

Integrative Medicine

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the latest developments in integrative therapies [ALERT]

SEIZURES

ABSTRACT & COMMENTARY

Ketogenic Diet for Refractory Pediatric Seizures

By *Ellen Feldman, MD*

Altru Health System, Grand Forks, ND

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

SYNOPSIS: This retrospective study of 59 children with refractory seizures of genetic etiology investigates the impact of a strict low-carb diet (either modified Atkins or ketogenic diet) on seizure reduction.

SOURCE: Jagadish S, Payne ET, Wong-Kisiel L, et al. The ketogenic and modified Atkins diet therapy for children with refractory epilepsy of genetic etiology. *Pediatr Neurol* 2019;94:32-37.

“**T**he keto craze is hitting the mainstream,” proclaimed a banner headline on CNN in September 2018.¹ “The high-fat, low-carb diet has swept Hollywood,” noted *The New York Times* in March 2019, pointing to weight loss and energy gain as the main attraction of this diet.² All of the hype and recent attention may lead to the idea that the ketogenic diet (KD) is a new phenomenon.

The medical world, however, has been aware and interested in dietary control of disease since the ancient time of Hippocrates.³ More recently, medical interest in the benefits of a diet mimicking a fasting state and

specifically promoting ketosis emerged in the early 1900s. Based on a theory that a toxin released in the intestines causes seizures and that a fasting state could help free the body of these poisons, most of the early 20th century studies of controlling seizures and epilepsy revolved around dietary interventions. In 1921, after ketones were noted to be produced by the liver in response to a fasting state or a low-carbohydrate and high-fat diet, Mayo Clinic physician Russell Wilder coined the term “ketogenic diet,” and was among the first to use this ketone-producing diet plan to treat epilepsy. Subsequent investigations developed an optimal formula for KD in children, which remains as a

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Summary Points

- This retrospective investigation looked at decrease in seizure frequency in 59 children with seizures of genetic etiology who were treated with a low-carb diet (modified Atkins diet or ketogenic diet).
- A reduction in seizures > 50% was measured periodically, beginning at one month into the study and ending at two years (24 months).
- Response rates to this diet for refractory seizures in children are about 50%; in this population, response rates were 63% at the end of the first month and showed a gradual decline to 41% at the end of the study (24 months.)
- Adverse effects included hypoglycemia, vomiting, and refusal to feed. At study conclusion, 47% of the study group remained on the diet.

guideline today: 1 g of protein/kg of body weight daily, 10-15 g of carbohydrate daily, and the remainder of daily calories (55-60% of total calories) in fat.^{4,5}

The low-carbohydrate intake in this diet leads to several metabolic shifts including gluconeogenesis (endogenous glucose production) and ketogenesis. Once the body's stores of glucose are depleted, ketones are available as an alternate source of energy. Notably, this metabolic condition is termed a “nutritional ketosis,” which is different from life-threatening ketoacidosis — a state in which ketone bodies are produced in much larger quantities.^{4,5}

However, the restrictive nature and some of the adverse effects of this diet made it unappealing to many families. The advent of new antiepileptic drugs (AEDs) during the late 1900s led to a slowing of the use of KD in seizure control. However, when it became clear that about 10-20% of children remained with intractable seizures (defined as seizures that occur despite two adequate trials of appropriately dosed AEDs), the use of KD re-emerged in the early 2000s.^{4,5} Jagadish et al set out to define the reach and limits of KD, which currently is considered an alternative therapy for intractable seizures, by determining response rate and tolerability of the diet in children with refractory epilepsy of genetic origin.

This work is a single-center, retrospective chart review of 59 patients with refractory epilepsy of genetic origin presenting to the Mayo Clinic in Rochester, MN between 2005 and 2016. While 53 of the 59 children were started on the KD, six were started

on a modified Atkins diet (MAD). The International Ketogenic Diet Study Group noted MAD as one of four recognized KDs useful in seizure control: classic KD, MAD, medium-chain triglyceride diet, and low glycemic index treatment.

The children were a median age of 6 months when seizures first were noted and 2.2 years when starting the diet. While the type of seizure varied, just over 50% were focal seizures.

According to the International Ketogenic Diet Study Group, the expected rate of seizure reduction in children with intractable seizures of any origin on the KD is about 50% patient response (based on a response of > 50% seizure reduction). This consensus group reported a specific diagnosis with a more robust response rate, but noted that evidence-based studies are needed to confirm such conclusions.⁶

In this evidence-based study by Jagadish et al, the overall response rates at each time point between months one and 24 are noted in Table 1. Also noted in this table is the proportion of children remaining on the chosen diet at each study follow-up point, as well as the children remaining in the study for follow-up. There was no specified control group because response was defined as a reduction in seizures > 50% from baseline prior to diet initiation.

When analyzed for differences in response according to gender, age of diet onset, age of seizure onset, and specific genetic etiology, no statistically significant differences were identified.

Table 1: Results at Each Time Point for 59 Children With Intractable Seizures of Genetic Etiology on Ketogenic Diet or Modified Atkins Diet

	Month 1	Month 3	Month 6	Month 12	Month 24
> 50% seizure reduction	63%	61%	54%	53%	41%
Available for follow-up (%)	56/59 (95%)	56/59 (95%)	49/59 (83%)	40/59 (68%)	33/59 (56%)
Still on diet (%)	56/59 (95%)	51/59 (86%)	41/59 (69%)	38/59 (64%)	28/59 (47%)

Tolerability of the KD was important to determine in this young population. During initiation of the chosen diet, of the 59 patients, 46 were hospitalized. Of these 46 patients, 20 (43%) experienced a complication during initiation, ranging from mild emesis to significant hypoglycemia. Ten of the children required intervention during this time; the majority of these patients were under 2 years of age. During the 12-month study, seven patients reported adverse effects, including severe reflux, severe ketoacidosis, weight loss, and persistently increased triglycerides, and stopped the diet. Eighteen patients reported a variety of adverse effects, including mild weight loss, mild abdominal pain, food refusal, mild emesis, and constipation, and did not stop the diet.

■ COMMENTARY

On the surface, this study appears mostly relevant to the providers, patients, and families of those with intractable seizures of genetic origin. It certainly gives validation of the KD as a treatment option for this population, and adds important data for this group. However, the impact of this study is even more widespread, and serves as a reminder of the need to investigate all interventions with the care and scientific scrutiny given to conventional pharmacologic treatments.

We know that medication dosage and indications vary according to the disorder and individual; it is only logical that these parameters vary for nonpharmacologic interventions as well. The widespread popularity of the KD for nonmedical uses as well as investigatory uses for a variety of disorders, including type 2 diabetes, obesity, Alzheimer's disease, and autism spectrum disorders is exciting,⁷ but studies such as this remind us of the need for robust and scientifically rigorous studies. Results from such investigations can clarify the reach, applicability, and limits of the KD, while potentially revealing underlying mechanisms of action.

There are many theories regarding how the KD helps with seizure control, but a definitive answer remains elusive. Investigators agree that an increase in ketone bodies and a decrease in blood glucose may modify neuronal excitability, and that the research into mechanism of action is a priority in the field.⁷ As we further our understanding of the KD and its effect on a metabolic and cellular level, more targeted uses of this potentially powerful, nonpharmacologic tool can emerge.

Jagadish et al noted several limitations of their study, including the difficulty of determining why children were lost to follow-up. The design itself is a limitation — as with any retrospective study, cause and effect is difficult to determine with certainty. Additionally, there was no control for concurrent use of AEDs, or changes in AEDs, over the course of the study.

Maintenance of a stringent KD in a child requires strong parental involvement. The link between response rate and parental oversight is unknown, but remains a clear direction for future studies.

The take-home message for the primary care and integrative provider is two-fold. Certainly for those working with this patient population, it is important to consult with a dietician and neurologist to implement, maintain, and monitor a KD. This diet can be difficult to initiate, harder to maintain, and has potential serious side effects; working with a skilled team can help address these challenges on multiple levels. There is also utility in thinking about such a diet for adults with intractable seizures of genetic etiology, although that age group was not covered in this study.

In a broader sense, this study reminds us of the importance of diet to health and the often significant, clinically relevant impact of dietary changes. ■

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ABSTRACT & COMMENTARY

Organic Food Consumption and Cancer Risk

By Traci Pantuso, ND, MS

Adjunct Faculty, Research Investigator, Bastyr University, Seattle, WA

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

SYNOPSIS: In this prospective cohort study, high amounts of organic food consumption were associated with a significant decrease in the risk of overall cancer, particularly postmenopausal breast cancer, non-hodgkin lymphoma, and other lymphomas.

SOURCE: Baudry J, Assmann KE, Touvier M, et al. Association of organic food consumption with cancer risk: Findings from the nutriNet-santé prospective cohort study. *JAMA Intern Med* 2018;178:1597-1606.

In 2018, the estimated number of new cancer cases was more than 17 million worldwide.¹ Although it has not been well-researched, environmental risk factors include exposure to pesticides.² There is a growing body of evidence demonstrating an association between pesticide exposure and the development of cancer.^{2,3}

The authors of this population-based cohort study investigated the association between an organic food-based diet and the risk of cancer in 68,946 French adults. This study is part of a larger research project called the NutriNet-Santé study, which is investigating the associations between nutrition and health and other determinants of dietary behaviors and nutritional status in France.⁴ Adults 18 years and older were recruited into the NutriNet-Santé study using a web-based platform. Of the 68,946 participants, 78% were female, with a mean age at baseline of 44.2 years. After registration, participants were followed through a website that was designed specifically for this purpose with an online, secure HTML interface.

At enrollment, participants completed a set of questionnaires investigating sociodemographics, health status, lifestyle, physical activity, anthropometrics, and diet. These questionnaires were pilot tested and either objectively validated or compared against traditional assessment methods. At two months post enrollment, participants provided information on their consumption of 16 groups of organic products. These 16 groups of organic products included vegetables; fruits; soy-based products; dairy products; meat and fish; eggs; grains and legumes; bread and cereals; flour; vegetable oils and condiments; ready-to-eat meals; coffee, tea, and herbal tea; wine; biscuits, chocolate, sugar and marmalade; other foods; and dietary supplements. The authors calculated the frequency of organic foods using the following categories: 1) most of the time, 2) occasionally, 3) never (“too expensive”), 4) never (“product not available”), 5) never (“I am not interested in organic products”), 6) never (“I avoid such products”), 7) never (“for no specific reason”),

Summary Points

- Some mechanisms support a decreased risk of cancer and organic food consumption, although it has not been well studied.
- A cohort study of more than 60,000 French adults examined diet and cancer associations.
- The results showed that a higher frequency of organic food consumption is negatively associated with risk of cancer when compared with either a low- or high-quality diet with lower frequency of organic food consumption.

8) “I don’t know.” For each category, points were allocated to each response, with two points being allotted to “most of the time,” one point for “occasionally,” and zero for the “never” categories. The 16 categories of food with frequency of consumption data (points) were summed to provide an organic score from 0 to 32 points.

Baudrey et al also evaluated the participants’ dietary intake at baseline using three random, 24-hour diet diary recalls during a two-week period. This period included two weekdays and one weekend day, and was separate from the organic food intake information the participants provided.

Participants recorded all foods and beverages eaten, and estimated portion sizes by looking at photographs from a previously validated picture booklet, or by weight, volume, or the purchased unit. Seafood intake was measured by a specific frequency question. The authors accounted for ultra-processed food and assessed it using the NOVA classification system. Nutrient intake was assessed from individual food consumption calculated using the NutriNet-Santé food composition table. The authors excluded under-reporters of food intake.

The authors also assessed diet quality using a modified version of the validated Programme National Nutrition Santé Guideline Score (PNNS-GS) without the physical activity component, reflecting adherence to the official French National Guidelines. The French National Guidelines recommend a diet high in fruits and vegetables, whole grains, legumes, and potatoes, with moderate consumption of dairy, eggs, and meat.⁵ Currently, the French National Guidelines are under review, and an update will be released in 2021.⁶

In this study, participants self-declared medical health events annually. When patients reported a case of cancer, the clinical research study physician requested to be provided the medical records. An independent medical expert committee reviewed all major health events. Medical records were obtained in 90% of all self-reported cancer cases. The study included all new primary cancers, with the exception of basal cell carcinoma, diagnosed between study initiation and Nov. 30, 2016. The authors used the COX proportional hazards regression model to calculate hazard ratios and 95% confidence intervals (CI), and $P < 0.05$ was considered statistically significant.

During the follow-up period of 4.56 years, the researchers identified 1,340 first-incident cancer cases, including 459 breast cancer cases, 180 prostate cancers, 135 skin cancers, 99 colorectal cancers, 47 non-Hodgkin lymphomas (NHL), and 15 other lymphomas.

High organic food scores were associated linearly and negatively with the overall risk of cancer (hazard ratio [HR] for fourth quartile vs. first quartile, 0.75; 95% CI, 0.63-0.88, P trend = 0.001). The authors also removed early cancer cases and found that the overall association remained significant for fourth quartile vs. first quartile (0.70; 95% CI, 0.56-0.88; P trend = 0.004). When analyzing the results by cancer site, the authors found a decreased risk of postmenopausal breast cancer ($P = 0.03$), NHL ($P = 0.049$), and lymphomas ($P = 0.02$) in patients with high-frequency organic food consumption. The authors did not report any worsening of health outcomes or adverse events.

Since this study is part of the larger NutriNet-Santé Study, the authors controlled for overall diet quality calculated from 24-hour food recall questionnaires. The authors found that when combined with a high-quality diet or a low-quality diet, organic food consumption was associated with a reduced risk of overall cancer. Although this finding was not significant, it suggests that high-frequency organic food consumption is a major factor in the reduction in the risk of overall cancer.

■ COMMENTARY

There is limited epidemiological research investigating the association between cancer risk and organic food

consumption, which makes this study important. It is one of the first studies to examine the frequency of organic food consumption and cancer risk while incorporating detailed information on pesticide exposure and controlling for diet quality. The sample size for this study was large, and the authors performed a stratified analysis on cancer sites, indicating a decreased risk of postmenopausal breast cancer, NHL, and lymphomas with increased organic food consumption. The authors also used detailed questionnaires on organic food frequency, and clinical research physicians reviewed the cancer cases.

The authors of The Million Women Study, carried out with 623,080 women in the United Kingdom, found that organic food consumption was not associated with a reduction in overall cancer incidence.⁷ They also found that women who reported usually or always eating organic food had a small increase in breast cancer incidence compared to women who reported never eating organic food. Interestingly, The Million Women Study authors did find that increased organic food consumption was associated with a 21% lower risk of NHL than nonconsumption of organic food.⁷

More recently, the authors of the Sister Study found a lower risk of breast cancer with higher frequency of organic food consumption in 39,563 women.⁸ The Sister Study is a research study investigating the environmental and genetic risk factors for breast cancer in the United States. The authors found that any organic food consumption was inversely associated with breast cancer (HR, 0.87; 95% CI, 0.80-0.95), particularly estrogen receptor-negative cancer (HR, 0.77; 95% CI, 0.61-0.98).⁸

Since the Million Women Study, the Sister Study, and the NutriNet-Santé study have differing results regarding the risk of breast cancer and organic food consumption frequency, more research studies with longer follow-up periods are needed. The Million Women Study had a follow-up period of 9.3 years, the Sister Study had a 9.0-year follow-up, and the NutriNet-Santé study had a follow-up period of 4.56 years. The Million Women Study authors suggested that future prospective studies investigating the role of organic food consumption and cancer risk, particularly with NHL, should enroll 500,000 participants with a follow-up period of at least a decade.⁷

There are a number of limitations to this study and to research in organic food consumption in general. Specific limitations include the self-selected participants who may be more likely to be concerned about their health. In addition, the participants were mostly female, exhibited healthier behaviors (e.g., higher quality diet and decreased smoking), and had a higher education level than the general population in France, limiting the generalizability of the findings.⁹ The follow-up time for this

study was 4.56 years, which may not be long enough to capture nuances of cancer causation. Further limitations to commenting on causation result from this being a prospective cohort study rather than a controlled trial. In general, organic food consumption information has been obtained from responses on food frequency questionnaires, limiting the reliability.

Individuals who regularly consume organic food also tend to have healthier dietary patterning, eating less meat and more fruits, vegetables, and whole grain products.³ In addition, consumers who purchase organic foods are also less likely to smoke and are more likely to be physically active.³ The NutriNet-Santé Study previously demonstrated that individuals who consumed increased amounts of organic food had a decreased risk of obesity, hypertension, type 2 diabetes, and hypercholesterolemia compared to those who consumed low amounts.⁸ They also found that men had a decreased risk of cardiovascular disease with increased frequency of organic food consumption.¹⁰ Although the authors controlled for numerous confounding variables (physical activity, smoking status, alcohol intake, family history of cancer, body mass index, energy intake, fiber intake, processed meat intake, red meat intake, postmenopausal status, hormone treatment for menopause, and oral contraceptives), there may be other unknown risk factors.

[Provided that the extra cost is not prohibitive and there is reasonable availability of organic food, clinicians can recommend a focus on these foods for all demographics.]

More research is needed to further delineate the risk of cancer and whether to eat organic food, which may be related to pesticide residue on food. Organic food has been found to be higher in beneficial nutrients, such as antioxidant compounds in fruits and vegetables and higher omega-3 fatty acids in meat and dairy products.^{11,12} There is also a lack of long-term interventional studies researching the link between organic food and human health, making it difficult to assess the effect of organic food consumption on health.³

These prospective cohort studies are an important first piece of the puzzle to spur more research with trial designs that are properly powered to infer causation. In the meantime, there are benefits to supporting organic farming, such as the health and environmental benefits associated with decreasing or eliminating pesticide use. Decreasing the use of pesticides in farming through

organic farming is more sustainable for the environment, it decreases the risk of occupational pesticide exposure, and it decreases pesticide residues on food. Organic food often is more expensive than conventionally grown food, which may be unaffordable for some patients. The Environmental Working Group produces a Shopper's Guide listing fruits and vegetables that the group recommends for people to purchase organic.¹³ This list is determined by the USDA reports on pesticide testing.¹³

Bottom Line: There may be health benefits with eating organic food, as shown by the decreased risk of certain cancers in this observational analysis. Provided that the extra cost is not prohibitive and there is reasonable availability of organic food, clinicians can recommend a focus on these foods for all demographics. Future research will hopefully both clarify the specific benefits of these foods, as well as the mechanisms of action. ■

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ABSTRACT & COMMENTARY

Omega-3 Fatty Acids vs. Olive Oil to Prevent Vascular Events

By Jessica Orner, MD

Family Medicine Physician, Lebanon, PA

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

SYNOPSIS: In a cohort of 15,480 adults with diabetes, there was no significant difference in the risk of serious vascular events when comparing supplementation with 1 g of omega-3 fatty acid vs. an olive oil placebo.

SOURCE: ASCEND Study Collaborative Group, Bowman L, Mafham M, et al. Effects of n-3 fatty acid supplements in diabetes mellitus. *N Engl J Med* 2018;379:1540-1550.

Cardiovascular disease is a major cause of mortality and morbidity. There are an estimated 630,000 deaths per year in the United States from cardiovascular disease.¹ The American Heart Association continues to recommend omega-3 fatty acid consumption to the public, preferably through food, and states that it has preventive benefits even in healthy people.²

In the ASCEND (A Study of Cardiovascular Events in Diabetes) trial, researchers assessed the efficacy of daily omega-3 fatty acid supplementation in adults with diabetes and without cardiovascular disease.³

The researchers identified potential trial participants from regional registries and general practice data. They mailed screening questionnaires to eligible patients to determine their willingness to participate. Those interested and eligible then began a prerandomization run-in phase. The researchers requested, but did not require, that patients discontinue over-the-counter fish oil or omega-3 fatty acid supplements prior to and during the study. However, patients were still eligible to participate while taking these supplements as long as the daily dose was less than 1 g.

During the eight- to 10-week run-in phase, participants were asked to notify their doctor of their potential participation in the study; record basic anthropomorphic data, including blood pressure, height, and weight; and provide blood and urine samples. Participants were given capsules containing the olive oil placebo. If participants adhered to the trial regimen, continued to meet the eligibility criteria, and confirmed their willingness to continue, they remained eligible for the trial. (See Table 1.)

The researchers determined the evidence of cardiovascular disease by reviewing the patients' reported myocardial infarction, angina, stroke, coronary artery bypass surgery, or arterial revascularization.⁴ Contraindication to aspirin therapy included an allergy to aspirin, recent

Summary Points

- This was a 7.5-year randomized, controlled trial that included 15,480 adults with diabetes mellitus in the United Kingdom.
- Participants were randomized to receive a capsule containing 840 mg of marine omega-3 fatty acids (460 mg of eicosapentaenoic acid and 380 mg of docosahexaenoic acid) or olive oil (placebo) daily.
- Serious vascular events occurred in 8.9% of patients in the omega-3 fatty acid group and 9.2% in the placebo group.
- Those who received omega-3 fatty acid did not have significantly lower incidences of serious vascular events than those who received the olive oil placebo.

gastrointestinal bleeding, or being prescribed aspirin, warfarin, or any other blood-thinning agent at the time of the study. Much of this information was gathered from the study screening questionnaire.⁴

From June 2005 through July 2011, 15,480 participants were randomized to receive 1-g capsules containing either 840 mg of marine omega-3 fatty acids or an olive oil placebo. The marine omega-3 fatty acid included 460 mg of eicosapentaenoic acid (EPA) and 380 mg of docosahexaenoic acid (DHA). Of note, participants were randomized to receive either 100 mg of aspirin or placebo as well. Every six months until the end of the trial, participants were sent follow-up questionnaires regarding serious and nonserious adverse events, adherence to trial regimen, symptomatic bleeding events, and use of nontribal antiplatelet or anticoagulant therapy. Blood and urine samples, blood pressure readings, and weight

were requested from 1,800 randomly selected patients after a mean follow-up period of 2.5 years.

The primary endpoint was the first serious vascular event, including nonfatal myocardial infarction, stroke, transient ischemic attack (TIA), or vascular death, excluding intracranial hemorrhage. The secondary endpoint was any serious vascular event or arterial revascularization procedure. Of note, the duration of the follow-up period was extended to 7.5 years, and TIA was included in the definition of serious vascular events during recruitment to increase the power of the trial.

Mean adherence to the trial regimen was 77% for the omega-3 fatty acid group and 76% for the placebo group. There was no significant difference between the groups regarding over-the-counter fish oil supplement use, with 10% of participants reporting use at baseline and 6% reporting use at 6.7 years of follow-up. There was no comment about whether the groups could differentiate between the marine oil and placebo based on eructation.

Serious vascular events occurred in 8.9% (689) of patients in the omega-3 fatty acid group and in 9.2% (712) in the placebo group (rate ratio, 0.97; 95% confidence interval [CI], 0.87-1.08; $P = 0.55$). The between-group difference was not statistically significant. There was also no significant difference between groups in the secondary outcome. Serious vascular effects or revascularization occurred in 11.4% (882) of the omega-3 group and 11.5% (887) of the placebo group. Rates of death were similar between the two groups, with 9.7% for the omega-3 group and 10.2% for the placebo group (rate ratio, 0.95; 95% CI, 0.86-1.05).

■ COMMENTARY

It actually appears that this study is more a comparison of marine oil vs. olive oil, showing that marine oil at low doses is no more beneficial than olive oil at a similar dose. One gram of olive oil is equivalent to approximately 1 mL. This is significantly less than the amount used the studies assessing the Mediterranean diet enriched with extra-virgin olive oil (EVOO), in which participants received approximately 1 L per week of EVOO.⁵

It is interesting that the study authors did not discuss the possibility of therapeutic benefits from olive oil supplementation for prevention of vascular events in those with diabetes, nor how this would affect the study results. Although these authors have labeled olive oil the placebo, authors of other studies have shown that olive oil has beneficial effects. The authors of a randomized, controlled trial published in 2017 showed that the Mediterranean diet enriched with virgin olive oil improved the atheroprotective functions of human high-density lipoprotein.⁶ Given that olive oil was used as a placebo

Table 1: Eligibility/Exclusion Criteria

Eligibility Criteria

- ≥ 40 years of age
- Diagnosis of type 1 or type 2 diabetes
- No evidence of cardiovascular disease

Exclusion Criteria

- Contraindication to omega-3 fatty acids supplementation (e.g., allergy)
- Contraindication to aspirin therapy
- Presence of a condition that might limit adherence to five years of participation in the trial

in the active phase of the trial and that all participants received it during the run-in phase for eight to 10 weeks, there is certainly concern that it could have affected the study results.

Another factor that could confound the results is that the participants were randomized to receive 100 mg of aspirin or a placebo. Antiplatelet agents, such as aspirin, play a major role in the prevention of vascular events, such as myocardial infarction and ischemic stroke. There was no discussion in the study about how this may have affected the study outcome.

Although this study is thought-provoking in evaluating fish oil for primary prevention of cardiovascular disease in a high-risk group, before changing clinical practice, it would be prudent to have a trial with a true placebo, that did not contain active substances that could affect health. Based on this study, I would not recommend abandoning the American Heart Association's recommendation that supports omega-3 supplementation as secondary prevention of sudden cardiac death and coronary heart disease for patients with a history of coronary heart disease or heart failure. ■

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ABSTRACT & COMMENTARY

Plasma Omega-3 Polyunsaturated Fatty Acids and Healthy Aging

By *Jessica Orner, MD*

Family Medicine Physician, Lebanon, PA

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

SYNOPSIS: In a cohort of 2,622 adults, higher levels of plasma long-chain omega-3 polyunsaturated fatty acids were associated with a lower risk of unhealthy aging.

SOURCE : Lai HT, de Oliveira Otto MC, Lemaitre RN, et al. Serial circulating omega 3 polyunsaturated fatty acids and healthy aging among older adults in the cardiovascular health study: Prospective cohort study. *BMJ* 2018;363:k4067.

With our aging population, there is an increased focus on aging well and staying healthy. Healthy aging has different meanings to different people. Lai et al defined healthy aging as “living a meaningful lifespan without chronic disease and with intact physical and mental function,”¹ based on a previously established definition in the Cardiovascular Health Study (CHS). Specifically, CHS defines healthy aging as survival without cognitive dysfunction, physical dysfunction, cardiovascular disease, cancer, pulmonary disease, and severe chronic kidney disease, or as death after age 65 without the mentioned conditions.¹

The researchers sought to determine the relationship between omega-3 polyunsaturated fatty acids (PUFA) and health outcomes, including the likelihood of healthy aging. PUFAs include both omega-3 and omega-6 fatty acids. While part of the same group, even omega-3 PUFAs can have differing sources and properties. For example, alpha-linolenic acid (ALA) is present in plant oils, while eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) are synthesized by microalgae and are present in fish and krill oils. Also, while ALA can be converted to EPA, this rate of conversion is estimated to be less than 15%.² The researchers chose to use the omega-3 PUFA biomarkers as opposed to dietary questionnaires to try to avoid recall bias and intake estimation errors.

In the subsequent analyses, healthy aging was further separated into functional healthy aging and disease-free healthy aging. Functional healthy aging was defined as the absence of cognitive and physical dysfunction or death from dementia. Disease-free healthy aging was defined as the absence of cardiovascular disease, severe chronic kidney disease, cancer, and lung disease.

Information for this analysis was gathered from the CHS data from 1992 to 2015. The CHS is a multicenter

Summary Points

- This was a 25-year prospective cohort study that included 2,622 adults in the United States.
- Plasma omega-3 polyunsaturated fatty acid levels were measured in 1992-1993, 1998-1999, and 2005-2006.
- Higher levels of eicosapentaenoic acid (EPA), docosapentaenoic acid (DPA), and combined EPA, docosahexaenoic acid (DHA), and DPA were associated with a lower risk of unhealthy aging.

prospective cohort of independent ambulatory adults from four communities: Sacramento County, CA; Washington County, MD; Forsyth County, NC; and Pittsburgh, PA. Although the main study goal was identifying risk factors for cardiovascular disease related to onset of coronary heart disease and stroke in adults 65 years of age or older, it also investigated other topics such as diabetes, vascular dementia, and frailty.³

CHS is funded by the National Heart, Lung, and Blood Institute. Trained examiners performed annual assessments through 1999 and in 2005-2006. Participants continue to be contacted via phone at six-month intervals.⁴ Clinical exam assessments were not conducted between 1999 and 2005. Therefore, for outcomes that require annual clinical examination, such as physical and cognitive function, participants were assumed to have no incidence during the that time. From 1989 to 1990, 5,201 adults were recruited from a random sample of the Medicare eligibility list in each community. In 1992-1993, an additional 687 African-American participants were enrolled, bringing the total to 5,888. Of the 5,888

enrollees, 2,622 met the criteria for the study and were eligible for analysis.

As a part of the study, plasma specimens were collected in 1992-1993, 1998-1999, and 2005-2006. Forty-six distinct plasma phospholipid omega-3 PUFA levels were measured as weight percentage of total fatty acids. This included EPA, DHA, ALA, and docosapentaenoic acid (DPA). For each subsequent measure, the average of the current and previous measures was calculated. Equal weight was given for the most recent omega-3 PUFA measurement and the average of the previous omega-3 PUFA measures. For participants with missing omega-3 PUFA levels, the previous measurement was used. This was the case for 6.0% of the samples in 1998 and 23.6% in 2005.¹

The following participant information was collected: anthropometrics (height, weight, and waist circumference); family history of myocardial infarction or stroke; ethnicity; depression score; education; presence of arthritis; income; alcohol use; physical activity; dietary habits; self-reported general health status; low-density lipoproteins, high-density lipoproteins, and triglycerides; high-sensitivity C-reactive proteins; use of antihypertensives; smoking status; and use of lipid-lowering medication.

A total of 2,622 participants were eligible for analysis. The mean age of participants was 74.4 years. Participants with high levels of serum omega-3 PUFAs were more likely to be female, white, and more educated than those with lower omega-3 PUFA levels; they were also more likely to have higher income and healthier lifestyles.

Overall, the group with the highest level of combined EPA, DHA, and DPA had an 18% (95% confidence interval [CI], 3% to 30%; $P = 0.001$) lower risk of unhealthy aging in general. Compared to the group with the lowest serum levels, participants in the highest EPA or DPA groups had a 24% (11% to 35%; $P < 0.001$) and 18% (6% to 29%; $P = 0.003$) lower risk of unhealthy aging, respectively. This was not true for those participants in the highest ALA-only or DHA-only groups.

In regard to dietary factors, participants in the group with the highest serum long-chain omega-3 PUFAs consumed an average of one additional serving of fish per week than the group with the lowest levels. This was, on average, two servings of fish per week for the group with the highest serum long-chain omega-3 PUFAs. Participants with higher ALA levels tended to have lower income, lower body mass index, and lower CRP levels, and consumed more alcohol than the other participants.

■ COMMENTARY

In one of the first studies on the association between healthy aging and omega-3 PUFAs, these researchers

Table 1: Eligibility/Exclusion Criteria

Eligibility Criteria

- ≥ 65 years of age at time of examination
- Noninstitutionalized
- Able to give informed consent

Exclusion Criteria

- Requiring a proxy respondent at baseline
- Receiving hospice services
- Receiving radiation therapy or chemotherapy for cancer
- Wheelchair bound
- Deceased before the 1992-1993 assessment
- Presence of unhealthy aging in 1992-1993
- Lack of available blood measurements
- Baseline fish oil supplement use

found a positive association between PUFAs and healthy aging. There are several potential mechanisms, including anti-inflammatory benefits and advantageous effects on endothelial function. The study authors noted that ALA did not seem to have the same beneficial effects as DHA or EPA. This could be because of the low conversion rate to EPA, and subsequently, DHA, but more studies are needed.

One concern with studies on this topic is that the definition of healthy aging varies in society and across other research studies. This can be seen in the difference between the World Health Organization (WHO) definition and the CHS definition. WHO defines healthy aging as “the process of developing and maintaining the functional ability that enables wellbeing in older age.”⁵ This includes the ability to contribute to society, stay mobile, and live in supportive environments. They specifically noted that being free from disease is not a requirement for healthy aging. Instead, they focused more on creating opportunities that enable people to continue to do what they value throughout their life.

Although the researchers used a different definition, they did a great job of defining this term in the context of their study. A standard definition is needed to make studies on this topic more easily comparable.

In addition, more studies are needed to determine causality and to elucidate ways to increase helpful plasma PUFA levels. These authors suggested that one way to increase plasma PUFA levels is to consume two servings of fish per week, as the highest serum long-chain omega-3 PUFAs were found in the group of participants who reported this dietary pattern. Should we counsel patients to increase omega-3 PUFAs in their diet? It would be more prudent to advocate for a healthy diet than to champion one part of the diet, such as PUFAs, over the whole. ■

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CANCER

ABSTRACT & COMMENTARY

Poor Diet May Cause More Than 80,000 Cancers Each Year in the United States

By *Joseph E. Scherger, MD, MPH*

Core Faculty, Eisenhower Health Family Medicine Residency Program, Eisenhower Health Center, La Quinta, CA; Clinical Professor, Keck School of Medicine, University of Southern California, Los Angeles

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

SYNOPSIS: In a recent analysis, investigators noted a correlation between a diet loaded with processed red meat and various types of cancers.

SOURCE: Zhang FF, Cudhea F, Shan Z, et al. Preventable cancer burden associated with poor diet in the United States. *JNCI Cancer Spectrum*. Published May 22, 2019. Accessed June 20, 2019.

Editor's Note: This review adds to the emerging evidence behind nutritional connections to the prevention and causation of cancer. Integrative Medicine Alert authors have detailed results from studies that show a possible connection between non-organic foods and cancer (this issue), global dietary factors that may connect with cancer mortality (June 2019), hot beverages and cancer risk (August 2019), among others. We will continue to showcase research that guides our nutritional recommendations relevant to health and well-being.

— David Kiefer, MD

A team from the Friedman School of Nutrition Science and Policy at Tufts University used some databases from multiple sources to conduct a comparative risk assessment of diet and cancer in the United States. Zhang et al found an estimated 80,110 new cancer cases attributable to a suboptimal diet. A total of 67,488 of these were direct dietary associations and 12,589 were obesity-mediated associations. Colorectal cancer accounted for both the highest number of new cancer cases (52,225) and the highest proportion of cases (38.3%). Other cancers associated with a poor diet were cancers of the mouth, pharynx, and larynx (14,421) as well as endometrial (3,165), breast (3,059), kidney (2,017), stomach (1,564), liver (1,000), pancreatic (538), and esophagus (475). The authors noted that a high intake of processed meat carried the highest association with these cancers. A low consumption of whole grains and dairy also increased the risk. The authors did not study food that might prevent cancer, such as a plant-based diet.

■ COMMENTARY

This study adds to growing evidence showing that the modern industrial diet leads to a heavy cancer burden. In

2010, an oncology fellow named Siddhartha Mukherjee published *The Emperor of All Maladies: A Biography of Cancer*.¹ In it, he reported that early in human history, cancer was a rare disease. However, over time, cancer has become increasingly common, especially since the Industrial Revolution. This increase cannot be blamed on genetics; it has to do with the environment, including what we eat.

Empiric and epidemiologic research has shown that food can cause cancer.^{2,3} Other research suggests that healthy foods prevent cancer and may even reverse the disease.^{4,5} Still, clinicians lack data from large clinical trials of nutrition and cancer that could reveal more information. Until more researchers conduct such trials, it is important for clinicians to include nutrition education based on current evidence as part of discussions about cancer.

Certainly, it would be foolish to recommend that a patient reject cancer treatment and follow only a modified nutrition and lifestyle approach. There are instances of cancer reversals with a healthy diet and lifestyle changes; still, overall, those who choose only that route die more

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often than those who choose cancer treatment.⁶ Cancer treatment is moving away from using only the toxic and damaging drugs of chemotherapy to include health-enhancing methods such as immunotherapy. Everyone should eat a healthy diet, exercise daily, manage stress, engage in restorative sleep, and create social connections that can lead to meaning and purpose in life. Along with new health-enhancing cancer treatments, we could return to an earlier time when cancer was a rare disease. ■

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CME QUESTIONS

1. Which of the following is true regarding the ketogenic diet?
 - a. This popular diet, originally developed and promoted for weight loss, may have a new role in seizure control, with about 75% of children with intractable seizures of genetic origin responding with a lessening of seizures when on this diet.
 - b. This newly popular diet has much older origins and was developed in the 1920s for control of headache, seizure, and other neurologic disorders; the Jagdish et al study confirmed the usefulness of this diet in children with intractable seizures of genetic origin.
 - c. This newly popular diet has much older origins and was developed in the 1920s specifically for seizure control; the Jagdish et al study confirmed the usefulness of this diet in children with intractable seizures of genetic origin.
 - d. This popular diet, originally developed and promoted for weight loss, may have a role in seizure disorder, with 47-64% of children with intractable seizures of genetic origin showing a reduction in seizures.
2. In the study by Bowman et al, what amount of omega-3 fatty acid was evaluated in the treatment arm?
 - a. 4 g
 - b. 2 g
 - c. 1 g
 - d. 3 g
3. Participants in the Bowman et al study also were randomized to receive which of the following?
 - a. Warfarin
 - b. Aspirin
 - c. Metformin
 - d. Clopidogrel
4. According to the study by Lai et al, which omega-3 polyunsaturated fatty acids were associated with a lower risk of unhealthy aging?
 - a. Combination of eicosapentaenoic acid (EPA) and alpha-linolenic acid (ALA)
 - b. Combination of docosahexaenoic acid (DHA) and ALA
 - c. Combination of docosapentaenoic acid (DPA), DHA, and EPA
 - d. ALA only

CME OBJECTIVES

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

- present evidence-based clinical analyses of commonly used alternative therapies;
- make informed, evidence-based recommendations to clinicians about whether to consider using such therapies in practice; and
- describe and critique the objectives, methods, results, and conclusions of useful, current, peer-reviewed, clinical studies in alternative medicine as published in the scientific literature.

[IN FUTURE ISSUES]

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