Prevention of dementia

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INTRODUCTION — Dementia is an increasing problem, primarily affecting elderly patients. Alzheimer's disease (AD) is the most common form of dementia in the elderly, accounting for 60 to 80 percent of cases. Asymptomatic patients often present with concerns about developing dementia, especially when they have a family history. The first, large-scale, randomized, primary prevention trials are coming to completion, testing vitamin E and donepezil versus placebo for the prevention of dementia. In addition, hormone replacement therapy (HRT) has been investigated and appears to have no role. Finally, growing epidemiologic data suggest a possible role for NSAIDS, HMG-CoA reductase inhibitors, and antioxidants, with large trials of both types of agents underway. The data for these and other possible interventions are reviewed below.

VITAMIN SUPPLEMENTATION

The use of antioxidants for prevention of dementia has been evaluated in several observational studies with varying results. While two large, prospective cohort studies reported that higher dietary intake of antioxidants was associated with a lower risk of AD, these studies had significant limitations. As an example, the use of a food frequency questionnaire to estimate nutrient intake may have limited accuracy in patients with cognitive dysfunction. Also, neither study found an association between antioxidant supplements and AD risk; only antioxidant intake from food affected outcomes. Other studies have not found an association between dietary antioxidant intake and the development of AD or cognitive impairment.

Randomized clinical trials have not found a benefit for vitamin E in improving cognitive outcomes:

- Among 2166 participants followed for a median of 6.9 years, antioxidant supplementation including vitamin E 400 IU daily was not associated with any effect on cognitive function compared with placebo. However, in this trial, cognitive function was not a primary outcome measure, not all patients had cognitive testing, and cognitive testing was performed only once at the end of the study.

- The Alzheimer's Disease Cooperative Study (ADCS) tested vitamin E and donepezil against placebo for effectiveness in slowing the conversion of amnestic mild cognitive impairment (MCI) to AD in 769 patients. Vitamin E had no apparent benefit. While vitamin E failed to slow the rate of conversion from MCI to AD, this study does not necessarily rule out a possible effect earlier in the disease process, before the development of any clinical symptoms.

- In the Women's Health study, 6377 healthy women over 65 years in age received either vitamin E (600 IU every other day) or placebo. Cognitive examinations performed at 2-year intervals revealed that vitamin E had no impact on cognitive changes observed over the follow-up period (9.6 years).

Supplementation with beta carotene, another antioxidant, was studied in a subset of 4052 patients enrolled in the Physicians' Health Study who agreed to re-enroll in a follow-up study. While the investigators reported a benefit in cognitive scores for individuals receiving long-term supplementation (18 years) compared to those on placebo, methodological issues with this study cast doubt on the validity of these findings.

In summary, there are no convincing data to suggest that the intake of antioxidants can prevent AD. Since there is growing concern regarding the risk of vitamin E supplementation, we do not recommend supplementation with Vitamin E or other antioxidants for the prevention of AD or other types of dementia.

Vitamins B6, B12, and folate — There is some evidence that elevated serum homocysteine and/or low serum levels of folate, vitamin B6, and vitamin B12 may be associated with impaired cognition and risk of dementia. However, there are no convincing data that vitamin supplementation prevents dementia.

A possible benefit from folate therapy was suggested in a longitudinal study of 965 older individuals, in which a lower incidence of AD was noted among those in the highest quartile of total folate intake after adjustments for age, sex, education, ethnicity, and other comorbidities. Neither vitamin B6 nor B12 intake were associated with risk of AD.

Published trials of vitamin supplementation in older adults do not specifically address the efficacy of this approach for the prevention of dementia. Treatment durations are relatively short, often only several weeks. In addition, the outcome is usually measured by performance on cognitive tests rather than the by the incidence of dementia, and study populations have also varied with respect to baseline cognition and age.

Two examples of longer-term, double-blind randomized studies include:

- A trial in 276 healthy adults over 65 years with elevated serum homocysteine found that supplementation with folate and vitamins B12 and B6 was not associated with improved cognitive performance after two years, despite the fact that homocysteine levels were on average lower in the treated group.

- Another trial in 818 participants with elevated serum homocysteine who were between 50 and 70 years of age found that folate supplementation (800 mcg daily) for three years was associated with decreased homocysteine levels (26 percent) and improved performance on two of five cognitive measures. Cognitive outcome was not a primary outcome of this trial, which also looked at a number of other endpoints, making it likely that a positive result was due to chance alone.

DIET — A number of cohort studies have examined a possible relationship between dietary components and risk of AD and other dementias. However, because of the inherent confounders in epidemiological studies, specific recommendations regarding diet in the prevention of dementia will require a randomized controlled design, and **at present, no conclusive recommendations can be made.**

Cholesterol and fatty acid — High dietary intake of fish and omega-3 fatty acids may decrease the risk of cognitive impairment and Alzheimer's disease (AD), while cholesterol and fatty acid intake may increase the risk, but the evidence is conflicting.

In large prospective cohort studies, as well as cross-sectional studies, higher rates of cognitive decline and/or incident dementia have been associated with higher dietary intake of saturated fats, transunsaturated fats, or cholesterol; others have not found an association. This has led to studies measuring the effect of cholesterol-lowering therapies, specifically the statin drugs, on the risk of dementia, which have also had mixed results.

The potential healthful affects of dietary intake of fish and omega-3 fatty acids on the risk of dementia as well as cardiovascular disease and other health conditions have been studied as well. The findings have been mixed, but most large, longitudinal studies have shown a benefit for higher fish consumption on the risk of dementia or cognitive decline, with some exceptions . Interest has focused on specific omega-3 fatty acids, especially eicosapentaenoic acid and docosahexaenoic acid. In the Framingham study, individuals with the top quartile levels of DHA measured at baseline had lower rates of incident dementia over nine years of follow-up.

These studies are observational and subject to bias. It is possible that any apparent protective effects of dietary fish intake are due to residual confounding from factors such as education and economic status or due to the effects of fish intake on other processes such as vascular disease.

Fruit and vegetables — A diet high in fruits and vegetables is supported by the health benefits of reduced cardiovascular risk. High fruit and vegetable intake may also decrease the risk of cognitive decline, but the data are less clear. One cohort study of 1836 older Japanese-Americans found that consumption of fruit and vegetable juices was associated with decreased incident dementia over seven to nine years of follow-up. In another large population-based cohort of 8085 individuals, daily consumption of fruit and vegetables was associated with decreased risk of incident dementia (HR = 0.72). Two large, prospective, observational studies found that high consumption of vegetables but not fruits was associated with less cognitive decline. Earlier cross-sectional studies reported

that both fruit and vegetable intake were associated with improved cognitive performance in elderly subjects.

Mediterranean diet — There is no single Mediterranean diet, but such diets are typically high in fruits, vegetables, whole grains, beans, nuts, and seeds and include olive oil as an important source of fat. There are typically low to moderate amounts of fish, poultry, and dairy products, and there is little red meat.

Two studies used dietary questionnaires to assess and quantify adherence to the diet in different population cohorts. Both studies found that patients who were most adherent to the diet had a lower incidence of AD compared with those who did not follow this diet. These studies are subject to the same limitations discussed above regarding confounding from economic and educational factors. In addition, the use of questionnaires to assess diet may be problematic given that individuals at risk for AD may have baseline mild cognitive impairment.

Further support for a beneficial effect of the Mediterranean diet on the course of AD comes from a community-based study of 192 patients with AD. Incremental reductions in AD-related mortality were noted in higher diet adherence groups suggesting a possible dose-response effect.

LIFESTYLE AND ACTIVITY — Accumulating evidence, mainly from longitudinal observational studies, suggests that higher levels of physical and mental activity as well as social interaction may help maintain cognitive function during aging. However, methodologic issues in observational trials make it difficult to be certain of the exact relationship between exercise, physical fitness, cognitive leisure activities, and dementia. These issues are discussed separately.

Given the current data and biologic plausibility regarding the relationship between lifestyle and dementia risk (as well as other health benefits), it seems reasonable to encourage patients to maintain or increase physical activity, exercise, cognitive leisure activities, and social interaction. However, it is not known whether these interventions effectively reduce dementia risk.

PHARMACOLOGIC TREATMENTS

Antihypertensive therapy —Until more data are available, firm conclusions regarding antihypertensive treatment for prevention of dementia or cognitive impairment cannot be made. However, there are enough other reasons to treat patients with hypertension that the prevention of dementia alone is unlikely to influence therapeutic decisions.

Hormone therapy — Epidemiologic studies suggested that estrogen replacement might prevent dementia. However, data from the Women's Health Initiative (WHI) and the WHI Memory Study (WHIMS) do not support these observations, and suggest that estrogen replacement does not protect against dementia and may increase the risk. The

impact on dementia of HRT use in younger postmenopausal women is not known. **However, HRT is not recommended for the prevention of dementia.**

The hormone dehydroepiandrosterone (DHEA) is produced by the adrenal gland; peak production and serum concentrations occur in young adulthood and decline progressively thereafter. DHEA has been proposed to have many potential benefits in retarding diseases associated with aging, including cognitive impairment and dementia. A systematic review of three small clinical trials of DHEA concluded that the data **did not support a benefit for DHEA on cognitive function.**

NSAID therapy-**Their use is not currently supported by randomized clinical trials.**

Cyclooxygenase-2 (COX-2) inhibitors and NSAIDs should not be used for the treatment or prevention of dementia or cognitive impairment at this time.

Statins — There has been some interest in, but no established role for the use of HMG CoA reductase inhibitors (statins) in the prevention of dementia.

SUMMARY AND RECOMMENDATIONS — Most data on preventing dementia come from observational studies. Prospective studies and randomized controlled trials have not shown an overall benefit from cholinesterase inhibitors, vitamin E, or estrogen replacement. Ongoing studies should help to clarify the role of NSAIDs and statins.

- We no longer recommend vitamin E in patients at high risk of developing Alzheimer's disease (AD) because of the evidence that vitamin E supplementation increases the risk for all-cause mortality.

- Although there is observational evidence that NSAIDs are protective for dementia, we do not recommend their use even in patients at high risk for AD (ie, those with very strong family histories) because of the possible increased risk of cardiovascular events associated with NSAIDs and COX-2 inhibitors, and because of a lack of stronger clinical trial evidence of benefit.

- We encourage all patients, especially those with early dementia or at higher risk for dementia, to maintain or increase physical activity and exercise as long as there are no contraindications. Similarly, we encourage cognitive leisure activities and social interaction for as long as these are feasible. However, we recognize that these lifestyle factors remain unproven as a means of preventing dementia.