstream protective factor for multiple chronic diseases.

An important dietary note is that vegetables (small amounts), soybeans, nuts (especially walnuts and pecans) and seeds e.g. flaxseed, pumpkin seed

and their oils (e.g. canola, flax seed, pumpkin seed, perilla seed oil, and walnut oil), and purslane (a wild plant sometimes cultivated), are sources of shorter chain Omega-3's while only fish and marine algae, seaweed and other marine plants are sources of longer chain DHA and EPA so essential to brain health. While the human body can manufacture DHA and EPA from shorter chain Omega-3's, this ability often declines significantly with age. Hence the importance of direct dietary sources of DHA and the usefulness of DHA and EPA supplements for brain health.

Another review article concludes, "diet and apoE lipoproteins influence membrane lipid raft composition and the properties of enzymes, transporter proteins, and receptors mediating A-beta production and degradation, tau phosphorylation, glutamate and glucose uptake, and neuronal signal transduction." [33] Further, Morris has found that foods or water supplies with high copper content appear problematic only when accompanied by high saturated fat diets. Even more dramatic, if Marchesi's theory that A-beta does its real damage to the brain as an A-beta dimer relatively stable inside the lipid rafts of cell membranes, then the health status of the membrane's lipids may have multiple ways of affecting the AD etiology.

Thus a key dietary strategy in MPD is to avoid or greatly limit foods rich in saturated or trans-fats, both of which if taken in sufficient quantity to replace PUFAs in brain cell membrane, interfere with brain cell fluidity and thus neurotransmitter transmission. A related dietary strategy is to ingest foods and spices that help reduce absorption and retention of unhealthy fats and LDL cholesterol without reducing the "good" HDL cholesterol.

Some foods that assist in lowering LDL cholesterol and other problematic lipid include cinnamon, soy (FDA recommends at least 25 grams per day of soy plus plant sterols to help lower cholesterol), fenugreek, curryleaf, mustard seeds, coriander seeds, tumeric, garlic (modest effects), and fiber. Garlic also has anti-platelet activity facilitating increased blood flow. In the cinnamon study, decreases in LDL were 7 and 27%, in total cholesterol were 12 and 26% and in triglycerides were 23 and 30%, respectively, for doses of 1 gm and 6 grams of cinnamon for 40 days. [34]

Folates and B vitamins

The evidence is clear that B vitamins, other than folates and including niacin, are essential for brain health and protection against AD and cognitive decline. Generally both folates and other B-vitamins such as B-6 and B-12 appear to be critical in preventing excessive levels of homocysteine which has been identified as a risk factor for AD and cognitive decline as well as cardiovascular disease. While the role of folates in preserving brain

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health is beginning to be understood, the best way to achieve adequate folate content in ones' diet remains somewhat controversial. Some epidemiological studies suggest higher folic acid intake is highly related to reduced risk of AD, [35] dementia, and cognitive decline while others (Morris) show highest intake is related to increased risk, perhaps because it masks low vitamin B 12 intake. Some ethnic groups may have a lower intake of B vitamins than mainstream Caucasian populations. Animal studies thus far have supported the importance of folic acid to cognitive health. Folates as food-based dietary supplements were found to slow progression or reverse cognitive deterioration in AD transgenic mice; [23] folate deficiency also appeared to facilitate A-beta production and deposition. Other studies showed differential susceptibility of transgenic mice lacking one or both APOE alleles to folate and vitamin E deprivation.

S-adenosyl methionine (SAM) may play a critical role in whether folate deficiency results in potentiating the PS-1 to A-beta cascade in the genetically vulnerable. SAM also helps maintain levels of acetylcholine, the neurotransmitter that plays a key role in memory decline in AD, by methylating nicotin amide which then inhibits the degradation of choline. Further, SAM is essential for the homeostasis of the human body's own endogenous antioxidant, glutathione, acting as a co-factor for a key enzyme. However some clinicians caution against direct ingestion of SAM in the elderly as it may trigger mania in persons with (undiagnosed and untreated) bipolar disease or who are otherwise vulnerable, while others looking at the same evidence conclude it is generally a safe, effective alternative or adjunctive treatment for depression and that any induced mania disappears quickly when SAM treatment ceases.

Vitamin B12 is also especially important for brain health. It contains cobalt, and so is also known as cobalamin. B12's primary functions are in the formation of red blood cells and the maintenance of a healthy nervous system. B12 plays a vital role in the metabolism of fatty acids essential for the maintenance of myelin. B12 is necessary for the rapid synthesis of DNA during cell division. B12 deficiency can cause anemia, decreased metabolism of critical neurotransmitters, as well as excess homocysteine known to be connected to dementia and CVD; severe deficiencies can lead to irreversible nerve damage. Anemia may also be due to folic acid deficiency, folic acid also being necessary for DNA synthesis. [36]

Vitamin B12 is bound to the protein in food. Hydrochloric acid in the stomach releases B12 from proteins in foods during digestion. Up to 30 percent of adults 50 years and older may have atrophic gastritis, an overgrowth of intestinal flora, and be unable to normally absorb vitamin B12 in food. There is also a concern about effects on vitamin B 12 absorption of medications that suppress production of gastric acids. Older adults are,

however, able to absorb the synthetic B12 added to fortified foods and dietary supplements. Thus vitamin supplements and fortified foods may be the best sources of vitamin B12 for adults over the age of 50. [37]

Vitamin B6 is essential for red blood cell metabolism, protein metabolism, glucose metabolism, immune system function, and proper function of the nervous system including metabolism of most neurotransmitters. [38] B vitamins also help with sleep (B6 and niacin are co-factors needed to produce serotonin), and maintain healthy skin, eyes, digestive tract, and nervous system. Because B-vitamins help release energy from carbohydrates consumed, they also help decrease fatigue.

The goal of the MPD is to secure adequate folic acid and all B-vitamin intake primarily through whole foods with modest supplementation of folic acid and other B-vitamins, especially B-12. One excellent whole food source is brewer's yeast which contains vitamins B1, B2 and niacin(B3) and biotin, as well as 16 other amino acids and 14 minerals, and is an excellent source of chromium, selenium, zinc, phosphorus, and magnesium as well as protein.

The Food and Nutrition Board of the Institute of Medicine has established an upper tolerable intake level (UL) for vitamin B6 of 100 mg per day for all adults; there is no upper limit for vitamin B12 as no toxic level has been found. Folic acid intake from food and supplements should not exceed 1,000 micrograms (μ g or mcg) = 1 mg daily in healthy individuals because large amounts of folic acid can trigger the damaging effects of vitamin B12 deficiency. [37]

Insulin Resistance and Sensitivity

Plant science research followed by a human clinical trial [34] has established that the spice cinnamon is the most powerful nutrient identified to date that increases insulin sensitivity; in addition it decreases LDL and total cholesterol and triglycerides in people with diabetes mellitus type II. One gram of cinnamon per day over a 40 day period reduced mean fasting serum glucose by 18% and 6 grams daily reduced it by 29%. Another reason green tea is specifically relevant to an AD diet is that biological nutrient laboratory studies have shown it to be one of the most powerful nutrients (along with cinnamon) examined to date to improve insulin efficiency, thus to reduce insulin resistance. [39] Food research has indicated that many herbs and spices in addition to cinnamon improve insulin sensitivity, including witch hazel, black and green tea, allspice, bay leaf, cloves, nutmeg, tumeric, sage, mushrooms, and brewers yeast and suggest these plant nutrients improve glucose metabolism through hypoglycemic effects, and improve lipid metabolism, antioxidant status and capillary function. [40]

Still other studies add other plants, herbs, and trace minerals to the list of nutrients that have beneficial hypoglycemic effects in patients with diabetes: bitter melon, Gymnema, Korean ginseng, onions, garlic, flaxseed meal, and specific nutrients including α -lipoic acid, biotin, carnitine, vanadium, chromium, magnesium, zinc, and vitamins B₃, E, and K. Human clinical trials indicate that whole grain cereals also help increase insulin sensitivity. Studies have shown that brewer's yeast, in part, but not solely, due to its chromium and other mineral content, is effective in increasing insulin sensitivity and decreasing blood LDL cholesterol and total lipids in elderly subjects, especially in hypercholesterolemic subjects (cholesterol > 300 mg/dl). [41, 42] Chromium is bioavailable as part of brewer's yeast.

Inflammation

Several foods useful for other reasons, such as anti-oxidants and particular healthy fats, also help reduce inflammation. In addition, certain spices which are also helpful as powerful anti-oxidants and plant nutrients powerfully reduce brain inflammation. Cole's group reported that curcumin, also known as tumeric, the yellow substance in curry powder, is a strong anti-inflammatory agent as well as an anti-oxidant, and achieves its effects in slowing neuro-degeneration and cognitive impairment in transgenic mice through several mechanisms. [27] The compound's low molecular weight and polar structure allow it to penetrate the blood-brain barrier effectively and it binds to beta amyloid. In their related tissue culture study they reported curcumin inhibits the accumulation of destructive beta amyloid in the brains of Alzheimer's patients and also breaks up existing plaques. Several medical and nutrition sources say it is important to maintain an appropriate balance of Omega-3 and Omega-6 in the diet as these two substances work together to promote health. Omega-3 fatty acids help reduce inflammation while excess Omega-6 PUFAs (another type of essential polyunsaturated fatty acid) promote inflammation. For instance the Greek ATTICA study showed 25-33% lower levels of inflammatory markers in those eating 150-300 grams of fish per week (and 30-50% higher levels of the same markers in those consuming more than 200 ml of coffee per day).

Synergy among nutrients for multiple effects

A practicing neurologist explains the relationship to oxidative stress and increased risk conferred by APOE-4 alleles in some populations but irrelevant in other populations with non-Western diets. [43] The interaction

of dietary lipids and apolipoprotein E isoforms may determine the risk and rate of sustained autoperoxidation within cellular membranes and efficacy of membrane repair. This review concludes that interventions involving dietary lipids and lipid metabolism show great promise to slow or avert development of AD. Other researchers also have explored these possible linkages between diet and APOE isoforms. [44] There may be a link between dyslipidemia and risk of diabetes in some populations, and insulin plays a role in lipid metabolism. This suggests multiple pathways for dietary lipid intake to affect AD etiology or progression.

Higher levels of Omega-3 fatty acids help increase concentrations of vitamins C and E in blood and brain tissue, and lower levels of 8-epiPGF2__(F-2 isoprostanes), markers of oxidative stress. Omega-3's may act as free radical scavengers protecting patients against effect of oxidative stress.

Certain nutrients including vitamins E and C, improve vascular and brain health [45] as well as physical health in humans, both by serving as antioxidants and by decreasing inflammation, [45] e.g. vitamin C reduces inflammatory action of glial cells by accelerating the degradation of abnormal or damaged protein [46]. Martin's intervention studies with humans ingesting orange juice, which naturally contains vitamin C, demonstrate that this antioxidant can measurably lower both isoprostane markers of oxidative stress [45] and non-specific biomarkers of inflammation. [45]

The amount of fruit and vegetable intake by older adults is inversely and significantly associated with both C-RP, a major marker of inflammation, and homocysteine. Lab studies indicate that vitamin C, which quickly passes through the body in water, may boost the effects of vitamin E, which builds up in fat stores and remains in tissues longer.

HUMAN NUTRITION CLINICAL AND INTERVENTION STUDIES WITH PERSONS WITH AD

Results of the Elsa Study in France, a prospective study with 312 AD patients suggest that poor nutritional status is risk factor for rapid cognitive decline, as measured by MMSE, in persons with AD. [13]

A Japanese study found diets of AD and vascular dementia patients excessive in energy intake and Omega-6 PUFA, while deficient in Omega-3 PUFA, and in vitamins such as antioxidants, C, and B. It suggests higher intake of energy and lower intake of antioxidants may exaggerate the process of dementia through oxidative stress. There are a few studies completed or in progress which are testing pill-form use of one [29] or two

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vitamins (i.e. vitamins E and/or C, or folates) or a single supplement (e.g. fish oil) to slow progression or lower risk. The only AD diet study to date is Dr. Ueki's Japanese diet study that reported a daily regimen of fish and more fruits and vegetables, fewer sweets, slows progression of AD. [2] Preliminary results were presented at First International Symposium of Alzheimer's Disease and Nutrition and final results for the first 30 months of the diet trial were unveiled a year later at the Boston Alzheimer's Symposium. The study is a controlled clinical trial with about 50 subjects evenly distributed between diet and control groups in the Early AD group (MMSE 20-23). The diet protocol was simple; 80-90g fish per day, green vegetables at least twice a day, fruit at least once day, drink 1.3 liters of water each day and reduce sweets; the study had no coaches or behavioral change intervention. The control group received standard medical care; there was no active comparison intervention. All participants were on cholinesterase inhibitors. The Japanese diet study reported that the diet treatment participants compared to the control participants (in an intent to treat analysis) showed a statistically significant difference in MMSE scores, sustained over a 30 month period of time, achieved by stabilizing the treatment participants while control participants continued to decline by 6 points. Treatment subjects who did not adhere to the diet declined at the same rate as controls. The Japanese diet study further establishes the importance of fish, vegetables, fruit, and fewer sweets to slowing progression of AD, while leaving some questions unanswered.

POSSIBLE MECHANISMS OF ACTION FOR NUTRITIONAL INTERVENTIONS

The MPD diet can be effective because it influences AD pathogenesis (A-beta and tau) and decreases the risk factors caused by other diseases. AD pathogenesis is multifactorial including both genetic and environmental factors. Therefore, approaches seeking a single pharmacological or nutritional agent may be insufficient to prevent or delay onset, or to slow progression once symptoms appear.

We conclude that the evidence supports a nutritional invention emphasizing the synergistic contributions to brain cell health of the key constituents of the Memory Preservation Diet. The power of a comprehensive diet is that, unlike polypharmacy, "polynutrients" can work on multiple pathways at the same time, reinforcing each other and creating synergies with minimal serious side effects.

Based on the evidence to date, the proposed diet is expected to result in decreased oxidative stress; reduced insulin resistance and improved glucose

metabolism; reduced LDL cholesterol; increased HDL cholesterol; reduced inflammation in both body and brain; reduced homocysteine; improvements in methionine cycle including availability of folates and SAME; and reduced blood pressure in those with elevated pressure. In addition, the Memory Preservation Diet can reduce body fat mass, especially abdominal body fat (known to increase inflammatory processes and aggravate many health conditions). Increased insulin efficiency should in turn improve insulin signaling and the availability of insulin degrading enzyme (IDE) to degrade beta amyloid. Improvements in the methionine cycle should in turn reduce nitric oxide synthase and endothelial dysfunction. All or some of these changes should slow production, oligomerization and deposition of beta amyloid and formation of plaques in addition to inhibiting phosphorylation of tau and production of neurofibrillary tangles (NFTs). Mitochondrial damage should be slowed or repaired more quickly. In addition, neuronal membrane repair rates and function, dendritic branching and synaptic function will improve. All of these upstream and downstream changes will slow or stop neuronal degeneration and cell death, resulting in either delayed onset of AD or slowed progression of symptoms (e.g. decline in cognition, mood and behaviors) and underlying disease.

Although developed independently, based on brain health literature, the Memory Preservation Diet shares many elements with the latest heart healthy and diabetes prevention/treatment diets. Thus it should also help reduce risk of, or slow progression, of coronary heart disease, stroke, vascular disease and diabetes. In addition, the diet has parallels to other diets recommended for treatment of mental health conditions such as depression, anxiety, attention deficit disorders and behavioral issues.

These convergences are not surprising, even if arrived at by separate evidentiary pathways in silo fashion. We are now coming to understand that diet and lifestyle affect the etiology and progression of most major chronic diseases, through the intricate inter-relationships and synergies among so many nutrients and biological systems.

THE MEMORY PRESERVATION DIET™ ©2005 HAS 6 MAJOR STRATEGIES

(1) Increasing the amount and variety of anti-oxidants including vitamins E & C; by having 5 vegetables a day (especially green leafy), 2 fruits (especially berries), and lots of spices and nuts (especially almonds, and seeds for vitamin E).

(2) Achieving higher ratio of Omega-3 PUFA to Omega-6 PUFA to approach a 1: 4 ratio, by increasing Omega-3 fatty acids (walnuts, pecans,

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flaxseed, other nuts and seeds, wheat germ), especially DHA (fish, fish or marine algae oil; and reducing amount of Omega-6's (use olive & canola oils instead of corn oil).

(3) Assuring adequate levels of folates/folic acid and B vitamins, especially B-12 (by including green leafy & certain other vegetables, beans, orange juice & other citrus; strawberries, avocados (B-6), bananas (B-6, biotin), meat and fish (B12 and B6), dairy and eggs (B12), whole grains and brewers' yeast (B1, B2, and niacin). The only reliable unfortified sources of vitamin B12 are fish, meat, poultry, dairy products and eggs; liver is an especially good source. The current nutritional consensus is that no plant foods can be relied on as a safe source of vitamin B12. Fortified breakfast cereals and B12 supplements are a particularly valuable source of vitamin B12 for vegetarians and older adults. [36] Foods sources for Vitamin B-6 include fortified breakfast cereals, fish including salmon and tuna fish, meats such as pork and chicken, bananas, beans and peanut butter, some nuts and seeds such as walnuts and sunflower, and many vegetables and fruits including potatoes with skins, spinach, tomatoes and avocados. [38] Biotin is found in various foods, including liver, cauliflower, salmon, carrots, bananas, soy flour, cereals, and yeast.

(4) Reducing insulin resistance and hyper-insulinemia and maintain glucose balance by using more complex carbohydrates, reducing sweets and other simple carbohydrates; eliminating carbonated sodas; increasing consumption of spices (e.g. cinnamon, allspice, bay leaf, nutmeg, cloves, sage, basil) and other foods (e.g. green tea, mushrooms, brewers yeast) shown to improve insulin sensitivity;; limiting consumption of high glycemic foods (e.g. white bread, rice or potatoes) to when higher glycemic fruits and vegetables supply important nutrients (e.g. sweet potatoes, bananas, potato skins).

(5) Reducing inflammation by including berry fruits, tumeric (curcumin, found in curry), cinnamon, soy, more Omega-3's and fewer Omega-6's.

(6) Reducing LDL cholesterol and saturated fats, improve HDL cholesterol, by decreasing consumption of foods with unhealthy fats (high cholesterol, high saturated or trans-fats) and increasing consumption of healthy fats, Omega-3's, fiber, soy, brewers yeast, cinnamon, and other spices such as fenugreek, curryleaf, mustard and coriander seeds, tumeric, garlic .

These goals are to be achieved primarily through a whole foods diet. One key is eating fruits and vegetables daily, including fruit and vegetable juices, and two or more portions of green leafy vegetables (which are great sources of 2 of the 3 major types of nutrients emphasized in diet: folates, some B vitamins and a variety of antioxidants; most also have a small amount of Omega-3 fatty acids). A second key is eating fish at least three

times a week. It also specifies healthy proteins and fats and other desirable foods such as nuts and seeds, green and black tea, and the liberal use of certain spices. Tea, especially green tea, is suggested as an excellent choice of beverage because tea supplies an important category of antioxidants shown to be therapeutic for AD. It also helps avoid insulin resistance, is popular, inexpensive and has no adverse effects. Coffee intake should be reduced to no more than 1 or 2 cups as it appears to aggravate inflammation, abdominal fat, and high blood pressure.

The principles of the Memory Preservation Diet include:

- (1) A balanced diet is essential;
- (2) Nutrients are best obtained from whole foods or juices;
- (3) Multi-vitamins and supplements provide extra insurance, especially for hard to achieve critical nutrients such as vitamins E and B-12, and DHA;
- (4) Nutrient intense foods such as berries, juices, tea, seeds and nuts, and brewers yeast control calorie intake and are especially important for the elderly who tend to eat smaller volume;
- (5) Use of spices with heart/brain healthy attributes (e.g. ginger, rosemary, thyme, tumeric/curcumin, oregano, onion and garlic) that protect against inflammation, and provide antioxidants e.g. flavonoids & polyphenolics. Some spices also increase insulin sensitivity, and some do all three.

The diet also includes other elements necessary for good overall health such as sufficient vitamin D, calcium, zinc and chromium; sufficient water to assure hydration (a problem with many people); and no more than 1.5-2.0 gm of sodium (lower for those dealing with hypertension and other conditions). Caloric recommendations: generally reduce calories unless already losing too much weight. Aim for an average of 1800-2000 calories per day, adjusted for gender and Body Mass Index (BMI).

The Memory Preservation Diet suggests that most nutrients should come from food but it also includes recommended supplements and vitamins to ensure sufficiency of key nutrients. Very important are Omega-3 supplements. Preferred is DHA from either fish oil or marine algae which can be achieved with two 1000 mg soft gels a day (900 mg DHA). A less optimal alternative is 2 Flaxseed Oil 1000 mg soft gels with 450 mg each of Omega-3. (Flaxseed oil contains a shorter chain PUFA that needs to be converted by body to DHA). Also important are multivitamins with 300% or more of RDAs for vitamins C (250 mg), all B vitamins (B1 thiamine 10mg, B6 pyridoxine 10 mg, B12 10 mcg, as well as B2 riboflavin 10 mg, and niacin; 200 mcg folate; 400 IU of natural form of vitamin E containing mixed tocopherols including alpha, delta & gamma tocopherols. We advise against more than 400 mcg supplemental folate unless recommended by one's

doctor for high homocysteine levels since many foods are fortified with folate. We suggest minimal levels of supplements to protect people. The Memory Preservation Diet also includes a disclaimer “Before making changes in your diet consult your physician e.g. re specific conditions or drug interactions.”

To maximize effectiveness, dietary recommendations should be accompanied by a behavioral change strategy such as those used successfully with older adults dealing with other chronic diseases. [47]

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