AHC Media

Integrative Medicine [ALERT]

Vol. 17, Issue 3, March 2014
www.ahcmedia.com

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COGNITIVE FUNCTION

ABSTRACT & COMMENTARY

Long-term Multivitamin Use in Older Men: Are There Benefits for the Brain?

By Luke Fortney, MD

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Dr. Fortney reports no financial relationships relevant to this field of study.

SYNOPSIS: Over a period of 12 years, daily intake of a multivitamin among nearly 6000 healthy elderly male physicians did not provide any cognitive benefits or protection compared to placebo.

SOURCE: Grodstein F, et al. Long-term multivitamin supplementation and cognitive function in men. *Ann Intern Med* 2013;159:806-814.

The question of whether or not to take a daily multivitamin (MVI) has long been debated. But just as "healthy" can be defined in various ways, so too is this question. What, if any, for whom, and for what conditions does taking what vitamins and at what time potentially have any benefit or risk? Researchers from the Physician's Health Study II (PHS) evaluated this broad and elusive question in several ways, including change in cognitive decline. Many vitamins and nutritional cofactors are intrinsically involved in the cellular and physiologic function of the brain, and there are several indirect strands of evidence that point to a possible link between increased vitamin levels and improved brain function.[1]

From 1997 to 2011, researchers from the PHS II conducted a randomized, double-blind, placebo-controlled substudy that evaluated the effect of taking a general daily multivitamin (Centrum Silver) on cognitive function in male physicians aged ≥ 65 years. In total, nearly 6000 participants were evaluated using a total of five validated tests that assess cognitive function, which was a prespecified outcome measure. The primary outcome was a composite average score of global cognition, conducted by annual telephone interviews. Among these, verbal memory was identified specifically due to the fact that it is strongly associated with risk of Alzheimer's dementia.

Financial Disclosure: *Integrative Medicine Alert*'s executive editor David Kiefer, MD, peer reviewer J. Adam Rindfleisch, MD, MPhil, AHC Media executive editor Leslie Coplin, and managing editor Neill Kimball report no financial relationships relevant to this field of study.

Integrative Medicine
The Clinician's Evidence-Based Resource on Complementary Therapies [ALERT]

Integrative Medicine Alert,
Integrative Medicine Alert (ISSN 1096-942X) is published monthly by AHC Media LLC, One Atlanta Plaza, 950 East Paces Ferry Road NE, Suite 2850, Atlanta, GA 30326. Periodicals Postage Paid at Atlanta, GA, and at additional mailing offices.

GST Registration Number: R128870672.

POSTMASTER: Send address changes to Integrative Medicine Alert, P.O. Box 550669, Atlanta, GA 30355.

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In the end, this well-designed and conducted study found no cognitive change in any of the tests over time between the multivitamin and placebo groups. In fact, the changes they saw over time on these scores were smaller than the decline expected for every 1 year of aging. Researchers concluded that in male physicians aged ≥ 65 years, long-term use of a daily MVI did not provide any cognitive benefits.

■ COMMENTARY

The researchers of this PHS II substudy are forthcoming in identifying possible limitations, although there are few. First, results from other randomized, controlled trials of MVIs and cognition have not found any clear benefits among well-nourished and otherwise healthy adults.[2] In this study, it is very likely that the participants, who were older male physicians, were already too well nourished to observe any benefits. Further, this study population was highly educated, and outcomes may not be the same for people with less education or those who may be at risk for inadequate dietary intake of essential vitamins and minerals.

But the no effects outcome of this study also may be due to use of a low-quality product. A Consumerlab.com review of 75 different multivitamin brands found defects in nearly 40% of all products examined.[3] The Multivitamin Guide blog tested more than 100 brands for composition, bioavailability, synergistic effect, and potency. Out of a possible 10 points for overall quality, the product used in this study was given a score of 4.6 and ranked #54 overall.[4]

Yet another limitation may be that at ≥ 65 years of age, supplementation with a daily MVI may be too late to notice any meaningful benefit on cognitive decline. For example, it is known that the progressive deficits associated with dementia are part of a process that begins years before symptoms are detected. Interestingly, in another, but separate, substudy of the PHS II, younger participants who were randomly assigned to receive beta-carotene had better performance on overall global cognitive and verbal memory after an average of 18 years of supplementation, suggesting at least that very long-term supplementation at younger ages may be required to notice any meaningful benefit.

The strengths of this study are numerous. It boasts a large sample size — that was more than sufficiently powered — and had a long duration of randomized, placebo-controlled treatment. The use of multiple validated cognitive assessments over many years with few dropouts adds further strength to the validity of the results. What's more, the study benefited from high levels of MVI and placebo treatment adherence. Further, participant characterizations at the time of initial randomization are nearly identical between both the intervention and placebo groups as well. The researchers go on to suggest, very appropriately, that even though this study does not show any benefit in cognitive health by supplementing with a daily MVI among older male adults, there may still be other unknown health effects from regular MVI use in other groups of people.

In terms of general vitamin use overall, research is showing that at least some benefits for various conditions among different groups of people are very likely. For example, among people at risk for inadequate dietary intake of important relevant vitamins (e.g., folate, vitamin B12, iron, vitamin C, thiamine, etc.), there are clear and well-understood health benefits.[5] For cognitive health, research suggests that there may be some benefits for use of vitamin E in women with low levels[6] and for B-vitamins among women at high risk for cardiovascular disease (CVD).[7] However, the Nurses' Health Study found no association between intake of antioxidants from foods and vitamins and rate of cognitive decline over 4 years among more than 16,000 women.[8] Additionally, a recent 6-month, single-blind, randomized, controlled study among 56 non-obese adults found that, in addition to taking a daily MVI, the addition of 10 popular cardiovascular antioxidant supplements — resveratrol, green tea extract, pomegranate extract, quercetin, acetyl-l-carnitine, lipoic acid, curcumin, sesamin, cinnamon extract, and fish oil — did not demonstrate any

Summary Points

- Overall, there appears to be no significant cognitive benefit to supplementing with a daily multivitamin (MVI) among older, well-educated men.
- However, there is little to no harm associated with taking a daily MVI for most people.
- Other potential health benefits from daily MVI use may include a modest benefit in cardiovascular disease and cancer risk.
- Healthy lifestyle behaviors (not smoking, eating a Mediterranean-style diet, body mass index < 30 kg/m^2, and getting regular exercise) continue to demonstrate the best protection against chronic lifestyle-related disease, including cognitive decline and dementia.

change in arterial stiffness, endothelial function, body fat, blood pressure, lipids, glucose, insulin, IGF-1, or other markers of inflammation and oxidative stress.[9] This suggests that, at least in the short term among healthy non-obese adults, antioxidant supplementation beyond what's available from the diet may not have any effect on cognition or CVD one way or the other.

Evidence supporting the general use of MVIs for health benefits is mixed. In 2013, the United States Preventive Services Task Force (USPSTF) reported that only limited evidence supports any benefit from taking a daily MVI for the prevention of cancer or CVD.[10] However, the VITAL cohort study (VITamins And Lifestyle) found an inverse relationship between incidence of hematologic malignancies and high use of garlic and grape seed supplements over several years among 66,227 men and women aged 50-76 years in Washington state.[11] One limited study found that among 138 healthy adults, daily use of a MVI containing high levels of B vitamins was associated with improvements in measures of stress, physical fatigue, and anxiety compared to placebo over 16 weeks.[12] Another small, double-blind, placebo-controlled, crossover, randomized trial found that even use of a daily MVI for a short period of time may help facilitate psychological and physical recovery and ability during high-intensity military training.[13]

In another arm of the PHS II, daily MVI use was associated with a reduction in total cancers among 1312 men with a history of cancer. However, that reduction in cancer incidence did not differ significantly when compared to more than 13,000 men who did not previously have any history of cancer.[14] Adding to the uncertainty, the Iowa Women's Health Study found that some commonly used dietary vitamin and mineral supplements (such as iron) may be associated with increased total mortality risk.[15] At the very least, however, it appears that the daily use of MVIs does not increase all-cause mortality from CVD and cancer, and may even provide a modest protective benefit overall.[16]

A separate substudy of the PHS II examined the relationship between MVIs and various lifestyle, clinical, and dietary factors among 18,040 middle-aged men. Overall, the study found that 36% of participants reported current MVI use, which was in turn associated with an increased tendency to consume more fruit and vegetables, whole grains, tea, and nuts, and to be more physically active.[17] One obvious takeaway conclusion from this substudy is that healthier people appear to be more likely to take a daily MVI compared to unhealthy people.

Recent studies have shown, again, the significant benefits that a healthy lifestyle can have. Even the simplest things can have a big impact. For example, eating handful of mixed nuts every day has been shown to significantly reduce all-cause mortality by about 20%.[18] Furthermore, eating a Mediterranean-style diet over many years is associated with increased cognitive function[19] and healthier aging with a decreased risk of dementia among women.[20] Similarly, independent of metabolic health status, analyses show that obese individuals have an increased risk for death and CVD over the long-term.[21] Another study, which monitored the health habits of 2235 men over a 35-year period, found that exercise significantly reduces the risk of dementia.[22]

In deciding whether to use a daily MVI, it appears that ultimately there is very low risk with low cost, and it may have modest health benefits overall. However, it is clear that nothing trumps a healthy lifestyle, which continues to be the most important way to decrease the risk of CVD, cognitive decline, cancer, and risk of early death.[23-25] In his book *In Defense of Food*, Michael Pollan offers a solution that may, after all is said and done, be the most reasonable: "Be as vitamin-conscious as the person who takes supplements, but don't actually take them." ■

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CARDIOVASCULAR DISEASE

ABSTRACT & COMMENTARY

Red + Blue for Heart Protection

By Howell Sasser, PhD

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Dr. Sasser reports no financial relationships relevant to this field of study.

SYNOPSIS: **In a study of 93,600 women conducted over 18 years, those with the highest levels of anthocyanins in their diets had a risk of myocardial infarction 32% lower than those with the lowest levels, even after adjusting for other risk and protective factors.**

SOURCE: **Cassidy A, et al. High anthocyanin intake is associated with a reduced risk of myocardial infarction in young and middle-aged women. *Circulation* 2013;127:188-196.**

Researchers analyzed data from the Nurses' Health Study II (NHSII), which began in 1989 with the enrollment of women between the ages of 25 and 42. Each participant completed a questionnaire about health events every 2 years and a questionnaire about dietary patterns every 4 years. Follow-up continued for a maximum of 18 years.

Participants who reported having had a myocardial infarction (MI), stroke, other kinds of cardiovascular disease, or cancer before the study period began were excluded. The outcomes of interest were nonfatal MI and fatal coronary heart disease. Reported events were confirmed with medical records whenever possible.

Intake of a number of subclasses of dietary flavonoids, including anthocyanins, flavanones, flavan-3-ols, flavones, flavonols, and polymers, was estimated mathematically from reported

Summary Points

- Each increase of 15 mg in average anthocyanin intake over the period of follow-up was associated with a 17% reduction in the relative risk of MI.
- There was a trend toward reduced risk of MI with higher intake of flavonols and flavonoid polymers.
- Information on MI characteristics was not available, so it was not possible to draw conclusions about anthocyanins' protective mechanism.

consumption of relevant foods. Supplement use was not reported. Intake levels for each 4-year interval were included in the study's statistical models to allow for dietary changes over time. Other factors collected and used in the analysis to control for possible confounding included body mass index, physical activity, total energy intake, dietary fats, menopausal status, smoking, hormone use, and family history of MI. Secondary statistical models controlled for additional factors related to diet (potassium, folate, and fruit and vegetable intake) and health (hypertension, diabetes, angina, and hypercholesterolemia).

There were 405 cardiac events among 93,600 participants over 18 years of follow-up. There was a trend toward lower risk of MI with rising anthocyanin intake ($P < 0.047$), even after adjusting for potentially confounding factors. Those in the highest quintile of consumption had a risk 32% lower than those in the lowest quintile (hazard ratio, 0.68; 95% confidence interval, 0.49-0.96). For each 15 mg increase in consumption, the relative risk of MI declined by 17%. There also was evidence of some benefit with higher consumption of flavonols and flavonoid polymers, and with higher intake of flavonoid-containing foods, but these effects did not reach statistical significance.

■ COMMENTARY

The potential health benefit of foods, over and above their nutritional value, has been of interest since ancient times — Hippocrates said "Let your food be your medicine." The modern public is bombarded with advice about "superfoods" and advertisements promising miraculous results ("Eat this and never diet again!"). For a time, dietary supplements containing the active agents of various foods in concentrated form seemed promising, but careful research found little clinical benefit.[1] What appears to remain is the observation that some constituent(s) of foods, perhaps even combinations of foods, have healthful properties when consumed in their original forms. Table 1 lists some common sources of the flavonoid subclasses that showed positive results in the present study.

Anthocyanins, a flavonoid subclass and one group of the phytochemicals responsible for the red and blue coloring of many fruits and vegetables, have strong antioxidant properties in vitro.[2] However, this has not been found to correspond to strong antioxidant effects in vivo. Researchers speculate that anthocyanins and other flavonoids are too degraded by digestion to make their way into body tissue where they might scavenge free radicals. Instead, their effect may be achieved by stimulating other processes. In the case of the cardiovascular system, one theory is that anthocyanins increase the activation of nitric oxide synthase, which in turn affects vascular tone and inflammation.[2] Alternatively, they may inhibit cell growth factors in the vascular endothelium.[3] It should be noted that the present study did not have access to detailed medical information, and so could not shed any light on whether anthocyanin intake correlated with a reduced risk of atherosclerosis, or vascular spasm, or some other mechanism.

Table 1. Common Sources of Anthocyanins, Flavonols, and Flavonoid Polymers.

Flavonoid Subclass	Common Sources in Food or Beverages
Anthocyanins	Blackberries Blueberries Cabbage, Red Cherries Concord Grapes Radishes, Red Raspberries, Black Raspberries, Red
Flavonols	Capers Chocolate, Dark Fennel Tea, Black Tea, Green Hot Peppers
Flavonoid Polymers	Chocolate, Dark Grapes, Red Tea, Black Wine, Red

Table 2. Comparative Flavonoid Content of Several Common Foods

Food/Beverage Source	Anthocyanins (mg/100 g)	Flavonols (mg/100 g)	Proanthocyanins* (mg/100 g)
Blackberries	89-211	13-19	6-47
Blueberries	67-183	1	88-261
Grapes, Red	25-92	2	44-76
Plums	2-25	1-6	106-334
Strawberries	15-75	-	97-183
Wine, Red	1-35	1-55	24-70

*Proanthocyanins are a major class of flavonoid polymers, a group which also includes thearubigins and theaflavins.

Regardless of this, if the mechanistic hypotheses are correct, relatively small quantities of anthocyanins may be needed to realize the potential benefit. This is significant because the typical American diet contains only small amounts — far less than in some dietary supplements.[4] A study by Wu and colleagues found that while some foods contain large amounts of anthocyanins per unit of volume, data from the National Health and Nutrition Examination Survey showed that most Americans do not consume significant quantities of those foods. In the present study, the average anthocyanin intake was 2.5 mg/day in the lowest quintile of consumption and 25.1 mg/day in the highest. By comparison, some dietary supplements contain as much as 600 mg per dose.

This is important for the advice that clinicians might wish to give their patients. The present study demonstrated that measurable changes in risk could be achieved with relatively small dietary differences. Drawing on Wu et al's data, the difference between the low and high anthocyanin intake quintile averages is equivalent to two plums, one serving of black beans, or half a serving of red grapes. Changes in eating patterns on this scale should seem manageable to many if not most patients. Choosing to increase one's intake of anthocyanins in this way also has side benefits, such as increased consumption of dietary fiber, vitamins, and other phytochemicals, as well as perhaps crowding out some less healthy foods — in other words changing eating patterns.

Physicians and patients should bear in mind that it is these changes in patterns, rather than rigid adherence, that matter, as well as a consistent and long-term focus on a rainbow of colors in food. No one could — or should — eat an identical diet every day. Nor do foods contain precise and constant levels of any compound. Wu et al found anthocyanin levels in strawberries that varied from 35-69 mg per serving, and Table 2 gives examples of foods that contain several flavonoid subclasses in varying amounts.[5-7] Dietary variety, including multiple sources of the same desirable substances, offers the best chance to maintain appropriate consumption through seasonal fluctuations in availability and phytochemical composition. While this method requires more planning and thought than simply taking a pill, it yields benefits that likely extend beyond what we yet understand. ■

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ABSTRACT & COMMENTARY

Beneficial Brain Bacteria: Fermented Milk and Your Noggin'

By David Kiefer, MD, Editor

SYNOPSIS: In healthy women, the group receiving a fermented and probiotic-supplemented milk beverage showed baseline resting brain network changes and decreased responses to negative imagery.

SOURCE: Tillisch K, et al. Consumption of fermented milk product with probiotic modulates brain activity. *Gastroenterology* 2013;144:1394-1401.

There is some animal research showing a connection between the contents of the intestinal microbiota and neurological activity (including pain) and behavior, although there are limited human data exploring these relationships, an aim of this research study. In this 4-week trial, healthy women were randomized to one of three groups: 1) twice daily fermented milk product supplemented with probiotics (n = 12), 2) twice daily non-fermented milk product (n = 11), or 3) no intervention (n = 13).

The study participants were aged 18-55 years and were recruited from the community by an advertisement. Women were excluded if *Bifidobacterium lactis* was found in a pre-examination of their stool (representing possible effects of a non-allowed probiotic ingestion), if they had taken antibiotics or probiotics in the month before the study, or if their compliance with the study protocol was less than 75% of the doses provided.

The researchers described, in depth, the bacteria present in the fermented milk product, providing information that probably indicates the level of detail future clinical discussion on this topic will contain (*see Table*). The doses of the three probiotic species are also listed in the Table. The control milk product contained the same amount of lactose as the intervention milk product, but without the probiotic strains. Approximately one-half cup (125 g) of each of these milk products was given to study participants twice daily.

Study participants had their stool analyzed for bacterial content before and after the intervention. In addition, functional magnetic resonance imaging (fMRI) was taken of each study participant as they were presented with either emotional faces attention tasks using negative affect (fear and anger) or control tasks with geometric forms. Comparisons were made between different brain regions and their respective activities. In addition, an estimate of resting brain activity was made using a complicated series of computer calculations from the MRI images ("… resting scan correlation maps were calculated in Statistical Parametric Mapping using the peak voxel from 3 clusters of interest in the Partial Least Squares Analysis as seeds.") The original article describes this complex process in more detail should readers be interested.

Summary Points

- Healthy women were randomized to fermented, supplemented milk, normal milk, or no intervention.
- The fermented, supplemented milk product contained several probiotic bacterial species, amounting to approximately 15 billion cfu daily.
- The group ingesting the probiotic milk product showed changes in resting brain state, as well as a decreased response in several areas of the brain after exposure to negative emotion images, as demonstrated by functional MRI.

There were some dropouts in this study, including two people who took antibiotics, six with *B. lactis* positive stool at baseline or in the control groups, and one in the probiotic milk group who did not have *B. lactis* in ther stool and was presumed non-compliant. Of the subjects analyzed, the researchers found that study participants ingesting the probiotic milk product had a lessened response to emotional tasks in areas of the brain containing affective, viscerosensory, and somatosensory cortices when compared to the control tasks ($P = 0.004$). A series of fMRI brain images accompanied this paper, demonstrating these changes graphically. In addition, the treatment group showed changes in intrinsic

Table: Probiotic Strains Present in the Fermented Milk Product

Bacterial Species and Strain	Dose (cfu = colony forming units)
Bifidobacterium animalis subsp *lactis* (strain number I-2494)	12.5 billion cfu per cup
Streptococcus thermophiles (strain number I-1630)	1.2 billion cfu per cup
Lactobacillus bulgaricus (strain numbers I-1632 and I-1519)	1.2 billion cfu per cup
Lactococcus lactis subsp *lactis* (strain number I-1631)	Not listed

activity of the resting brain, more specifically in midbrain connectivity, which the authors postulate could explain the observed decreased responses to the emotional tasks in the probiotic milk product group. The authors make an analogy between the resting brain state and a template, in that the brain can respond quickly to the environment from the baseline template that has been created.

Interestingly, the researchers failed to find differences between groups in microbiota content of the stool after the intervention period.

■ COMMENTARY

The implications of these results, if replicated and expanded to other demographics, could be far-reaching. Imagine a day when we treat pain or mental health conditions with fermented foods or probiotics as adjuvant therapies to allopathic approaches, or maybe even the first-line treatments themselves. The researchers here extend animal trials to the human realm, finding what the authors claim are "widespread" changes in how the brain responds to a negative context. A fermented milk product seems to change brain activity; "Got Milk?" advertisers are going to have a field day with this.

There are mechanisms that could explain these findings, including numerous animal research references offered in the article for changes in afferent vagal signaling or systemic amino acid and polysaccharide metabolism from probiotic supplementation. As this experiment was not designed to specifically test the mechanisms of action, the authors hedge their bets by offering several competing hypotheses and metabolic pathways by which gut flora could account for the changes seen. For example, the authors allude to "monoaminergic modulation of multiple brain areas," mediated by the vagus nerve, referencing studies that show a vagal effect on the nucleus tractus solitarius, a key connector to many other areas of the brain. They also hypothesize that some cerebral effects from probiotics may occur from systemic metabolic changes.

It is a methodological flaw that the dropouts were not included in the statistical analyses as intention-to-treat. Furthermore, no discussion was offered to explain the lack of stool colonization changes in the fermented milk product group as compared to the other group. If the probiotic supplementation were successful in delivering live bacteria to the colon to the point where it was causing the posited metabolic and vagus-mediated shifts in brain activity, some change in stool microbiota should be seen. It definitely leads to confusion as far as the mechanisms behind the results. On that note, a control population is useful for some of the statistical analyses, but doesn't control for a placebo effect, which could be at play here.

My prediction is that the floodgates have opened on this intriguing topic: the whole body effects of the gut microflora. Perhaps this study wasn't perfectly designed or executed, but there is a growing body of evidence in animal and human research for probiotic effects on many organs, even the brain. Future research will surely help us understand this better. It seems early to offer a definitive clinical guideline from this study as there are too many details needing corroboration. That said, provided safety can be assured (and most probiotic supplementation studies demonstrate a good safety profile), we should now start to wonder about the probiotic dose and species necessary for tangible brain effects, and encourage our research colleagues to explore this. ■

ABSTRACT & COMMENTARY

Exercise and the Elderly: You are Never Too Old to Pump it Up!

By Martin S. Lipsky, MD

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***This article originally appeared in the Jan. 15, 2014 issue of* Internal Medicine Alert.**

SYNOPSIS: Poor fitness in the elderly can lead to serious consequences. This study showed that resistance training improved agility, lower limb strength, balance, and flexibility in a group of Alzheimer's disease patients.

SOURCE: Garuffi M, et al. Effects of resistance training on the performance of activities of daily living in patients with Alzheimer's disease. *Geriatr Gerontol Int* 2013;13:322-328.

Throughout the world, the population is aging. In 2008, about 13% of the U.S. population was older than age 65, and by 2030 more that 20% of the U.S. population is expected to be older than age 65.[1] Similar increases in the percentage of elderly individuals are expected worldwide, and by the year 2050, about 16% of the world's population will be older than age 65.[2] As people age, there is an increased risk of dementia suggesting a concomitant increase in the number of individuals with Alzheimer's disease (AD). The anticipated increase in prevalence of AD makes it critically important to find ways to reduce the burden of this devastating disease. Maintaining a healthy lifestyle and regular exercise might be ways of doing this. However, while there is evidence that exercise benefits individuals with AD and might improve both brain health and physical fitness, no consensus exists about what is the best type of physical activity or how to prescribe the right intensity and frequency of exercise.

Resistance training improves muscle strength. A review of strength training and chronic diseases reported an association between muscular strength and the risk for AD. However, this review did not report on the impact of resistance training on the functionality of this population.

In this study, Garuffi and colleagues explored the impact of resistance training on patients with mild-to-moderate AD. They took 34 patients with mild-to-moderate AD and divided them into two groups. Both groups had preintervention testing using a battery of tests to assess their performance in common activities of daily living. One group participated in a resistance training program consisting of three sets of 20 repetitions of five exercises. The second group was a social gathering group that participated in a variety of unstructured activities such as writing and reading. The social gathering group was designed to minimize biases associated with socialization that might cause benefits in patients who participated in the exercise intervention.

Summary Points

- Resistance training improves agility, lower limb strength, balance, and flexibility in Alzheimer's disease patients.
- With the help of one or two sessions with a physical therapist, resistance training could be implemented and supervised at home and offers the potential for a relatively low-cost, non-pharmaceutical alternative to improve the care and outcomes of patients with Alzheimer's disease.

After 16 weeks, both groups were retested to see if there was improvement in their ability to perform common activities of daily living. The researchers noted significant differences between the two groups with the individuals who participated in resistance training showing significant improvement in moving around the house, climbing stairs, standing up from the floor, and putting on socks. They concluded that resistance training improves agility, lower limb strength, balance, and flexibility in AD patients. Both protocols appeared to be effective in improving agility as measured by a moving around the house test.

■ COMMENTARY

While this study is small and should be verified

with larger numbers of patients, it adds to a body of knowledge that fitness and exercise benefit AD patients. Resistance training, which can be done at home with little cost, demonstrated significant improvement in tasks that can help maintain a higher degree of autonomy and, perhaps, improve quality of life. It was also exciting to see that improvement occurred in only 16 weeks. While the researchers did not study institutionalization as an endpoint, the improvements seen suggest that for some individuals, an exercise program, including resistance training, might be the difference between maintaining a patient with AD at home rather than the patient being transferred to a long-term care facility. The findings suggest that with the help of one or two sessions with a physical therapist, resistance training could be implemented and supervised at home and offers the potential for a relatively low-cost, non-pharmaceutical alternative to improve the care and outcomes of patients with AD. ■

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SHORT REPORT

RBC Level of Omega-3 Fatty Acids Inversely Correlated with Brain Volume Atrophy

By Carrie Decker, ND

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Dr. Decker reports no financial relationships relevant to this field of study.

SYNOPSIS: Higher combined eicosapentaenoic acid and decosahexaenoic acid level in red blood cells is correlated with decreased total brain and hippocampus volume atrophy in postmenopausal women 8 years later.

SOURCE: Pottala JV, et al. Higher RBC EPA + DHA corresponds with larger total brain and hippocampal volumes: WHIMS-MRI Study. *Neurology* 2014 Jan 22; [Epub ahead of print].

Brain volume atrophy, particularly in the hippocampus region, is seen with the development of the dementia of Alzheimer's disease (AD). Decosahexaenoic acid (DHA) is the fatty acid that makes up 30-40% of the gray matter of the cerebral cortex. Decreased serum, brain, and neuronal DHA and/or eicosapentaenoic acid (EPA) have been found in patients with AD. These factors promote interest in further evaluation of brain volume associated with EPA and/or DHA status.

A population of 1111 postmenopausal women from the Women's Health Initiative Memory Study were the subjects of this study. The RBC levels of EPA, DHA, and combined EPA and DHA were measured and compared to the brain volume in 13 regions measured by MRI an average of 8 years later. Findings were adjusted for multiple factors including hormone therapy, intracranial volume, time, and cardiovascular risk factors. Individuals who experienced a stroke or transient ischemic attack in the 8-year period were excluded. Significant findings were that one standard deviation increase in RBC EPA + DHA level was associated with a 2.1 cm^3 increase in total brain volume ($P = 0.048$; 95% confidence interval [CI], 0.0-4.3 cm^3) and a 50 mm^3 increase in hippocampal volume ($P = 0.036$; 95% CI, 3-97 mm^3). One standard deviation increase in DHA was associated with a 2.0 cm^3 increase in total brain volume, a marginally significant finding with $P = 0.063$. Information about omega-3 supplementation during the 8-year period and measurements of RBC fatty acid levels at the time of MRI assessment were not included in this study.

Summary Point

- Lower levels of omega-3 fatty acids may be associated with increased risk of age-related brain and hippocampus volume atrophy.

The results from this study add to the growing body of evidence about omega-3 fatty acids and brain health. For example, DHA and total fatty acid levels have been shown to be significantly lower in individuals with Alzheimer's disease and cognitive impairment.[1] However, this study is only a preliminary finding, a correlation that needs to be corroborated by a controlled clinical trial before sweeping changes are made in the clinical use of omega-3s in this context. Furthermore, as described in a related review about omega-3 levels,[2] there is

some debate about the best way to determine an individual's omega-3 status. Nonetheless, these are intriguing findings, which, given the overall safety profile of dietary and supplemental omega-3s, further nudge clinicians to expanding the recommendations about omega-3 intake. ■

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SHORT REPORT

Healing Touch for Pediatric Oncology

By David Kiefer, MD, Editor

SOURCE: Wong J, et al. The impact of healing touch on pediatric oncology patients. *Integr Cancer Ther* 2013;12:25-30.

Filling a need for non-pharmacologic solutions to symptoms associated with cancer and cancer treatments in children, healing touch may alleviate a variety of symptoms. Healing touch, defined as an energy therapy that works with a person's energy field to balance physical, mental, emotional and spiritual well-being (www.healingtouchinternational.org/), is also consider a mind-body therapy by some groups such as the National Center for Complementary and Alternative Medicine. Its purported mechanisms of action include an improvement in immune system function and the support of the mind and body's innate healing abilities. The researchers of this study followed up on this topic by randomizing nine pediatric oncology patients to either 30-minute healing touch sessions once daily at each inpatient or outpatient clinical encounter over 1 year (n = 6) or reading/play activities as the control group (n = 3). Via the Wong-Baker Faces Scale, the Feeling Thermometer Scale, and My Fatigue Meter, the children, parents, and health care providers rated pain, distress, and fatigue, respectively, pre-intervention and post-intervention. The healing touch group started with higher baseline scores on the above-mentioned scales, and accrued more sessions over the year (200 sessions vs 30 sessions in the control group). For each of the scales, patients, parents, and providers all reported an improvement in the patient's pain, distress, and fatigue when pre-intervention was compared to post-intervention ($P < 0.001$). No such improvement was seen in the control group. When the healing touch group was compared to the control group, the healing touch group had statistically significant differences in pain (children and parents) and distress (parents). Despite the fact that it was a very small study, the important differences between the healing touch and control enrollees, and that, of the nine enrollees, three dropped out during the year (two from complicated treatment regimens, one due to death, all in the healing touch group), it seems that healing touch is a viable treatment option for children undergoing treatment for cancer. On that note, there is little downside to the use of this modality as an adjunctive therapy provided that conventional therapies are not eliminated or delayed, and there is no significant out-of-pocket cost burden for the patient and their family. In a busy hospital or clinic environment, and during treatment for devastating illnesses such as childhood cancers, it may be easy to forget to incorporate any of a number of bioenergetic therapies into an integrative treatment plan. This study is a reminder for clinicians to keep healing touch in mind for one aspect of pediatric oncological care. ■

Summary Point

- This small pilot study demonstrated some improvements in pain, distress, and fatigue in children undergoing treatment for cancer who received a series of 30-minute healing touch sessions over 1 year.

Pharmacology Watch and *Clinical Briefs* Available Online

The March 2014 issues of *Pharmacology Watch* and *Clinical Briefs in Primary Care* are available exclusively by e-mail or online. You can access these two valuable supplements to *Integrative Medicine Alert* at http://www.ahcmedia.com/supplements/. We will send PDF copies of these supplements to you by e-mail if you prefer. Please send an e-mail with your name and/or subscriber number to customerservice@ahcmedia.com with Digital AHC Supplements in the subject line. We welcome your feedback and appreciate your continued support as a subscriber to *Integrative Medicine Alert*.

CME QUESTIONS

1. A daily adult multivitamin has been found to have benefits for which of the following situations?

a. Decreases cognitive decline in adults > 65 years of age
b. The USPSTF reports that there is some limited evidence to warrant MVI use for cancer and cardiovascular prevention overall
c. To improve cognition among healthy non-obese women with normal vitamin E levels
d. MVI with added popular antioxidants has been shown to improve endothelial function and reduce CVD risk

2. Anthocyanins are hypothesized to reduce the risk of myocardial infarction by:

a. free radical scavenging.
b. promotion of nitric oxide synthase production.
c. endothelial cell growth factor inhibition.
d. B or C, but likely not A

3. Which of the following is *true* regarding the brain effects of probiotics?

a. It is clearly mediated through changes in the gut colonization by healthy bacteria.
b. To date, animal research results are more convincing than that for humans.
c. The phrenic nerve seems to be one of the major pathways connecting the gut and brain via probiotics.
d. Interestingly, there is a heightened response to negative imagery in several parts of the brain.

4. Resistance training in the elderly can improve:

a. agility.
b. balance.
c. flexibility.
d. strength.
e. All of the above

5. Higher RBC levels of EPA + DHA were significantly associated with:

a. a decrease in total brain and hippocampus volume.
b. a decrease in total brain volume but not hippocampus volume.
c. an increase in hippocampus volume but not total brain volume.
d. an increase in hippocampus and total brain volume.

6. Which of the following is *true* about healing touch as demonstrated in the Wong et al study in pediatric oncology patients?

a. When compared to the control group, parents noted statistically significant differences in the child's pain and distress in the healing touch group.
b. When compared to the control group, the child's report of fatigue was significantly less in the healing touch group.
c. Pre-intervention and post-intervention findings were significantly different in both the healing touch group and the control group.
d. The healing touch sessions lasted a mere 5 minutes, whereas the control group (reading/play) sessions were 30 minutes long.

CME INSTRUCTIONS

To earn credit for this activity, please follow these instructions:

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2. Log on to www.cmecity.com to take a post-test; tests can be taken after each issue or collectively at the end of the semester. First-time users will have to register on the site using the 8-digit subscriber number printed on their mailing label, invoice or renewal notice.

3. Pass the online tests with a score of 100%; you will be allowed to answer the questions as many times as needed to achieve a score of 100%.

4. After successfully completing the last test of the semester, your browser will be automatically directed to the activity evaluation form, which you will submit online.

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[IN FUTURE ISSUES]

Walnuts and chronic diseases

Spirituality and in vitro fertilization

Mediterranean diet and diabetes