Omega-3 Fatty Acids and Athletics

Artemis P. Simopoulos, MD

Corresponding author
Artemis P. Simopoulos, MD
The Center for Genetics, Nutrition and Health, 2001 S Street NW, Suite 530, Washington, DC 20009, USA.
E-mail: cgnh@bellatlantic.net

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Human beings evolved consuming a diet that contained about equal amounts of ω-6 and ω-3 essential fatty acids. Today, in Western diets, the ratio of ω-6 to ω-3 fatty acids ranges from approximately 10:1 to 20:1 instead of the traditional range of 1:1 to 2:1. Studies indicate that a high intake of ω-6 fatty acids shifts the physiologic state to one that is prothrombotic and proaggregatory, characterized by increases in blood viscosity, vasospasm, and vasoconstriction, and decreases in bleeding time. ω-3 fatty acids, however, have anti-inflammatory, antithrombotic, antiarrhythmic, hypolipidemic, and vasodilatory properties. Excessive radical formation and trauma during high-intensity exercise leads to an inflammatory state that is made worse by the increased amount of ω-6 fatty acids in Western diets, although this can be counteracted by eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA). For the majority of athletes, especially those at the leisure level, general guidelines should include EPA and DHA of about 1 to 2 g/d at a ratio of EPA:DHA of 2:1.

Introduction

The health of the individual and population is determined by the interaction between their genetic endowment and a number of environmental factors (Fig. 1) [1,2,3••]. Both diet and exercise are two environmental factors of major importance. Hippocrates, in the 5th century BC, stated:

> Positive health requires a knowledge of man's primary constitution [which today we call genetics] and of the powers of various foods, both those natural to them and those resulting from human skill [today's processed food]. But eating alone is not enough for health. There must also be exercise, of which the effects must likewise be known. The combination of these two things makes regimen, when proper attention is given to the season of the year, the changes of the winds, the age of the individual and the situation of his home. If there is any deficiency in food or exercise the body will fall sick.

The first evidence of the importance of food and exercise in health appears in the *Hippocratic Corpus* in the 5th century BC. *Diet* did not refer simply to food but to the whole lifestyle, including nutrition and exercise. Among the Ancient Greeks, the concept of "positive health" was important and occupied much of their thinking. In fact, those who had the means and the leisure applied themselves to maintaining positive health. Their concept of positive health depended on man's primary constitution (genetics), food, and exercise. The combination of food and exercise constituted "regimen." Environmental factors played a role in formulating regimen. In developing regimen, they distinguished regimens for leisure from those for professional athletes and paid particular attention to changing regimens for different seasons. Furthermore, the regimens differed in accordance with the physique of the individual. They believed that special physiques needed special diets. The concept of positive health is not population-dependent, but specific to the individual. In essence, it is the forerunner of molecular medicine, genetic medicine, genetic nutrition, and genetic exercise. Today we know that diet and exercise are essential components for health.

Over the past 25 years, many studies and clinical investigations have been carried out on the physiology, metabolism, and gene expression of ω-6 and ω-3 fatty acids. Today we know that ω-3 fatty acids are essential for normal growth and development and play an important role in the prevention and management of coronary heart disease (CHD) [4,5,6••], and are beneficial in the management of hypertension, diabetes, arthritis and other autoimmune disorders, and cancer [7–9]. This article focuses on ω-3 fatty acids and athletics.

Biologic Effects of Omega-6 and Omega-3 Fatty Acids

A number of anthropologic, nutritional, and genetic studies indicate that the human diet, including energy intake and energy expenditure, has changed over the past 10,000 to 15,000 years, with major changes occurring during the past 150 years in the type and amount of fat and in physical activity (Fig. 2) [7–10]. Whereas major changes have taken place in terms of diet and physical activity in many populations, the genetic profile has changed very little, if any, in

the past 10,000 to 15,000 years [11]. Today, Western societies are characterized by sedentary lifestyles and obesity has reached epidemic proportions at all ages. Genetically speaking, humans today live in a nutritional environment and have adopted sedentary lifestyles that differ from those for which our genetic constitution was selected. It has been estimated that the present Western diet is deficient in ω-3 fatty acids with a ratio of ω-6 to ω-3 fatty acids of 10:1 to 20:1 instead of 1:1 as is the case with wild animals and (presumably) human beings [12,13]. Human beings evolved on a diet in which there was a balance between the ω-6 and ω-3 fatty acids, which is a more physiologic state because both ω-6 and ω-3 polyunsaturated fatty acids (PUFA) influence cellular metabolism and gene expression.

Linoleic acid (LA; 18:2ω6) and alpha-linolenic acid (ALA; 18:3ω3) and their long-chain derivatives are important components of animal and plant cell membranes. When humans ingest fish or fish oil, the ingested eicosapentaenoic acid (EPA; 20:5ω3) and docosahexaenoic acid (DHA; 22:6ω3) partially replace the ω-6 fatty acids (especially arachidonic acid [AA; 20:4ω6]) in cell membranes, especially those of platelets, erythrocytes, neutrophils, monocytes, and liver cells [7,13]. As a result, ingestion of EPA and DHA from fish or fish oil leads to 1) decreased production of prostaglandin E_2 metabolites; 2) decreased concentrations of thromboxane A_2, a potent platelet aggregator and vasoconstrictor; 3) decreased formation of leukotriene B_4, an inducer of inflammation and a powerful inducer of leukocyte chemotaxis and adherence; 4) increased concentrations of thromboxane A_3, a weak platelet aggregator and vasoconstrictor; 5) increased concentrations of prostacyclin PGI_3, leading to an overall increase in total prostacyclin by increasing PGI_3 without decreasing PGI_2 (both PGI_2 and PGI_3 are active vasodilators and inhibitors of platelet aggregation); and 6) increased concentrations of leukotriene B_5, a weak inducer of inflammation and a chemotactic agent [14,15].

Because of the increased amounts of ω-6 fatty acids in the Western diet, the eicosanoid metabolic products from AA, specifically prostaglandins, thromboxanes, leukotrienes, hydroxy fatty acids, and lipoxins, are formed in larger quantities than those formed from ω-3 fatty acids, specifically EPA. The eicosanoids from AA are biologically active in small quantities and if formed in large amounts contribute to the formation of thrombi and atheromas; the development of allergic and inflammatory disorders, particularly in susceptible people; and cell proliferation. Thus, a diet rich in ω-6 fatty acids shifts the physiologic state to one that is prothrombotic and proaggregatory, with increases in blood viscosity, vasospasm, and vasoconstriction, and decreases in bleeding time. Bleeding time is shorter in groups of patients with hypercholesterolemia [16], hyperlipoproteinemia [17], myocardial infarction, other forms of atherosclerotic disease, type 2 diabetes, obesity, and hypertriglyceridemia. As the ratio of ω-6 to ω-3 fatty acids increases, the prevalence of type 2 diabetes also increases [18].

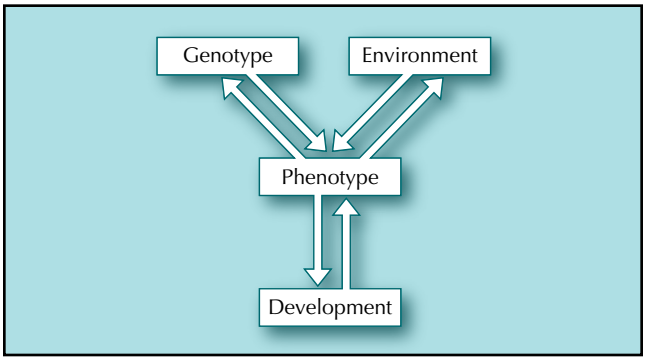

Figure 1. Relationships among genes, environment, and development are dynamic.

The hypolipidemic, antithrombotic, and anti-inflammatory effects of ω-3 fatty acids have been studied extensively in animal models, tissue cultures, and cells [7,13]. As expected, earlier studies focused on mechanisms that involve eicosanoid metabolites. More recently, however, the effects of fatty acids on gene expression have been investigated, and this focus of interest has led to studies at the molecular level [1,2,3••,11]. Previous studies have shown that fatty acids, whether released from membrane phospholipids by cellular phospholipases or made available to the cell from the diet or other aspects of the extracellular environment, are important cell-signaling molecules. They can act as second messengers or substitute for the classic second messengers of the inositide phospholipid and cyclic AMP signal transduction pathways [19]. They can also act as modulator molecules mediating responses of the cell to extracellular signals [19]. It has been shown that fatty acids rapidly and directly alter the transcription of specific genes [20].

Exercise or Physical Activity and Athletics

Exercise or physical activity and athletics have been known to be associated with lower risk for cardiovascular disease, hypertension, obesity, and diabetes [21–29]. Exercise lowers blood pressure and decreases the overall risk for CHD by lowering triglycerides, raising high-density lipoprotein (HDL), and decreasing low-density lipoprotein (LDL) cholesterol. Table 1 shows some of the effects of ω-3 fatty acids and physical activity to be similar and to be opposite of those of the effects of the aging process. Therefore, in the athletic setting, the ω-3 fatty acids are essential for overall health of the athlete. Both ω-3 fatty acids and exercise increase fatty acid oxidation. ω-3 fatty acids increase the production of endogenous antioxidant enzymes such as catalase, glutathione peroxidase, and super oxide dismutase. Both exercise and ω-3 fatty acids increase sensitivity to insulin and prevent hyperglycemia. ω-3 fatty acids increase oxygen delivery to the heart muscle so that the heart does not have to work as hard to get the oxygen it needs for work [30]. Many of the health benefits of exercise are due to increased fat utilization

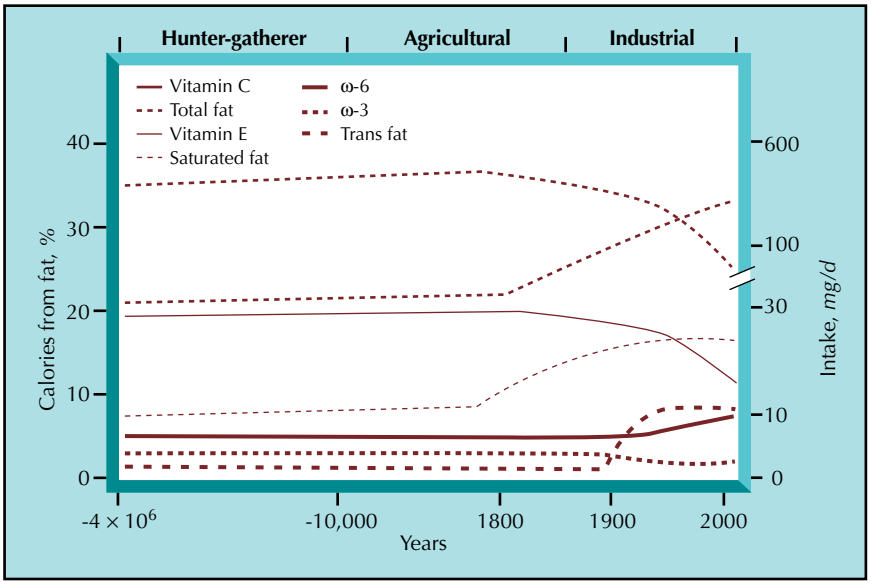

Figure 2. Hypothetical scheme of fat, fatty acid (ω6, ω3, trans, and total) intake (as percent of calories from fat), and intake of vitamins E and C (mg/d). Data were extrapolated from cross-sectional analyses of contemporary hunter-gatherer populations and from longitudinal observations and their putative changes during the preceding 100 years. (*Data from* Simopoulos [10].)

associated with exercise and with endurance training. Exercise has an important role in body weight regulation. The increasing incidence of obesity is more closely related to measures of inactivity than overconsumption of food. This was shown at the 5th International Conference on Nutrition and Fitness, held June 9–12, 2004, in Athens, Greece [28,29]. In their paper on adolescent obesity and physical activity, Hwalla et al. [31] describe the study carried out in Lebanon. The results of this first national population-based study show that adolescent obesity is largely caused by lack of physical activity, and the boys fare worse than the girls. The authors recommend multicomponent intervention strategies at the societal and individual levels for weight control that include health professionals, families, schools, businesses, and health care organizations, in order to increase programs and opportunities for physical activity.

During exercise, there is an increase in the generation of superoxide radical (O_2-) in the lipid bilayers of muscle mitochondria, and trauma to the muscles [32]. Excessive radical formation and trauma during high-intensity exercise leads to a state of inflammation that is made worse by the increased amounts of ω-6 found in the Western diet. Fish oil concentrates rich in EPA and DHA have been used to counteract the effects of the inflammatory state [33]. For the majority of athletes, especially at the leisure level, general guidelines could include fish oils EPA and DHA of about 1 to 2 g/d at a ratio of EPA to DHA of 2:1. A more individualized approach with exercise stress testing is essential and the background diet should be balanced in ω-6 and ω-3 fatty acids by lowering ω-6–rich oils such as corn oil, sunflower, safflower, cottonseed, and soybean oils, and substituting olive oil and canola oil instead. Changes and improvements in the background diet and an additional 1 to 2 g/d of EPA and DHA should prevent the inflammation in muscles and joints. For the elite athlete, the above prophylactic measures are essential.

Omega-6 to Omega-3 Fatty Acid Ratio: The Effect of Exercise

Training affects muscle phospholipid fatty acid composition in humans. Dietary fatty acid profile plays an important role for the incorporation of fatty acids into the muscle membrane phospholipids in humans [34–36]. In addition to the effect of diet, there is some evidence that physical activity per se could also be a possible moderator of membrane phospholipid fatty acid composition. Andersson et al. [37] demonstrated that 6 weeks of low-intensity exercise training resulted in significant changes in muscle phospholipid fatty acid composition with a significant increase in oleic acid (18:1ω9) and a decrease in AA (20:4ω6). Although great care was taken to attempt to control dietary fatty acid profile, the subjects were free living.

Helge et al. [38] investigated the effects of regular exercise training on skeletal muscle phospholipid fatty acid composition in humans applying a one-leg training model in which the other leg served as a control. Dietary fatty acid composition, initial level of training, and other relevant variables were controlled. Their working hypothesis was that regular training, primarily through its effect on substrate flux and substrate storage, induces an adaptive response in muscle membrane phospholipid fatty acid composition. Training improves insulin sensitivity, which in turn may affect performance by modulation of fuel availability. Insulin action, in turn, has been linked to specific patterns of muscle structural lipids in skeletal muscle. This study investigated whether regular exercise training exerts an effect on the muscle membrane phospholipid fatty acid composition in humans. Seven men performed endurance training of the knee extensors of one leg for 4 weeks. The other leg served as a control. Muscle biopsies were obtained from the vastus lateralis before, after 4 days, and after 4 weeks. After 4 weeks, the phospholipid fatty acid contents of oleic acid (18:1ω9) and DHA (22:6ω3) were significantly higher in the trained (10.9% ± 0.5%

Table 1. Comparison of the effects of omega-3 fatty acids and exercise on risk factors for chronic diseases

Risk factors	Omega-3 fatty acids	Exercise	Aging
Depression	Decrease	Decrease	Increase
Heart rate variability	Increase	Increase	Decrease
Bleeding time	Increase	Increase	Decrease
Fibrinogen	Decrease	Decrease	Increase
Platelet aggregation	Decrease	Decrease	Increase
Plasma viscosity	Decrease	Decrease	Increase
Arrhythmias	Decrease	Decrease	Increase
Erythrocyte deformability	Increase	Increase	Decrease
Nitric oxide production	Increase	Increase	Decrease
Triglycerides	Decrease	Decrease	Increase
High-density lipoprotein cholesterol	Increase	Increase	Decrease
Brachial artery dilation and blood flow	Increase	Increase	Decrease
Exercise-induced bronchoconstriction in elite athletes	Decrease	Increase	?
Inflammation and inflammatory markers	Decrease	Increase	Increase
Blood pressure	Decrease	Decrease	Increase
Basal metabolic rate	Increase	Increase	Decrease
Insulin sensitivity	Increase	Increase	Decrease
Fat mass	Decrease	Decrease	Increase
Risk of metabolic syndrome	Decrease	Decrease	Increase
Fatty acid oxidation	Increase	Increase	?
Fatty acid-binding protein	Increase	Increase	?
ω6:ω3 ratio in phospholipids	Decrease	Decrease	?

?—uncertain of effect.

and 3.2% ± 0.4% of total fatty acids, respectively) than the untrained leg (8.8% ± 0.5% and 2.6% ± 0.4%; $P < 0.05$). The ratio between ω-6 and ω-3 fatty acids was significantly lower in the trained (11.1 ± 0.9) than the untrained leg (13.1 ± 1.2; $P < 0.05$). In contrast, training did not affect muscle triacylglycerol fatty acid composition. Citrate synthase activity was increased by 17% in the trained compared with the untrained leg ($P < 0.05$). In this model, diet plays a minimal role, as the influence of dietary intake is similar in both legs. Therefore, regular exercise training per se influences the phospholipid fatty acid composition of muscle membranes but has no effect on the composition of fatty acids stored in triacylglycerols within the muscle.

In this study, a 4-week regular exercise training induced changes in the muscle membrane phospholipid fatty acid profile; therefore, exercise training should be considered as a modulator of muscle phospholipid fatty acid composition. The ratio of 18:1ω9 to 16:0 was significantly higher after training, suggesting an increase in the Δ-desaturase activities induced by training. A lower AA was not found by Helge et al. [38] but it was found in the study by Andersson et al. [37]. Muscle triacylglycerol fatty acid composition was unaltered by regular exercise training, indicating that the effect of regular exercise training on muscle phospholipid fatty acid composition is not directly linked to changes in the muscle triacylglycerol fatty acid composition. The fraction of oleic acid in muscle triacylglycerol was significantly increased by exercise training, indicating a preferential recruitment and uptake of oleic acid during and after exercise.

There is good evidence that endurance training increases insulin sensitivity [39–41]. There is some evidence that prolonged adaptation to regular exercise training will lead to increased muscle membrane phospholipid content in humans [42] and rats [43]. In humans, the 16% increase in phospholipid content was almost completely due to an increased phosphatidylcholine content. It may be that some correlate of physical activity rather than the activity itself is responsible for the changes in phospholipid fatty acid composition. Gudbjarnason [44] showed that catecholamine stress by repeated administration of epinephrine can alter the fatty acid composition of cardiac phospholipids. In that study, catecholamine stress caused an increase in AA and DHA content and a decrease in LA from 2.6% ± 0.4% to 3.2% ± 0.4% ($P < 0.05$)—changes that were not detected in the study by Helge et al. [38]. However, the increase in percent of DHA

was consistent between the studies by Helge et al. [38] and Gubjarnason [44], as was the decreased ω-6 to ω-3 ratio. Exercise performed in the one-leg exercise model at submaximal levels only results in moderate increases in circulating catecholamine levels [45].

ω-3 Fatty acids enhance exercise-induced increases in brachial artery diameter and blood flow during rhythmic exercise, whereas safflower oil rich in ω-6 fatty acids had no effect. Results indicate that treatment with 5 g (2 g/d DHA and 3 g/d EPA) of ω-3 fatty acids enhances brachial artery blood flow and conductance during exercise [46••]. These findings may have implications for individuals with cardiovascular disease and exercise intolerance (eg, heart failure).

Fish Oil Supplementation Reduces Severity of Exercise-induced Bronchoconstriction in Elite Athletes

Dietary fish oil supplementation has a markedly protective effect in suppressing exercise-induced bronchoconstriction (EIB) in elite athletes, and this is most likely attributed to EPA and DHA anti-inflammatory properties. EIB is a condition characterized by transient narrowing of the airway during or after exercise, which results in decreased pulmonary function following exercise. EIB is more prevalent in elite athletes compared with nonelite athletes and the general population. In the elite athlete, a high prevalence of EIB and asthma-like symptoms such as wheezing, chest tightness, abnormal breathlessness, cough, and sputum production have been noted. The relatively high incidence of EIB in elite athletes may be due to exercise hyperventilation, prolonged exposure to allergens and bronchial irritants, and excessive inhalation of cold, dry air.

Although the mechanisms responsible for bronchial hyperactivity after exercise in asthmatics have been extensively investigated [47,48], EIB in elite athletes is less understood and most likely involves many mechanisms. It has been suggested that transient dehydration of the airways activates the release of inflammatory mediators, such as histamine, neuropeptides, and AA metabolites, leukotrienes, and prostaglandins from airway cells, resulting in bronchial smooth muscle contraction. Repetitive high-intensity exercise itself may contribute to the development of EIB by the release of inflammatory cytokines [49]. Recent evidence of airway remodeling in cross-country skiers, and the fact that EIB does not respond to pharmacologic agents prophylactically [50], strongly suggests that EIB pathologically is quite different from asthma. Whether dietary modification through supplementation with 3.2 g of EPA and 2.2 g of DHA could decrease the EIB was studied by Mickleborough et al. [51] in a randomized double-blind crossover study. The diet had no effect on pre-exercise pulmonary function in either group nor on postexercise pulmonary function in the control group; however, in the subjects with EIB, the ω-3 fatty acid diet improved postexercise pulmonary function compared with the normal and placebo diets. Similarly, leukotriene E_4 (LTE_4), 9α, 11β-prostaglandin F_2, LTB_4, tumor necrosis factor-α, and interleukin-1β, all significantly decreased on the ω-3 polyunsaturated fatty acid diet compared with normal and placebo diets and after the exercise challenge. Thus, this small study of 10 elite athletes with EIB and 10 normal elite athletes (without EIB) suggests that fish oil supplementation has a significant protective effect in suppressing EIB in elite athletes, most likely due to the anti-inflammatory properties of the ω-3 fatty acids.

Conclusions

Essential fatty acids, both ω-6 and ω-3, have been part of our diet since the beginning of human life. Before the agricultural revolution 10,000 years ago, humans consumed about equal amounts of both. Over the past 150 years this balance has been upset. Current estimates in Western cultures suggest a ratio of ω-6 to ω-3 fatty acids of approximately 10:1 to 20:1 instead of 1:1 or 2:1 as was the case during evolution and prior to agribusiness and modern agriculture that led to the production of vegetable oils high in ω-6 fatty acids.

Both ω-6 and ω-3 fatty acids are the parent fatty acids for the production of eicosanoids (eg, prostaglandins, thromboxanes, and leukotrienes). Eicosanoids derived from ω-6 fatty acids have opposing metabolic properties to those derived from ω-3 fatty acids. A balanced intake of both ω-6 and ω-3 fatty acids is essential for health. ω-3 fatty acids have anti-inflammatory, antithrombotic, antiarrhythmic, hypolipidemic, and antiproliferative properties that account for their beneficial effects in CHD, hypertension, diabetes, obesity, and cancer.

Exercise or physical activity and athletics have been known to be associated with lower risk for CHD, hypertension, obesity, and diabetes. Exercise lowers blood pressure and decreases the overall risk for CHD by lowering triglycerides and LDL cholesterol while raising HDL cholesterol. Many of the effects of ω-3 fatty acids are similar to the effects of exercise. For example, both increase basal metabolic rate, insulin sensitivity, nitric oxide production, erythrocyte deformability, heart rate variability, and bone density, and decrease the risk of metabolic syndrome, bone fractures, platelet aggregation, and depression. ω-3 fatty acids decrease EIB in the athletes and counteract the inflammatory state brought on by exercise.

For the majority of athletes, especially those at the leisure level, general guidelines should include fish oils EPA and DHA of about 1 to 2 g/d at a ratio of EPA to DHA of 2:1. A more individualized approach with exercise testing is essential, and the background diet should be balanced in ω-6 and ω-3 fatty acids by lowering ω-6–rich oils such as corn oil, sunflower, safflower, cottonseed, and soybean oils and substituting olive oil and

canola oil instead. Changes and improvements in the background diet and an additional 1 to 2 g/d of EPA and DHA per day should prevent the inflammation in muscles and joints. Therefore, in the athletic setting, the ω-3 fatty acids are essential for overall health of the athlete.

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