Beta Carotene Supplementation May Improve Cognitive Function Over the Long Term

Grodstein F, Kang JH, Glynn RJ, et al. A randomized trial of beta carotene supplementation and cognitive function in men: the Physicians' Health Study II. Arch Intern Med 2007;167:2184–90.

Study Overview

Objective. To determine the impact of short- and long-term beta carotene supplementation on cognitive function.

Design. Randomized, placebo-controlled trial.

Setting and participants. 4052 participants from the original Physicians' Health Study (PHS), which randomized male physicians to low-dose aspirin or beta carotene, and 1904 new participants were recruited to this study (PHSII). Participants from the original PHS study retained treatment assignment to beta carotene (50 mg) or placebo, while the new participants were randomized to either beta carotene or placebo. Cognitive testing, which measured general cognition, verbal memory, and category fluency, was performed on all participants.

Main outcome measure. Global score of cognitive tests.

Main results. Among new participants (mean treatment duration, 1 year), there was no difference in cognition between those who received beta carotene and those who received placebo. Among continuing participants from the PHS (mean treatment duration, 18 years), the mean global cognition score was significantly higher in the beta carotene group compared with the placebo group; however, the magnitude of the difference was modest (mean difference in *z* score, 0.047; $P = 0.03$). Participants in the original PHS receiving beta carotene performed significantly better on verbal memory than the placebo group (mean difference in *z* score, 0.063; $P = 0.007$).

Conclusion. Short-term beta carotene supplementation had no impact on cognitive performance, but long-term supplementation may provide cognitive benefits.

Commentary

Cognitive decline is a source of disability among many elderly patients and is an important concern associated with aging. Patients and physicians are constantly searching for ways to preserve cognitive function and stave off dementia.

A potential culprit related to cognitive decline among the elderly is oxidative stress, which occurs when oxygen-based compounds cause cellular damage. Antioxidants, which reduce the toxicity of these compounds, have generally failed to demonstrate benefit, whether in preventing cardiovascular disease, cancer, or cognitive decline. Proponents of antioxidants point out that cognitive decline may result from years of cumulative oxidative stress and that long-term antioxidant therapy is needed to observe any effect. Studies that failed to find benefits of antioxidants have generally lasted less than a decade, and proponents argue that this is too short a span to confer any benefits. Critics argue that if benefits cannot be observed over a decade, it is unlikely that they are substantial.

The study by Grodstein and colleagues provides support for both sides of this argument. Patients randomized to short-term beta carotene supplementation had no cognitive benefit; however, a subset of patients who received beta carotene for an average of 15 years appeared to have a modest benefit in cognitive function, including verbal and memory function. Although these differences were statistically significant, they were small. Problems with the generalizability of the findings limit their clinical value.

Study participants were male physicians, who are an atypically healthy group. It is unclear whether the benefits would carry over to the general population. Additional studies could confirm whether the small benefits observed among this healthy patient cohort represent the lower bound of a much larger effect in a sicker, general population. Second, the study's duration may undermine its applicability to the broader population, as most patients have a hard time taking medications regularly over the long term. If the benefits are only apparent after more than a decade of daily intake, the number of patients who could be compliant with such a regimen is likely to be small.

Applications for Clinical Practice

While there is likely no benefit of beta carotene supplementation in the short term, patients who are able to take this supplement regularly for longer than a decade may have modest benefits. Given the small number of patients who can be compliant with such a regimen and given concerns

that beta carotene supplementation may increase the risk of cancer in some patients [1], its applicability in clinical practice is unclear.

—Review by Ashish K. Jha, MD, MPH

Reference

1. Virtamo J, Pietinen P, Huttunen JK, et al; the ATBC Study Group. Incidence of cancer and mortality following alpha-tocopherol and beta-carotene supplementation: a post-intervention follow-up. JAMA 2003;290:476–85.