Hemostatic Factors; Lipid Theory; Prevention. **Diabetes Mellitus**: Dietary Management. **Fatty Acids**: Omega-6 Polyunsaturated. **Lactation**: Dietary Requirements. **Pregnancy**: Nutrient Requirements; Safe Diet for Pregnancy.

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Omega-6 Polyunsaturated

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Structure, Function, and Nutritional Requirements

Omega-6 (n-6) fatty acids are a class of polyunsaturated fatty acids (PUFA). They have two or more *cis* double bonds, with the position of the first double bond six carbon atoms from the methyl end of the molecule. The general formula of n-6 fatty acids is $CH_3(CH_2)_4(CH{=}CHCH_2)_x(CH_2)_yCOOH$ [where $x = 2–5$]. Linoleic acid (*cis*-9, *cis*-12-octadecadienoic acid, 18:2n-6, LA) and α-linolenic acid (*cis*-9, *cis*-12, *cis*-15-octadecatrienoic acid, 18:3n-3, ALA) are the precursor fatty acids of the n-6 and omega-3 (n-3) fatty acids, respectively. These two fatty acids cannot be made by mammals and are therefore termed essential fatty acids (EFA). In addition, mammals are unable to interconvert LA and ALA, or any of the n-6 and n-3 fatty acids, because mammalian tissues do not contain the necessary desaturase enzyme. Plant tissues and plant oils tend to be rich sources of LA. ALA is also present in plant sources such as green vegetables, flaxseed, canola, and some nuts. Once consumed in the diet, LA can be converted via chain elongation and desaturation to γ-linolenic acid (GLA, 18:3n-6), dihomo-γ-linolenic acid (DGLA, 20:3n-6), and arachidonic acid (AA, 20:4n-6) (**Figure 1**). The same enzymes involved in elongation and desaturation of the n-6 fatty acids are common to the n-3 series of fatty acids (**Figure 1**). Thus, ALA can be converted to eicosapentaenoic acid (EPA, 20:5n-3) and docosahexaenoic acid (DHA, 22:6n-3). EPA and DHA are found in relatively high proportions in marine oils.

The n-6 and n-3 fatty acids are metabolically and functionally distinct and often have important opposing physiological functions. Indeed, the balance of EFA is important for good health and normal development. Historically, human beings evolved on a diet in which the ratio of n-6 to n-3 fatty acids was about 1:1. In contrast, Western diets have a ratio of

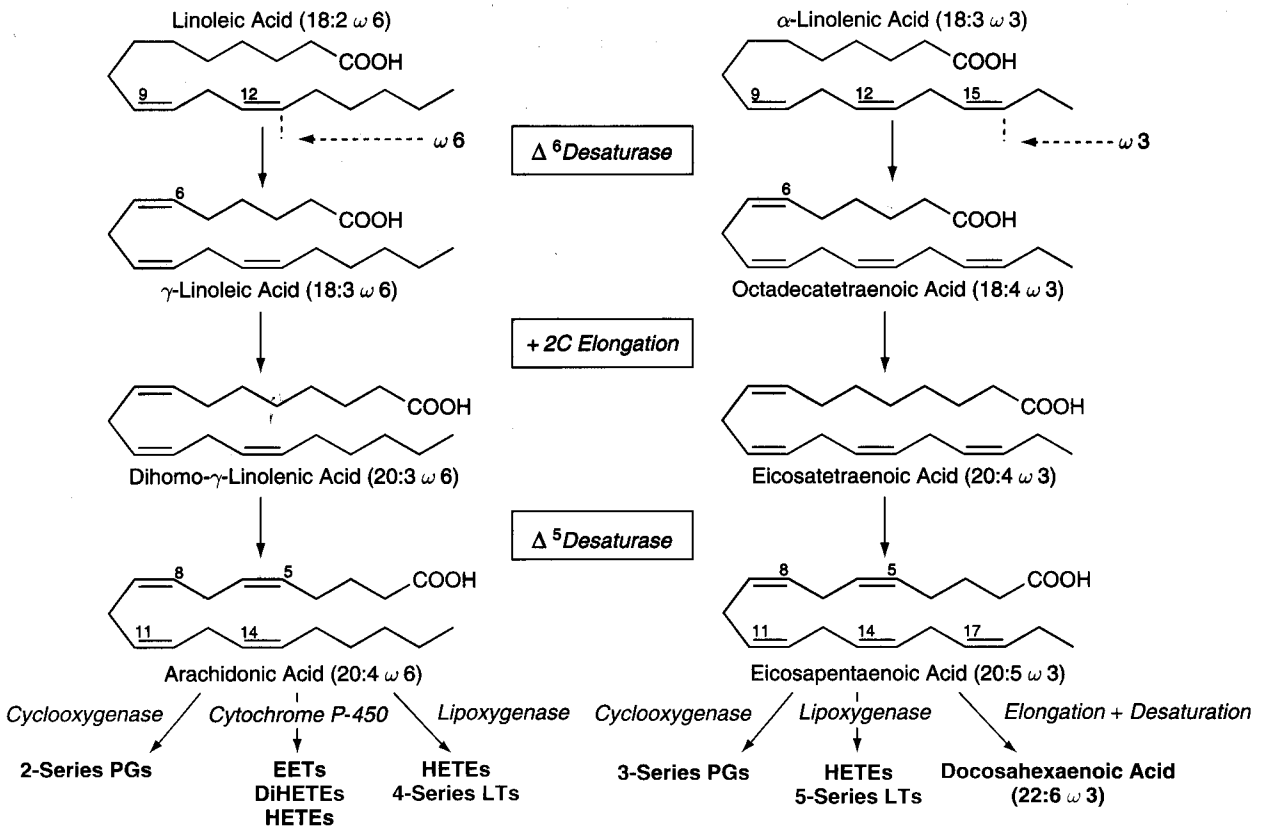

Figure 1 Essential fatty acid metabolism.

approximately 15:1. Evidence for this change in diet through history comes from studies on the evolutionary aspects of diet, modern-day hunter–gatherers, and traditional diets. Modern agriculture has led to a substantial increase in n-6 fatty acids at the expense of n-3 fatty acids, which has resulted in excessive consumption of n-6 fatty acids by humans.

The n-6 EFAs have two main functions. First, they act as structural components of membranes forming the basis of the phospholipid component of the lipid bilayer of plasma membranes in every cell in the body, thus providing a membrane impermeable to most water-soluble molecules. The length and degree of saturation of the fatty acids determine how the phospholipid molecules pack together and consequently affect membrane fluidity, signal transduction, and the expression of cellular receptors. The second role of n-6 fatty acids is as precursors to the eicosanoids (**Figure 1**). The eicosanoids are a family of 'hormone-like' compounds including prostaglandins (PGs), leukotrienes (LTs), and hydroxy- (HETEs), dihydroxy- (DiHETEs), and epoxy- (EETs) fatty acids. Eicosanoids, however, are distinct from most hormones in that they act locally, near their sites of synthesis, and they are catabolized extremely rapidly. Thus, they are considered to be locally acting hormones. The eicosanoids modulate renal and pulmonary function, vascular tone, and inflammatory responses. The enzymes involved in AA metabolism include the cyclooxygenases and lipoxygenases, which yield the 2-series PGs and 4-series LTs, respectively. Lipoxygenase also utilizes AA for the formation of the HETEs. A third pathway for the utilization of AA involves the cytochrome P-450 enzymes found in the liver, kidney, lung, intestines, heart, small blood vessels, and white blood cells. AA metabolized via cytochrome P-450 yields EETs, DiHETEs, as well as HETEs. The cytochrome P-450 metabolites play an important role as paracrine factors and second messengers in the regulation of pulmonary, cardiac, renal, and vascular function and modulate inflammatory and growth responses.

Endothelial Function, Atherosclerosis, and Cardiovascular Disease

Differences in n-6 fatty acid intake have the potential to influence several chronic diseases and disorders. This article will focus on the effects of n-6 fatty acids on cardiovascular disease and atherosclerosis.

The vascular endothelium is the most important organ controlling vascular function and consists of a single layer of epithelial cells lining blood vessels. Its primary function is to regulate vascular tone, but it plays a critical role in modulating coagulation and fibrinolysis, inflammation, smooth muscle cell proliferation, and macrophage function. Many of these functions are regulated through the release of various mediators including eicosanoids. There is multiple and close interaction of the endothelial cells with circulating cells, smooth muscle cells, and macrophages. There is also evidence that endothelial dysfunction precedes clinically apparent atherosclerosis.

Atherosclerosis is an inflammatory disease involving multiple cellular and molecular responses that lead to an alteration in vascular function and structure, and the development and progression of cardiovascular disease. Atherosclerosis is characterized by degenerative changes, deposition of cholesterol, proliferation of smooth muscle cells, involvement of a range of circulating proinflammatory cell types, and fibrosis. Resulting atheromatous plaques cause narrowing of arteries and increase the likelihood of thrombosis and occlusion. When this process occurs in the coronary arteries, the outcome is myocardial infarction and with possible death.

Eicosanoids: Relevance to Endothelial Function, Thrombosis, Inflammation, and Atherosclerosis

In general, the eicosanoids derived from AA have potent prothrombotic and proinflammatory activity. In contrast, the eicosanoids derived from EPA have reduced biological activity and are less prothrombotic and proinflammatory. Eicosanoid production is generally tightly controlled through homeostatic mechanisms. However, eicosanoid production can be significantly altered in situations in which endothelial dysfunction, atherosclerosis and plaque rupture, or various thrombotic or inflammatory conditions are present.

Prostaglandins and Leukotrienes

Prostaglandins have a central role in the regulation of platelet aggregation and vascular tone. In this regard, two of the major prostaglandins derived from AA are thromboxane A_2, produced in platelets, and prostacyclin I_2, produced in endothelial cells. Thromboxane A_2 promotes platelet aggregation and blood vessel constriction, while prostacyclin I_2 has the opposite effects. An increase in availability of EPA can decrease platelet thromboxane A_2 and increase thromboxane A_3, the latter having considerably less physiological activity. EPA supplementation also stimulates formation of prostacyclin I_3, while prostacyclin I_2 is unaffected. Prostacyclin I_3 and prostacyclin I_2 are equipotent in their biological activity. The net result following intake of n-3 fatty acids is a shift in the thromboxane/prostacyclin balance toward a reduced prothrombotic state.

Leukotriene B_4 is a potent inflammatory mediator produced by neutrophils from 20:4n-6 at the site of injury. Leukotriene B_4 is also a powerful chemotactic factor responsible for attracting neutrophils to the site of injury. Leukotriene B_5, which is produced from EPA, has significantly lower biological activity. Therefore an increased availability of EPA has the potential to reduce inflammation.

Fatty Acid Intake and Eicosanoids

The proportional concentration of the eicosanoid precursor fatty acids both circulating and in tissues depends on dietary intake. DGLA and AA can be obtained from animal meat and fat, and by desaturation and chain elongation of LA. The major dietary source of EPA is fish. EPA can also be obtained indirectly from ALA, although desaturation and chain elongation of ALA appears to be a less important pathway in humans.

Only the free form of the fatty acid precursors of eicosanoids can be utilized by the enzymes for conversion to the biologically active metabolites. However, the amount of precursor free fatty acid in the cytoplasm and circulating is usually low and so too is basal eicosanoid formation. Furthermore, basal eicosanoid formation may depend on dietary and adipose tissue fatty acid composition. The amount of eicosanoid precursor free fatty acids is controlled to a large extent by incorporation and release from cellular phospholipids. Which eicosanoids are produced during stimulated synthesis may depend on membrane fatty acid composition as well as the cell type involved. Dietary fatty acid composition, therefore, has the potential to effect basal and stimulated synthesis of eicosanoids and influence endothelial function and thrombotic and inflammatory responses.

n-6 Fatty Acids and Risk of Cardiovascular Disease

Evidence that differences in n-6 fatty acid intake can influence cardiovascular disease risk derives from several sources. Population studies may provide useful data for establishing optimal intakes of n-6 fatty acids. However, valuable information on the potential mechanisms and effects of these fatty acids is

derived from studies focusing on their impact on thrombosis, inflammation, endothelial function, and other cardiovascular risk factors.

Cardiovascular Disease: Population Studies

The incidence of cardiovascular disease within populations with either very high or very low intakes of n-6 fatty acids may provide some indication for optimal intakes of n-6 fatty acids. Within populations with low n-6 fatty acid intakes (≤3%) there would appear to be a benefit of having a higher n-6 fatty acid intake on cardiovascular disease risk reduction. These observations suggest that very low n-6 fatty acid intakes increase the risk for cardiovascular disease. The presence of EFA deficiency in a significant proportion of such populations may explain the increased risk. Several populations, including the Israelis, Taiwanese, and !Kung bushmen in the African Kalahari desert, have high to very high intakes of n-6 fatty acids. The contribution of n-6 fatty acids to total energy intake is about 10% in the Israelis and Taiwanese and about 30% in the !Kung bushmen. Rates of cardiovascular disease are low in the Taiwanese, where dietary n-6 fatty acids are obtained mainly from soybean oil, and estimated to be very low in the !Kung bushmen, where dietary n-6 fatty acids were obtained mainly from the monongo fruit and nut. In the Taiwanese, the soybean oil is refined but is accompanied by a diet rich in antioxidant polyphenols, notably from tea, fruits, and vegetables. In the !Kung bushmen the oil is unrefined and is therefore likely to contain a range of phytochemicals. There is, however, a high prevalence of cardiovascular disease in the Israeli population, where n-6 PUFAs are obtained largely from refined sources. These observations suggest that a high n-6 fatty acid intake can be compatible with low risk of cardiovascular disease, but the dietary context may be very important. Given that n-6 fatty acids are susceptible to lipid peroxidation, high n-6 fatty acid intake may increase risk for cardiovascular disease when consumed against a background diet low in antioxidants. The potential impact on eicosanoid metabolism remains uncertain.

Several factors may need to be considered in the interpretation of the results of population studies. First, the effect of LA on atherosclerosis and cardiovascular disease may depend on the background intake in the population being studied. Second, any relationships observed may be confounded by intake of other foods from which LA derives. Third, LA may have differential effects on aspects of the aetiology of cardiovascular disease, including endothelial function, thrombosis, arrhythmia, and atherosclerosis.

Thrombosis

Dietary fatty acids influence thrombosis by altering the activity and function of endothelial cells, platelets, and other circulating cells—effects that can be mediated, in part, by alterations in eicosanoid metabolism. Replacement of dietary saturated fatty acids with unsaturated fatty acids, including n-6 fatty acids, generally lowers the risk of thrombosis and cardiovascular disease. Furthermore, studies have shown that an increase in n-3 fatty acid intake can increase vasodilation, attenuate platelet aggregation, and alter circulating concentrations of factors involved in coagulation and fibrinolysis. The net effect of increasing n-3 fatty acid intake is a tendency toward reduced risk for thrombosis. These findings are supported by population studies demonstrating that n-3 fatty acids may reduce the risk of thrombosis. It remains uncertain whether the major factor influencing these functions is the absolute increase in n-3 fatty acids or the relative proportions of n-6 and n-3 fatty acids in the diet and cell membranes. There is evidence, however, that increased n-3 fatty acid intake may be more beneficial in populations consuming relatively small quantities of fish, which includes many Western populations.

Much of the evidence for a potential impact of n-6 fatty acids on thrombosis derives from research on platelet function. The role of platelets in thrombosis is established and the influence of fatty acid intake on platelet function has been assessed in many studies. Platelets play a part in thrombosis by adhering to, and aggregating at, the site of injury. Platelet reactivity and increased platelet activation may increase the risk of thrombosis. *In vitro* and *in vivo* studies assessing effects of n-6 fatty acids on platelet aggregation are inconsistent. To date there is little evidence that a high n-6 fatty acid diet in humans decreases platelet aggregation and some studies are suggestive of increased aggregation with high n-6 fatty acid diets, primarily in the form of LA. The effects of AA on platelet aggregation are also not clear. One of the main difficulties in interpreting these studies is the unresolved issue as to how the *in vitro* aggregation test reflects platelet function *in vivo*.

Inflammation

Conditions of increased inflammation, such as inflammatory arthritis, dermatological conditions such as psoriasis and atopic dermatitis, chronic

inflammatory bowel disease, autoimmune diseases, and bronchial asthma, appear to be beneficially influenced by n-3 fatty acids but not by n-6 fatty acids.

Whether or not increased intake of n-6 fatty acids can exacerbate inflammation *via* increased production of proinflammatory eicosanoids remains uncertain. Results of *in vitro* studies and intervention studies in humans are generally consistent with this theoretical potential of n-6 fatty acids to enhance inflammation, at least in comparison to n-3 fatty acids and probably n-9 monounsaturated fatty acids. The importance of absolute and relative intakes of n-6 fatty acids to inflammatory processes also remains unclear. The effects of changes in n-6 fatty acid intake on inflammatory processes may depend on the background dietary fatty acid intake, as well as proportional and absolute intake of n-3 fatty acids.

Cholesterol and Lipoproteins

The major classes of circulating lipoproteins in human plasma are chylomicrons, very low-density lipoproteins (VLDL), low-density lipoproteins (LDL), and high-density lipoproteins (HDL). High fasting plasma concentrations of LDL cholesterol and triglycerides—predominantly circulating as part of VLDL—and low plasma concentrations of HDL cholesterol are associated with increased risk of cardiovascular disease. Dietary fatty acids can influence lipoprotein metabolism and therefore have the potential to influence atherosclerosis and cardiovascular disease risk. Most studies examining the effects of n-6 PUFAs on cholesterol metabolism have focused on LA, the major dietary n-6 fatty acid.

It is now established that LDL cholesterol lowering reduces the risk of cardiovascular disease. In the fasting state LDL is the major cholesterol carrying lipoprotein in human plasma. The mechanisms through which raised plasma LDL cholesterol concentrations increase cardiovascular disease risk are not entirely understood but oxidative modification of LDL is thought to be involved. An increase in LA intake results in a lowering of plasma LDL cholesterol concentrations and therefore has the potential to reduce cardiovascular disease risk. These effects may not be linear over the entire range of LA intake and most of the benefits appear to be gained by moving from lower (<2% of energy) to moderate (~4–5% of energy) intakes. In addition, it is worthy of note that the effects of dietary n-6 PUFAs are less than half that of lowering dietary saturated fatty acids. Therefore, if total fat intake is maintained, the LDL cholesterol lowering effects of increasing n-6 PUFA intake are greatly enhanced if saturated fatty acid intake is decreased.

HDL cholesterol is inversely associated with cardiovascular disease risk. The mechanism by which HDL reduces cardiovascular disease risk may involve reverse cholesterol transport and reductions in cholesterol accumulation in the arterial wall. Intakes of LA within the normal ranges of intakes in most populations do not appear to alter HDL cholesterol concentrations. However, very high intakes—above 12% of energy—can lower HDL cholesterol concentrations.

Oxidative Stress

Several lines of evidence suggest that oxidatively modified LDL plays an important role in the development of atherosclerosis. Oxidative modification of LDL involves peroxidation of PUFAs. LDL particles enriched in PUFAs have been shown to be more susceptive to oxidative modification compared to LDL particles rich in monounsaturated fatty acids. Others have also suggested that a diet high in PUFAs may overwhelm the antioxidant defenses of cells. In particular, studies have shown that LA-enriched LDL is more prone to *in vitro* oxidation than oleic acid-enriched LDL. Concern also remains with respect to the potential for increased lipid peroxidation following n-3 fatty acids. To date, however, the data *in vivo* are inconclusive, with observations of increased, unchanged, and decreased lipid peroxidation. The most plausible explanation relates to differences in the methodologies employed to assess lipid peroxidation. Much of the literature relating to PUFAs and lipid peroxidation is based on indirect and nonspecific assays, including measurement of LDL oxidative susceptibility, which relies on the isolation of LDL from plasma. In this regard, the recent discovery of F_2-isoprostanes, which are nonenzymatic prostaglandin-like products of free radical peroxidation of arachidonic acid, has allowed for the direct assessment of *in vivo* lipid peroxidation. There is now good evidence that quantitation of F_2-isoprostanes provides a reliable measure of *in vivo* oxidative stress. Using measurement of F_2-isoprostanes, recent data have demonstrated that n-3 fatty acids decrease oxidative stress. It has also been suggested that the concentration of PUFAs may be a more important factor affecting lipid peroxidation than the degree of unsaturation. Further research using better markers of lipid peroxidation is required before definitive statements can be made relating to the effect of n-6 fatty acids, and indeed PUFAs in general, on oxidative stress.

Blood Pressure

The possible effects of dietary fatty acids on blood pressure have been explored in population studies and dietary intervention trials. With the exception of studies comparing vegetarian and nonvegetarian populations, from which there is a suggestion of a blood pressure lowering effect of diets high in PUFAs, including LA, and lower in saturated fatty acids, the results of most within- and between-population studies have generally not found significant associations. The results of intervention studies suggest that n-6 fatty acids, LA in particular, may be responsible for a small blood pressure lowering effect. However, these studies are also inconsistent, with several failing to find a significant blood pressure lowering effect.

Conclusions

Diets low in n-6 fatty acids, principally LA, appear to be associated with an increased risk of cardiovascular disease. The results of studies examining the effects of LA on risk factors for atherosclerosis and cardiovascular disease are consistent with this observation. An increase in n-6 PUFA intake from a low to a moderate intake level, in conjunction with decreases in total and saturated fat intake, may beneficially influence lipoprotein metabolism, lower blood pressure, and reduce cardiovascular disease risk. Observations in populations with high n-6 PUFA intake indicate that high intakes of n-6 fatty acids (>10%) can occur together with low rates of cardiovascular disease and possibly also cancer. However, where antioxidant composition of the diet is low, there is the potential for increased risk of cardiovascular disease. An increased susceptibility of PUFAs to oxidative damage, particularly in the presence of low concentrations of protective antioxidants, may be an important factor involved. The source of n-6 PUFAs in the diet, refined versus unrefined, and the composition of the background diet may therefore be important determinants of whether high n-6 fatty acid intake increases or decreases risk of cardiovascular disease. In addition, the proportion of n-6 to n-3 fatty acids in the diet may also play an important role in determining cardiovascular risk.

The available evidence suggests that n-6 fatty acid-derived eicosanoids are generally proinflammatory and prothrombotic. In contrast, eicosanoids derived from n-3 fatty acids have attenuated biological activity on cardiovascular risk factors. The effects of altering n-6 PUFA intake, in conjunction with changes in other polyunsaturated fatty acids, as well as other classes of fatty acids, on endothelial function, thrombosis, and inflammation are not understood. The relative proportion of all the classes of fatty acids in the diet may well be more important and relevant to cardiovascular risk reduction than any single class of fatty acids. Clearly such research warrants further investigation.

See also: **Cholesterol**: Sources, Absorption, Function and Metabolism; Factors Determining Blood Levels. **Coronary Heart Disease**: Lipid Theory. **Fatty Acids**: Metabolism; Monounsaturated; Omega-3 Polyunsaturated; Saturated; *Trans* Fatty Acids. **Fish**. **Lipoproteins**. **Prostaglandins and Leukotrienes**.

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