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Urologic Oncology: Seminars and Original Investigations 23 (2005) 36–48

UROLOGIC ONCOLOGY

Seminar article

An introduction to dietary/supplemental omega-3 fatty acids for general health and prevention: Part II

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Abstract

The correction of a subtle nutritional deficiency that may reduce the risk of a future chronic disease is indeed a challenge. However, some specific examples in the past, such as the addition of folic acid to prevent neural tube defects and calcium and vitamin D to prevent osteoporosis, should provide some encouragement that some conditions can be prevented with the appropriate addition of a deficient compound. One of the most intriguing current and future impacts on public health may come from a higher intake of omega-3 fatty acids, such as alpha-linolenic acid (ALA), eicosapentaenoic acid (EPA), and docosahexaenoic acid (DHA). The omega-3 fatty acids continue to accumulate research that suggests that they may prevent a variety of diverse chronic diseases and potentially some acute clinical scenarios. In the first part of this article, the potential for these compounds to prevent certain cardiovascular conditions are discussed. In the second part, the potential for an impact in arthritis, numerous areas of cancer research, depression, maternal and child health, neurologic diseases, osteoporosis, and other medical disciplines are also briefly covered. The future appears bright for these agents, but specifically which conditions, who qualifies, testing, frequency, adequate sources, future trials, and numerous other questions need to be addressed and answered before the potential impact can catch up to the recent hype.

Keywords: Omega-3 fatty acids; Eicosapentaenoic acid; Docosahexaenoic acid; Cancer; Cardiovascular disease; Prevention

Introduction

The triumphs of treating nutritional deficiencies to improve health and, prevent and treat disease throughout medical history have and continue to abound. One of the most famous, oldest but actually antiquated examples usually cited in classrooms and textbooks is the example of vitamin C for the amelioration of survey [1]. However, this condition is obviously not prevalent in modern society because of the increasing availability of this vitamin in the food supply. Other more pertinent examples that are still being used today are the addition of folic acid and other B vitamins to prevent neural tube defects, certain forms of anemia, and side effects of isoniazid treatment for tuberculosis [1,2]. Calcium and vitamin D supplements have become the standard treatment for individuals at risk for osteoporosis with or without standard drug treatment [3,4]. Indeed, the list of possible conditions that can be potentially prevented by diet or dietary supplements continues to grow as we begin to learn how to deal best with certain acute and chronic conditions as the result of an ever increasing life span, and individualizing medicine for a specific patient based on age, environmental impacts, family history and genetics, and current high probability disease occurrences.

However, determining what constitutes a so-called "true deficiency" using a specific diet or dietary supplement intervention that normalizes a certain tissue or blood level back to an appropriate level in today's world is indeed a major challenge because as we age and consider other factors, a so-called "deficiency" does not necessarily manifest itself acutely but rather chronically. In addition, even after a so-called "deficiency" is normalized through diet, the chance of individuals becoming "overdosed" or consuming supraphysiological doses of a specific nutrient is plausible, because of the food and dietary supplement industries' at-

Abbreviations: *n-3 Class of polyunsaturated fatty acids:* ALA;C18:3n-3, alpha-linolenic acid (ALA); EPA;C20:5n-3, eicosapentaenoic acid (EPA); DHA;C22:6n-3, docosahexaenoic acid (DHA). *n-6 Class of polyunsaturated fatty acids*: LA;C18:2n-6, linoleic acid (LA); AA;C20:4n-6, arachidonic acid (AA).

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1078-1439/05/$ – see front matter
doi:10.1016/j.urolonc.2005.03.001

tempt to incorporate this nutrient throughout the food supply [5].

Thus, today a delicate balance between correction and overcorrection needs to be considered in clinical studies and future recommendations (i.e., in other words the risk-benefit ratio may be ever changing and challenging [5]). For example, the impact of correcting selenium deficiencies to prevent a variety of cancers is currently being studied in some of the largest randomized trials in the United States [6]. In 1996, with the publication of a selenium trial that showed a potential to reduce a number of cancers [7], it now seems that higher amounts of selenium are found not only in the general food supply but also in a variety of basic dietary supplements, such as a general multivitamin.

A potential dietary manipulation that is beginning to emerge is the potential impact of correcting low levels of omega-3 fatty acids to prevent a variety of medical conditions from occurring or progressing, such as arthritis, some cancers, cardiovascular disease, depression, maternal/fetal well-being, and neurologic disease [8]. This article is an introduction to omega-3 fatty acids and their potential benefits for normalizing intake compared to the detriments of insufficient consumption or their potential detriments in over-consumption of these compounds. Indeed, these fatty acids may serve, along with a variety of other examples, as one of the primary potential so-called "scurvies of our time" unless of course it is dealt with by society, medicine, and the individual at risk for such a specific deficiency, but the potential risk-benefit ratio also needs appropriate attention as is the case with any nutritional intervention [5].

Update on omega-3 fatty acids and coronary heart disease and stroke: Meta-analysis of observational studies (2004)

During the preparation of the first and second parts of this article, one of the largest meta-analysis of the impact on fish consumption and the risk of coronary heart disease (CHD) was published [9], and so it has been added to this part of the publication. However, this meta-analysis was of interest because it only included observational studies of quality from 1966 through 2003. Studies that were included in this analysis meet the following criteria: adult human being studies only, case-control or cohort design, comparison of a group that consumed fish regularly versus those that did not, CHD used as an outcome, and potential associations had to be reported as a relative risk, hazard ratio, or odds ratio. A total of 19 observational studies (14 cohort and 5 case-control) met the inclusion criteria for this meta-analysis, and included a total of 228,864 individuals from a large and diverse geographic sample. The results of this analysis suggested that fish intake was associated with an approximate 20% significant ($P < 0.005$) reduction in the risk of fatal CHD and a significant ($P < 0.005$) 10% reduction in total CHD. The potential greater benefit for reducing fatal CHD could be a result of the numerous confounders or is just the ongoing finding that one of the biggest benefits of omega-3 fatty acid intake is for the reduction of sudden cardiac death.

Interestingly, the reduction in fatal CHD and fish consumption was more pronounced in individuals consuming 2 to ≤4 servings of fish per week compared to those consuming <2 servings per week. A slightly higher relative risk of fatal CHD was found in those individuals consuming ≥4 servings of fish per week compared to the other groups, which the investigators explained could be because of chance or higher levels of mercury exposure in these populations, and high concentrations of mercury in fish may increase the risk of CHD [10], but this is still controversial and preliminary [11]. There seem to be higher levels of mercury reported in fish in some Scandinavian countries, where the results were not as beneficial compared to other countries (non-Scandinavian) that reported higher reductions in fatal and total CHD [12,13].

The potential impact of n-3 fatty acids on the risk of nonhemorrhagic (ischemic) stroke needs more investigation, but the initial results suggest some protection. The Health Professional Follow-up Study of 43,671 men found a reduced risk of stroke, but a dose effect was not observed [14]. However, a reduced risk with increasing fish intake was found in the Nurses' Health Study cohort of 79,839 women. The largest impact was in women consuming fish ≥5 times a week [15].

Cardiovascular disease and children

Recently, a study was completed of how a low-fat diet (National Cholesterol Education Panel Step II), or docosahexaenoic (DHA) supplementation with this diet, could affect endothelial function in children with familial hypercholesterolemia or the phenotype of familial combined hyperlipidemia [16]. Secondary endpoints of this trial included lipid profiles and markers of oxidative stress. This randomized, placebo-controlled crossover study included 20 children (age 9–19 years) with familial hypercholesterolemia ($n = 12$) and familial combined hyperlipidemia ($n = 8$). Children received nutritional counseling for 6 weeks and then were randomly assigned to supplementation with DHA (1.2 g/day) or placebo for 6 weeks, followed by a washout period of 6 weeks, and finally crossover for 6 weeks. Endothelium dependent flow-mediated dilation of the brachial artery (determined via high-resolution ultrasound) increased significantly after DHA supplementation compared to baseline ($P < 0.001$), diet alone ($P < 0.002$), placebo ($P < 0.012$), and washout ($P < 0.001$) periods of the study without impacting the markers of oxidative stress or inflammation. DHA supplementation was associated with significantly higher levels of total cholesterol, low-density lipoprotein, and high-density lipoprotein (HDL) compared to the National Cholesterol Education Panel diet. This study suggested that DHA