Safety considerations of polyunsaturated fatty acids¹,²

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ABSTRACT The n-6 and n-3 polyunsaturated fatty acids (PUFAs) are essential nutrients; intake of relatively small amounts of these fatty acids prevents nutritional deficiencies. Replacing dietary saturated fat with PUFAs may confer health gains. Experimental data support the notion that high intake of n-6 PUFAs may increase in vivo lipid peroxidation. This effect may be countered by dietary antioxidant supplementation. The influence of a high n-3 PUFA intake on measures of lipid peroxidation has been equivocal. In clinical trials, subjects who consumed diets rich in n-6 or n-3 PUFAs had fewer atherothrombotic endpoints than did control groups. In this report, data regarding the influence of PUFAs on lipid peroxidation as well as on cholesterol and glucose metabolism, hemostasis, and other aspects of interest are reviewed and discussed. Currently, daily intake of PUFAs as >10% of total energy is not recommended. Below this ceiling there is little evidence that high dietary intake of n-6 or n-3 PUFAs implies health risks. Am J Clin Nutr 2000;71(suppl):197S–201S.

KEY WORDS Polyunsaturated fatty acids, adverse effects, lipid peroxidation, cholesterol, blood glucose

INTRODUCTION Polyunsaturated fatty acids (PUFAs) of the n-6 and n-3 families are necessary for proper growth and body function (1). They cannot be synthesized by humans and must be obtained from the diet (1, 2). Deficiency syndromes resulting from insufficient dietary n-6 and n-3 PUFAs have been described (3, 4); however, such syndromes can be prevented with low intakes of n-6 and n-3 PUFAs, which should be achieved in a normal diet (2). The optimal daily intakes of PUFAs, and the optimal ratio of n-6 to n-3 PUFAs, remain unknown. When addressing these questions, other dietary constituents must also be taken into account (2). Very high intakes of PUFAs may carry a risk of adverse effects; thus, relevant experimental and clinical data on safety aspects of PUFAs will be reviewed.

LIPID PEROXIDATION When exposed to oxidant stress, PUFAs can be attacked by free radicals and oxidized into lipid peroxides (5). The peroxidative breakdown of PUFAs involves chain reactions that result in a variety of products such as aldehydes, ketones, and cyclic peroxides (6, 7). These reactions may propagate and modify lipids and proteins, eg, in cell membranes and lipoproteins that contain PUFAs (5, 6). Although still not fully elucidated, lipid peroxidation is thought to be one important mechanism involved in the pathogenesis of inflammation, cancer, and atherosclerosis (5–7).

Foods containing lipid peroxides are potentially toxic, and the more PUFAs are present in the diet, the more likely is peroxidation (5, 7). However, the rancid and unpleasant taste of foods rich in peroxidation products (5) usually prevents the intake of large amounts of lipid peroxides. It is unresolved whether chronic intake of smaller amounts of peroxidation products in food or supplements containing PUFAs stored or processed under conditions allowing oxidation presents a health hazard (5, 7).

Oxidative modification of LDL is the best-substantiated example of in vivo lipid peroxidation. Oxidatively modified LDL (ox-LDL) is assumed to play an important role in atherosclerosis (8, 9). Compared with native LDL, ox-LDL has been shown to have several properties thought to promote the development of atherosclerosis, including uptake by the macrophage scavenger receptor, leading to the formation of foam cells (8, 9). There is evidence that LDL is oxidatively modified in vivo (8, 9), although it has been difficult to develop reliable methods to quantify such modification (5, 10).

The susceptibility of LDL to oxidative modification under conditions of artificial oxidative stress can be measured in vitro (11). Although the clinical relevance of such tests can be questioned (10), an association between the susceptibility of LDLs to oxidation in vitro and estimates of coronary atherosclerosis has been described (12). The situation in vivo, however, is much more complex than that under controlled in vitro conditions. In the organism, various defense mechanisms including enzymes, other proteins, and water- and lipid-soluble antioxidants act protectively against lipid peroxidation in the circulation and in tissues, ie, artery wall (7). The ideal test for ox-LDL formation should reflect the presence and amounts of ox-LDL in the arterial intima, but so far this is possible only in specimens obtained from animal studies or in pathoanatomical samples. Several methods based on analyses of plasma have been used to assess ox-LDL formation, but none is considered ideal (5, 10). Measurement of thiobarbituric acid–reactive substances (TBARS), thought to reflect the formation of malondialdehyde, is applied commonly in clinical settings. This test is sensitive and suitable for application in large study populations; however, it is rather nonspecific and has other

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limitations as well (5, 10). The general lack of reliable methods for assessing lipoprotein oxidation in the circulation and in artery walls may help explain conflicting results of in vitro testing and clinical data from PUFA dietary studies.

In several clinical dietary trials it was shown that when PUFA intake is increased, the PUFA content of the LDL particles increases (13–15). The in vitro susceptibility of LDLs to undergo oxidative modification was reported to increase when the diet is rich in n–6 PUFAs compared with monounsaturated fats (13, 14, 16–18). Also, an increase in plasma TBARS concentrations during an n–6 PUFA–enriched dietary period was reported (19). In some but not all studies, supplementation with antioxidants increased the resistance of the LDL particles to oxidation (14, 15, 20). At present, whether a diet high in n–3 PUFAs increases the oxidative modification of LDLs is controversial (21). In the large Shunt Occlusion Trial, patients were supplemented with 4 g n–3 PUFA concentrate (which also supplied ~15 mg vitamin E) daily; compared with the nonsupplemented control group, no significant differences in serum TBARS concentrations were seen after 9 mo (22).

Thus, on the basis of in vitro assessments and best substantiated in vivo for n–6 PUFAs, increased dietary intake of PUFAs may enhance the susceptibility of LDLs to undergo oxidative modification. However, when it comes to clinical endpoints there is little evidence to suggest that a high PUFA intake increases the risk of an adverse outcome. On the contrary, data from intervention trials show that when saturated fats are replaced by n–6 PUFAs, subjects are less prone to develop atherothrombotic complications (23–25). Epidemiologic data on large intakes of n–6 PUFAs are lacking.

Traditional Mediterranean diets, to which health-promoting effects are attributed, are rich in monounsaturated fatty acids (26). Only recently has the use of plant-derived n–6 PUFAs increased in various populations, and the long-term effects of such dietary changes are unknown (26). The results of epidemiologic studies suggest that high n–3 PUFA intake reduces the risk for cardiovascular disease (27–30), and in intervention trials an increased n–3 PUFA intake was reported to act favorably on the incidence of atherothrombotic endpoints (31, 32). The Shunt Occlusion Trial showed a significant linear trend toward fewer aortocoronary vein graft occlusions with increasing positive changes in serum phospholipid n–3 PUFA concentrations (33).

Thus, regardless of the influence on LDL oxidation, there seems to be a net beneficial effect on clinical outcomes by enrichment with dietary PUFAs. Several factors may account for these observations. First, serum LDL-cholesterol concentrations tend to decline when saturated fatty acids are replaced with PUFAs in the diet (1). Second, PUFAs—in particular n–3 PUFAs—may have antiatherothrombotic effects on growth factors, cytokines, and signal molecules (34–37). Third, PUFA-rich food sources are often rich in antioxidants. Fourth, the microenvironment of the artery wall is different from that of the circulation and, evidently, widely different from in vitro conditions. Finally, as mentioned previously, the assessment methods for lipid oxidation in vivo have inherent limitations in reflecting the processes in the arterial intima.

The dietary requirement of antioxidants with a diet rich in PUFAs has not been defined. However, along with a PUFA-rich diet, it seems reasonable to encourage a high intake of antioxidants, preferably incorporated in the habitual diet.

**Effects on Serum Cholesterol**

Generally, when saturated fatty acids are replaced with PUFAs in the diet, total and LDL-cholesterol concentrations decrease (1). In some studies in which saturated fatty acids were replaced with n–6 PUFAs and the ratio of polyunsaturated to saturated fat increased, an HDL-cholesterol-lowering effect was shown (38–40), although not consistently (41). However, because LDL-cholesterol concentrations also decline with such n–6 PUFA–rich diets (42), the ratio of LDL to HDL cholesterol may not change significantly (39, 40). When n–3 PUFAs were given as supplements to the habitual diet, LDL-cholesterol-raising effects were noted by some (43–45), whereas HDL-cholesterol concentrations were unchanged or increased slightly (43). In the Shunt Occlusion Trial, daily supplementation of 4 g highly purified n–3 PUFA concentrate/d did not significantly influence serum concentrations of total, HDL, or LDL cholesterol compared with the unsupplemented group (22). Such factors as characteristics of the subjects (ie, their hyperlipemic phenotypes and background diet) and of the study (ie, the type of supplement given, time of follow-up, and design details) may affect study outcomes significantly.

**Effects on Glucose Homeostasis**

In some n–3 PUFA–supplementation studies, a deterioration of glycemic control was reported in subjects with type 2 diabetes (46, 47). Data from later reports, however, do not support this conclusion (48, 49). Again, factors associated with study individuals, their habitual diet, the n–3 PUFA sources, and study design can be of relevance to explain conflicting results. In controlled trials in hypertensive (50) and hypertriglyceridemic (49, 51) individuals, no influence on glucose homeostasis was ascribed to n–3 PUFA supplementation. In the aforementioned Shunt Occlusion Trial, no effects of n–3 PUFAs on plasma glucose, serum insulin, or serum C-peptide concentrations were seen when the supplemented group was compared with the control group after 9 mo of follow-up (22).

**Effects on Hemostasis**

The bleeding tendency (eg, from the nose and urinary tract and obstetric bleedings) of traditionally living Greenland Eskimos was described (52). Later, prolonged cutaneous bleeding time and reduced platelet in vitro aggregability, compared with Danish control subjects, were reported (53, 54). These findings were associated with the unique diet of Greenland Eskimos, whose estimated n–3 PUFA intake is ≥7–10 g/d (2, 55). This inhibition of platelet function has been explained by a shift in eicosanoid metabolism when arachidonic acid (20:4n–6) is replaced by eicosapentaenoic acid (20:5n–3) in platelet membranes. This shift results in the generation of thromboxanes and prostacyclins which, overall, leads to a more vasodilatory and antiaggregatory hemostatic profile (1, 53). Also, a small—or, less often, a large—decline in platelet count during periods of high n–3 PUFA supplementation has been described (1, 54). In periods of moderate n–3 PUFA supplementation (2–5 g/d), however, there was no clinical evidence of an increased bleeding tendency (30). In the Shunt Occlusion Trial, all patients were treated with either aspirin or warfarin and followed clinically for 1 y. There were no more clinically detected bleeding episodes in the n–3 PUFA–supplemented group than in the control group.
(56). Also, there were no significant changes in a broad panel of hemostatic variables that could be attributed to the supplement, which consisted of 3.4 g eicosapentaenoic and docosahexaenoic acids/d (56). Thus, from a clinical point of view, a moderate n−3 PUFA supplement does not seem to increase the risk of bleeding, with a possible caveat for individuals with inherited or acquired hemorrhagic diathesis.

**IMMUNOSUPPRESSION**

There is evidence of favorable effects of n−3 PUFAs on some immunologic and inflammatory disorders (57–60), perhaps through an influence on cytokine and leukotriene generation (35, 37, 61). Hypothetically, large intakes of n−3 PUFAs could weaken defense mechanisms against infections or malignancies, but so far there are no definite clinical data on these issues.

**CARCINOGENESIS**

In several populations, a positive correlation between fat intakes and mortality rates from certain cancers, particularly of the breast but also of the colon and prostate, has been described (62–64). This association applies to intakes of total as well as saturated fat (63, 64), but on the basis of experimental animal models a minimum requirement of n−6 PUFAs seems necessary for tumorigenesis enhancement (63). Several mechanisms that could contribute to this putative tumorigenesis have been proposed, among them effects mediated by oxidation products, by the generation of leukotrienes, or by cellular membrane changes (63, 65, 66). It has also been proposed that the association between fat intake and cancer could be attributed to the trans fatty acid component (67), but this hypothesis is controversial (66). In animal models, n−3 PUFAs tend to be neutral or to inhibit tumorigenesis (63, 66).

In one intervention study, a higher incidence of fatal carcinomas was reported in the group with high n−6 PUFA intake compared with the control group (68). This finding has not been confirmed in reports from other studies (69). Thus, a certain influence of n−6 PUFAs on carcinogenesis cannot at present be excluded. Most investigators recommend that intake of linoleic acid not exceed 10% of total energy (70).

**LIVER FUNCTION**

A slight increase in the serum activity of liver enzymes during n−3 PUFA supplementation has been noted repeatedly (22, 71). The mechanisms remain unclear and these observations are presumed to be of no clinical significance. Autopsy reports have provided opposing data on the incidence of cholesterol gallstones in n−6 PUFA trials (72, 73). No prospective observations on this outcome have appeared.

**OTHER CONCERNS**

An increase in PUFA intake should be at the expense of saturated fat intake because in the long run, a substantial addition of energy-dense PUFAs to the habitual diet could result in weight gain and accompanying metabolic disorders (70). Regarding toxicity, commercial and concentrated PUFA products should report and declare potentially toxic substances such as heavy metals, organic pesticides, fat-soluble vitamins, and lipid peroxides, as well as the amounts of other fatty acids and cholesterol (1).

**CONCLUSION**

Evidence suggests that dietary PUFAs, when substituted for saturated fatty acids, will confer net health gains, most notably in cardiovascular disease. An upper limit of 10% of energy for n−6 PUFAs is presently recommended by experts, but a palatable and practicable diet will usually not exceed this limit. It also seems wise to ensure a high dietary intake of antioxidants. The risk of adverse effects of dietary PUFAs, whether on cholesterol or glucose metabolism or hemostatic function (except for large doses of n−3 PUFAs), seems small.

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