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ABSTRACT & COMMENTARY

Coffin Nail for Omega-3 Fatty Acids?

By Michael H. Crawford, MD

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

SYNOPSIS: A meta-analysis of 10 randomized, controlled trials of omega-3 fatty acids for the prevention of coronary heart disease and major vascular events showed no significant effect on fatal and nonfatal coronary heart disease or any major vascular event. These results do not support the use of omega-3 fatty acids supplements in patients with prior coronary heart disease.

SOURCE: Aung T, Halsey J, Kromhout D, et al. Associations of omega-3 fatty acid supplement use with cardiovascular disease risks: Meta-analysis of 10 trials involving 77,917 individuals. *JAMA Cardiol* 2018;3:225-233.

The authors of observational population studies have reported that increased fish or omega-3 fatty acid (FA) consumption reduces the risk of dying from coronary heart disease (CHD). However, studies in patients with CHD or at high risk for it have shown mixed results.

Thus, the omega-3 treatment trialists collaboration performed a meta-analysis of 10 randomized, controlled trials of omega-3 FA supplements for the prevention of cardiovascular disease. The primary endpoints were fatal CHD, nonfatal myocardial infarction (MI), stroke, major vascular events, and all-cause mortality in prespecified subgroups. Data were obtained directly from the principal investigator in nine of the 10 trials. The prespecified subgroups included age, sex, prior CHD, prior stroke, diabetes, blood lipids, statin use, and trial design (blinded or open-label). A total of 77,917 individuals participated in the 10 trials. Eight trials were blinded and two were open-label. Men comprised 61% of the participants and the mean age was 64 years. Two-thirds reported a prior history of CHD, 28% experienced a prior stroke, and 37% were diabetic. Major vascular events occurred in 16% (3% MI, 3% CHD deaths, 2% stroke, 8% revascularization).

Randomization to omega-3 FA supplementation resulted in no significant associations with CHD death (relative risk [RR], 0.93; 95% confidence interval [CI], 0.83-1.03; $P = 0.05$), nonfatal MI (RR,

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0.97; 95% CI, 0.87-1.08; *P* = 0.43), any CHD event (RR, 0.96; 95% CI, 0.90-1.01; *P* = 0.12), or major vascular events (RR, 0.97; 95% CI, 0.93-1.01; *P* = 0.10) in any subgroups. Also, there was no effect noted on all-cause mortality (RR, 0.96; 95% CI, 0.92-1.01; *P* = 0.16). The authors concluded that this meta-analysis of 10 randomized, controlled trials of omega-3 FA treatment fails to support the use of these supplements in patients with CHD.

■ COMMENTARY

Although a properly designed and powered randomized, controlled trial is preferable, a well-conducted meta-analysis of smaller randomized, controlled trials generally is better than observational studies. Given the tremendous public interest in omega-3 FA, this meta-analysis of 10 randomized, controlled trials is of interest. This analysis featured several strengths. First, in all but one trial, study level data were obtained from the principal investigator. For the one exception, the published data were detailed enough for inclusion, and when this study was eliminated the results did not change. Second, Aung et al excluded studies in which the intervention was dietary advice or fish consumption. Third, the authors excluded trials with < 500 participants and with less than one year of follow-up. The mean follow-up for the 10 trials chosen was 4.4 years. Finally, these investigators evaluated prespecified subgroups of clinical importance such as diabetics, statin use, various lipid levels, and prior cardiovascular diseases. All but one trial used a combination of omega-3 FA with doses up to 1,800 mg/day for each ingredient. These doses are not high enough to reliably decrease triglycerides, but there are trials underway to evaluate this. One weakness of this analysis is that there were not prespecified subgroups for smoking and cancer history. However, there was no adverse cancer signal observed. Generally, the trials were markedly consistent. There was some weak heterogeneity in three subgroups. No history of prior stroke favored therapy, as did age > 65 years and an open-label study design. Hopefully, these nuances will be addressed in larger randomized, controlled trials underway. At this time, the European Society of Cardiology does not recommend omega-3 FA supplementation (2016), but the American Heart Association (AHA) does for those with prior CHD or heart failure with reduced left ventricular function (2017). This meta-analysis does not support the AHA recommendation. ■

ABSTRACT & COMMENTARY

Neurogenesis in Older, Healthy Brains

By Joseph E. Scherger, MD, MPH

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

SYNOPSIS: Healthy aging allows for hippocampal neurogenesis in the brains of adults into the eighth decade of life.

SOURCE: Boldrini M, Fulmore CA, Tartt AN, et al. Human hippocampal neurogenesis persists throughout aging. *Cell Stem Cell* 2018;22:589-599.

A group of investigators from New York and Macedonia performed 28 autopsies on healthy human individuals aged 14-79 years, focusing on the hippocampus, the main memory center of the brain. While older individuals exhibited less angiogenesis and neuroplasticity, investigators found similar numbers of intermediate neural progenitors and thousands of immature neurons capable

of becoming mature neurons. The authors postulated that stem cell activity persists in the healthy aging brain.

■ COMMENTARY

These results provide further support for previous investigations that revealed cognitive decline may be reversed in elderly patients with a healthy lifestyle.[1-3] Other researchers have documented growth of the hippocampus in seniors. More work remains to determine the most important determinants of healthy aging, but low-glycemic and anti-inflammatory nutrition, regular exercise, restful sleep, stress management, and executive cognitive function all play some role.[3-5]

Promoting a healthy lifestyle should be at the foundation of primary care practice. Patient education and motivational counseling toward better health practices are crucial skills for primary care physicians. This puts medication and procedures as secondary interventions when needed. Two influential figures in history reportedly predicted this role for physicians long ago. Maimonides was said to have advised that a disease that could be treated by diet should not be treated by any other means. Later, Thomas Edison's focus on diet reportedly led him to predict that rather than focusing on dispensing medicine, doctors in the future would instruct patients in the care of the body, in diet, and in preventing disease. ■

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ABSTRACT & COMMENTARY

Sleep Habits and the Development of Dementia

By Alan Z. Segal, MD

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

SYNOPSIS: The relationship between quality of sleep and the development of dementia is controversial and not yet clearly elucidated nor understood.

SOURCE: Suh SW, Han JW, Lee JR, et al. Sleep and cognitive decline: A prospective nondemented elderly cohort study. *Ann Neurol* 2018;83:472-482.

Quality sleep is known to facilitate the consolidation of memory and enhance daytime cognitive function. Over the long term, sleep also may protect against the development of dementia. Restorative sleep, both stage three (slow-wave sleep) and rapid eye movement sleep, have been shown to reduce the deposition of amyloid beta (Aβ) in the brain and facilitate Aβ clearance. Sleep also has been shown to enhance the so-called "glymphatic" system of the brain, widening gap junctions and allowing drainage of metabolic toxins.

Most studies of sleep and cognition, including this work by Suh et al, rely on patient questionnaires rather than hard data from polysomnography. This introduces a significant degree of subjectivity into the analysis. Furthermore, it can be difficult to distinguish whether poor sleep is a cause or effect of cognitive decline (since effects may be "bidirectional"), and there may be pathological effects at the extremes of sleep, which may be protective in a more moderate range (with U- or J-shaped relationships). For example, exceedingly short or long sleep duration may both be more damaging than moderate sleep times, and such extremes of sleep duration may be more of an effect of dementia rather than a truly causal factor. Further ambiguity is created by the plethora of sleep-related variables used. These include latency to sleep onset (falling asleep), sleep disruption (poor sleep architecture or frequent waking after sleep onset), overall sleep duration (which does not itself account for

fragmentation), advance or delay of sleep phase (so-called "night owls" or "larks"), use of hypnotics/other psychotropic medications, and several other subjective patient perceptions of sleep quality.

Suh et al studied 2,238 Korean, non-demented individuals prior to the development of significant cognitive change. A smaller cohort of 655 subjects with mild cognitive impairment also was included. There was an association found between long sleep latency (> 30 minutes) and cognitive decline (odds ratio [OR], 1.4). Additionally, long sleep duration (> 8 hours) showed a similar risk for dementia (OR, 1.67), and there appeared to be a protective effect for subjects with an overall delay in their sleep phase. The odds of cognitive decline was 0.61 in subjects with a "mid-sleep" time later than 3 a.m. (maintaining an overall sleep schedule generally later than 11 p.m. to 7 a.m.).

Among the participants with established mild cognitive impairment, a proportion (approximately 30%) reverted to "normal cognition" at four-year follow-up, but this was significantly less common among subjects with long sleep latency times.

■ COMMENTARY

These results, particularly those regarding long sleep latencies, can be considered a valuable supplement to the large existing literature exploring sleep and cognition. However, these findings conflict with large cross-sectional epidemiological analyses, which not only associate prolonged sleep latency with dementia, but also implicate a deleterious effect of truncated sleep duration. Suh et al found the opposite, with longer sleep times associated with cognitive decline. Additionally, because Suh et al's data are prospective, conclusions can be drawn regarding cause and effect relationships that cannot be drawn from other studies. Although prior studies have suggested an association between cognitive compromise and "advanced sleep phase" (with early bed and wake times), Suh et al's data suggested that this circadian shift may not be the result of dementia, but rather, may be a risk factor for dementia or at least a predictive, pre-existing condition. When studied prospectively, starting at a younger, normal cognitive state, "larks" appear more likely than "night owls" to subsequently develop cognitive impairment. ■

ABSTRACT & COMMENTARY

Running and Health

By Ellen Feldman, MD

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

SYNOPSIS: In a review and meta-analysis of the effects of running and longevity, researchers concluded that running provides specific and significant health benefits and proposed a threshold above which more running provides diminishing returns.

SOURCE: Lee DC, Brellenthin AG, Thompson PD, et al. Running as a key lifestyle medicine for longevity. *Prog Cardiovasc Dis* 2017;60:45-55.

The roots of running as a sport are deep, dating back to ancient Greece and the original Olympic Games.[1] In 1896, the first organized marathon occurred at the first modern Olympic Games. This race was created with a nod to the myth of Pheidippides, an ancient Greek long-distance running courier. According to legend, Pheidippides ran 25 miles from Marathon to Athens carrying news of victory in battle but died just after his proclamation, making him perhaps one of the most famous cases of sudden death associated with running.[2] Today, we know that physical activity is linked with several significant health benefits, including a reduction in all-cause mortality. Investigators are studying the intensity and type of exercise needed to maximize benefits as well as any adverse effects of intensive physical activity.[3]

In 2014, Lee et al published a study involving running, all-cause mortality, and cardiovascular mortality in more than 55,000 adults. The results pointed to a reduction in mortality with even minimal levels of running.[4] To address unanswered questions from the original 2014 study, Lee et al reviewed other related studies and conducted a meta-analysis.

Among the stated goals of this comprehensive work: review the effect of running on specific health conditions and longevity; explore the specificity of running vs. other physical activities to health; explore mechanisms behind the health benefits; quantify any additional life expectancy associated with running; and investigate any evidence linking attenuation of health benefits with higher rates of running.

The Effect of Running on Longevity and Specific Health Conditions. Results were drawn from pooled results of five large studies published between 2008 and 2016. Adjustment for age and sex was followed by adjustment for multiple variables, including smoking, alcohol use, socioeconomic factors, and body mass index; adjustment for these multiple variables does not significantly affect results.

Running vs. Other Types of Physical Activity. The first results are drawn from results from the original group of more than 55,000 adults (most of whom were white, non-Hispanic) in the 2014 Lee et al study. To analyze specific health benefits from running compared to other forms of exercise, the data were re-analyzed and divided into four categories: inactive non-runners (reference group); active non-runners; solely runners inactive in other physical activities; and runners active in other physical activity. Data collected from more than 44,000 men in the Health Professionals Follow-up study were consistent with these results, with only running, brisk walking, and tennis revealing an inverse association with cardiovascular disease risk. The authors of a study of more than 80,000 men and women reported a reduction of mortality and cardiovascular disease only in association with swimming, racquet sports, and aerobics but not with running or cycling.

Proposed Mechanisms. Multiple studies have revealed associations between robust exercise of any type and mitigation of chronic disease risk factors, such as hypertension, hypercholesterolemia, glucose regulation, and bone density. However, cardiorespiratory fitness (CRF) is emerging as the most strongly predictive factor associated with lowering of mortality. Lee et al noted that running enhanced CRF and found this association was key in understanding the health benefits of this exercise.

A meta-analysis of 49 studies (all randomized, controlled trials) covering more than 2,000 adults found that after one year, runners showed improvements in CRF and lipid profile when matched with inactive peers. After adjusting for CRF, the mortality benefits of running were not significant. One of the studies showed a significant association between reduced adiposity and improved CRF in runners compared to energy expenditure equivalent to other forms of physical activity.

Life Expectancy of Runners. The authors of several large studies concluded that after adjusting for multiple factors, the life expectancy of runners is increased by an average of three years when compared with non-runners. This is similar to the mortality benefits found for persons engaging in other forms of physical activity when meeting the minimum recommended threshold of 150 to 229 minutes per week of brisk walking.

Attenuation of Health Benefits. Excessive endurance exercise has been linked to potential adverse health events, such as increased inflammation and cardiac structural changes. Lee et al examined three studies to compare results regarding "dosage" of running as well as address concerns of the potential adverse effect of running with increases in frequency and intensity.

In all three studies, longevity benefits of running were flattened at the highest levels of running. In two smaller studies, there did seem to be a higher risk of mortality associated with the highest level of running. However, in the largest study,[4] no such association was found when comparing the highest frequency running group of > 4.5 hours/week with the lowest of < 51 minutes/week. To calculate an upper limit of running beyond which there are no noticeable health benefits, Lee et al extracted data from at least three large studies from the United States and Britain. The suggested upper limit of running is up to 4.5 hours or 30 miles weekly with at least one day off.

■ COMMENTARY

Public interest in these results was widespread, with articles appearing in *GQ* ("Science: Running Is Better Than Every Other Exercise"[5]) to *Runner's World* ("Experts: Surprisingly Little Running Extends Lifespan"[6]) to *The New York Times* ("An Hour of Running May Add 7 Hours To Your Life"[7]). Although these publications need headlines to attract attention, our job as physicians and clinicians requires a different slant — interpreting the research in a clinically relevant, factual manner to educate patients and enable informed decision-making.

What can we tell patients regarding this comprehensive review and meta-analysis? Clearly, evidence for a link between physical activity and health is compelling. When discussing running, in particular, it is important to note that most of the studies were observational and the quantity of running was based on self-reporting. Thus, associations may be drawn, but we are not yet able to prove causation. Future randomized trials with objective measurable interventions are necessary.

The association between CRF and longevity is interesting. Lee et al noted that CRF improvement may be the most important factor in the link between running and longevity. If so, it would be useful to understand the extent to which other active pursuits increase CRF and if these are associated with

a significant increase in longevity. Hopefully, future studies will delve into this relationship. Understanding the benefits of specific forms of physical activity on health parameters certainly will advance this field and allow firm recommendations for patients. With relatively low cost, easy accessibility, and significant health benefits, running has the potential for clear public health effect. However, studies must be conducted under various conditions and move from a relatively homogenous sample population to diverse gender, racial, socioeconomic, and ethnic groups.

Lee et al mentioned that increases in frequency of running often were accompanied by injury, which limits further running, even temporarily. Also noted was that running activity decreased with age. Studies of other physical activities that carry health benefits equivalent to running could address both problems.

Providers can tell patients that strong evidence exists linking physical activity to longevity, and, running in particular, to cardiovascular health and lower cancer mortality. These authors found a significant decrease in all-cause mortality risk for "active" runners who engaged in other physical activity in addition to running; this is clear evidence in support of active lifestyle for all ages. Equally important is the idea of balance and limits; even with exercise, more is not always better and may lead to diminishing or negative returns. The level of running associated with health benefits is unclear, but evidence suggests that even incremental changes in activity level may be significant — a welcome message to patients who find the prospect of running intimidating. In our role as healthcare providers, we are well situated to convey to patients the findings, nuances, subtleties, and limits to current research and assist with incorporating these results into personalized wellness plans. ■

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PHARMACOLOGY UPDATE

Fostamatinib Disodium Hexahydrate Tablets (Tavalisse)

By William Elliott, MD, FACP, and James Chan, PharmD, PhD

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Dr. Chan is Associate Clinical Professor, School of Pharmacy, University of California, San Francisco.

Drs. Elliott and Chan report no financial relationships relevant to this field of study.

The FDA has approved an oral tablet for the treatment of chronic immune thrombocytopenia. Fostamatinib disodium hexahydrate is a first-in-class tyrosine kinase inhibitor against spleen tyrosine kinase.[1] Fostamatinib has demonstrated a reduction in antibody-mediated destruction of platelets. It is marketed as Tavalisse.

INDICATIONS

Fostamatinib is indicated for the treatment of thrombocytopenia in adults with chronic immune thrombocytopenia (ITP) with insufficient response to a previous treatment.[1]

DOSAGE

The recommended dose is 100 mg twice daily, with or without food.[1] After four weeks, the dose may be increased to 150 mg twice daily, if needed, to achieve a platelet count of at least 50×10^9/L as necessary to reduce the risk of bleeding. The drug should be discontinued after 12 weeks if the platelet count does not increase to a level adequate to avoid clinically important bleeding.[1] Fostamatinib is available as 100 mg and 150 mg tablets.

POTENTIAL ADVANTAGES

Fostamatinib provides another treatment option that targets a new mechanism in the pathogenesis of ITP.[2]

POTENTIAL DISADVANTAGES

The most common adverse reactions (vs. placebo) are diarrhea (31% vs. 15%), hypertension (28% vs. 13%), nausea (19% vs. 8%), dizziness (11% vs. 8%), respiratory infections (11% vs. 6%), and increase in alanine transaminase (11% vs. 0%).[2] Dose modification may be required for the following adverse reactions: hypertension, hepatotoxicity, diarrhea, and neutropenia.[1]

Complete blood counts, platelet counts, liver function tests, and blood pressure readings should be monitored appropriately.[1] Concomitant use with a strong CYP3A4 inhibitor increases the risk of adverse reactions.[1]

COMMENTS

The approval of fostamatinib was based on two identical, double-blind, placebo-controlled studies.[1,2] Subjects exhibited persistent, chronic ITP, with average platelet counts < 30×10^9/L within the three months preceding study entry. These subjects with long-standing ITP were difficult to treat (75% ≥ 3 years, with a median number of three prior unique treatments, and a median platelet count of 16×10^9/L).[2]

Subjects were randomized to placebo (n = 25 in Study 1, n = 24 in Study 2) or fostamatinib (n = 51 in Study 1, n = 50 in Study 2). Fostamatinib was initiated at 100 mg twice daily and could be increased to 150 mg twice daily after four weeks or later, depending on platelet count. The dose could be reduced to 100 mg or 150 mg once daily if dose-limiting adverse effects occurred. The primary efficacy endpoint was a stable response by week 24, defined as platelet count ≥ 50×10^9/L on at least four of the six clinic visits (assessed every two weeks).

Stable responses occurred in 18% of subjects in Study 1 and 16% of subjects in Study 2. Corresponding responses for placebo were 0% and 4%, respectively. Forty-three percent of subjects on fostamatinib exhibited ≥ 1 platelet count ≥ 50×10^9/L within the first 12 weeks compared to 14% on placebo.[2] The median time to response was 15 days, and 83% responded within eight weeks.

CLINICAL IMPLICATIONS

Primary ITP is an acquired autoimmune bleeding disorder characterized by low platelet count in the absence of other causes. This is because of the combination of platelet destruction and inhibition of platelet production.[3,4] Platelet destruction is mediated via the spleen tyrosine kinase signaling pathway, the target for fostamatinib. The current American Society of Hematology and other international guidelines recommend corticosteroids (generally with intravenous immune globulin) as first-line treatment.[5,6] For those unresponsive or relapsed, options include splenectomy, thrombopoietin receptor agonists (romiplostim, eltrombopag), or rituximab. The international guidelines also include immunosuppressives, such as azathioprine, cyclosporine A, and cyclophosphamide.[6] Fostamatinib provides an orally administered option for those who have failed or relapsed after first- or second-line therapy. The cost for fostamatinib was not available at the time of this review. ■

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CME QUESTIONS

1. **A meta-analysis of 10 randomized, controlled trials of omega-3 fatty acid supplementation to prevent atherosclerotic cardiovascular disease showed a reduction in:**
   a. fatal myocardial infarction.
   b. stroke.
   c. all-cause mortality.
   d. None of the above

2. **What part of the brain was found to exhibit neurogenesis in older adults into the eighth decade of life?**
   a. Cerebral cortex
   b. Cerebellum
   c. Hippocampus
   d. Amygdala

3. **Which of the following statements regarding sleep habits and cognitive function is *false*?**
   a. Quality sleep at night enhances daytime cognitive function.
   b. Dementia causes disruption of normal sleep.
   c. Sleeping medication may aggravate dementia in elderly people.
   d. Poor sleep causes Alzheimer's disease.

4. **Which of the following statements is most true regarding running and longevity research?**
   a. The research is clear that running leads to specific health benefits, longer life spans (approximately three years longer), and improved cardiovascular health.
   b. The research reveals an association between running, cardiovascular health, and longevity; future prospective studies with multiethnic, multigender, and diverse socioeconomic subjects are needed before attributing causation.
   c. The research is inconclusive regarding running and health benefits; most likely, the studies showing an association between running and longevity reflect the benefits of physical activity in general.
   d. The few studies that exist are of poor quality, making any conclusions regarding running and health benefits premature.

CME OBJECTIVES

Upon completion of this educational activity, participants should be able to:

- describe new findings in the differential diagnosis and treatment of various diseases;
- describe the advantages, disadvantages, and controversies surrounding the latest advances in the diagnosis and treatment of disease;
- identify cost-effective treatment regimens;
- explain the advantages and disadvantages of new disease screening procedures.

[IN FUTURE ISSUES]

Risk of Endocarditis Revisited

The Pulmonary Embolism Rule-out Criteria in Low-risk Patients