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Are diets high in omega-6 polyunsaturated fatty acids unhealthy?

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This article reviews the connection between dietary omega-6 fatty acids and atherosclerosis, carcinogenesis and insulin resistance. These polyunsaturated fatty acids (PUFAs) may be likened to 'double-edged swords': on one hand they are considered essential for membrane function and eicosanoid formation necessary for vascular, immune and inflammatory cell function, while on the other they lead to increased susceptibility to lipid oxidation, stimulating neoplastic cell growth in culture and impairing insulin activity. Omega-6 function should not be considered in isolation but as part of a complex of nutrient interactions together with omega-3 fatty acids (shared enzymatic pathways) and antioxidants. Insulin sensitivity might be the common factor relating disease to fatty acid metabolism — both within and between the fatty acid pathways. A high linoleate to arachidonate concentration occurs in insulin resistance, in diabetic complications and also in some tumours. Since the interaction between the omega-6 and omega-3 pathways is neither linear nor stochastic, specific dietary recommendations have to await clarification of these relationships. Adipose tissue fatty acid composition and function may be a suitable biomarker with which to study these questions. Current epidemiological and clinical evidence supports the regular consumption of cold-water fish as part of a balanced diet, in which attention to lifestyle and the quantities eaten (to prevent obesity and the insulin resistance syndrome) may be more critical than the nature of the fatty acids consumed.

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Key Words: Polyunsaturated fatty acids, insulin resistance, heart disease, cancer, omega-6 fatty acids, omega-3 fatty acids.

Introduction

Omega-6 fatty acids are essential for normal growth, development and health; one should, therefore be extremely careful before deciding that they are harmful. The question is one of quantity, of course, since by analogy with some fat-soluble vitamins (or, in fact, most nutritional factors) more does not necessarily imply better, and toxicity may occur. The essential nature of the omega-6 fatty acids lies in their physiological functions in membranes, eicosanoid production and regulation of cholesterol metabolism.

Dietary polyunsaturated fatty acids (PUFAs) have long been known for cholesterol-lowering properties[1]. The most desirable level for intake of linoleic acid (LA,18:2n-6, the parent fatty acid of the omega-6 family of fatty acids) has not been determined. Most investigators believe that an intake of 6–10% of energy is optimal[2]. However, in spite of the widespread enthusiasm for increasing PUFAs in the diet some 20 years ago, more recent studies from a variety of disciplines suggest possible deleterious effects of a high consumption of LA.

Israel has one of the highest dietary polyunsaturated/saturated fat (P/S) ratios in the world; the population consumes some 8% more omega-6 PUFAs than in the U.S.A., and some 10–12% more than in most European countries[3]. Israeli Jews may be regarded as a population-based dietary experiment of the effect of a high omega-6 PUFA diet on disease, one which, until recently, was widely recommended. Despite such national habits, paradoxically there is a high prevalence of cardiovascular diseases, hypertension, non-insulin-dependent diabetes mellitus (NIDDM) and obesity — all diseases which are associated with hyperinsulinaemia and insulin resistance, and grouped together as the insulin resistance syndrome or syndrome X[4]. There is also an increased cancer incidence and mortality rate, especially in women, in comparison with Western countries. Studies suggest that high LA consumption might aggravate hyperinsulinaemia and insulin resistance, as well as being a substrate for lipid peroxidation and free radical formation. Thus, far from being beneficial, high omega-6 PUFA diets may have some serious long-term side-effects, acting as the link between hyperinsulinaemia, atherosclerosis and carcinogenesis.

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However, since these diseases are multifactorial in origin, the dietary influence must be considered in relation to other lifestyle and environmental factors (e.g. exercise and smoking).

There are a number of ways by which LA may adversely affect metabolic pathways: LA interferes with the metabolism of alpha-linolenic acid (18:3n-3), another essential fatty acid, the metabolites of which play an important role in the normal development of the retina, brain and clotting mechanism[5]. Excess LA increases the ratio of linoleic to alpha-linolenic acid, and thus affects a number of pathophysiological processes, ranging from immune-inflammatory reactions to atherogenesis and cancerogenesis[6]. Omega-6 and omega-3 fatty acids compete for the same enzymes involved in elongation and desaturation of their respective pathways, and the degree of this interaction with respect to the timing and quantities consumed in the diet is still not known[7]. Also, as has been shown by Lands, the interrelationship is not a linear one[8]. There are differential effects of PUFAs, e.g. n-6 PUFAs decrease cholesterol concentrations while n-3 PUFAs lower triglycerides, while in other pathways their actions are similar[9]. In general, eicosanoids formed from the omega-3 fatty acids are much less potent in causing biological responses than those formed from the omega-6 fatty acids, including such adverse reactions as the stimulation of cytokine production and inflammatory responses[10].

Atherosclerosis

Omega-6 PUFAs increase the susceptibility of low-density lipoprotein (LDL) to oxidative modifications[11,12] and, perhaps because of this, the risk for acute myocardial infarction and coronary thrombosis[13]. LA consumption may reduce the level of high-density lipoprotein (HDL) cholesterol[14], increasing the risk for coronary heart disease (CHD) mortality. Lipid peroxidation mediated by free radicals and/or hydroxy radicals is considered associated with the activation of radical scavengers, initiation and development of atherosclerosis[15], although a better term would be atherothrombosis — to emphasize the additional roles of platelet and endothelial function in the pathological process.

The Jerusalem nutritional study[16] compared, in normal subjects, the effects of different dietary fatty acids on lipoprotein structure and function. While omega-6 vegetable oil lowered LDL cholesterol the most, it was associated with the greatest tendency to in vitro oxidation. It is too simplistic to assume that this is the only mechanism for atherosclerosis since omega-3 fatty acids also increase thiobarbituric reactive substance formation[17] yet are considered to be protective[18]. The explanation might lie in the different effects on platelet function. LA and LA hydroperoxides reduce the activity of prostacyclins in the vascular wall[19], alter the production of thromboxane B_2 and the tendency for platelet aggregation.

Another aspect of lipoprotein oxidation concerns the antioxidant status. Oral vitamin C supplementation may prolong the lag time for LDL oxidation[20]. Since ascorbic acid is hydrophilic and not present in the lipoprotein particle, this implies that its role consists in regenerating vitamin E, suggesting a biological interaction between these antioxidants as has also been shown in epidemiological studies[21].

Arrhythmogenicity

The metabolites of arachidonic acid (20:4n-6) derived from LA via the cyclooxygenase reactions may be arrhythmogenic[22]. The protective effects of omega-3 acids involve a direct membrane interaction, which is not related to incorporation or covalent linkage since it is promptly reversed by washing out with fatty acid-free medium[23]. In other experiments, fatal ventricular fibrillation in rats was significantly reduced by omega-6 (sunflower seed oil) PUFAs during ischaemia or reperfusion. This was achieved significantly better than after olive oil or saturated fat diets but not as well as with fish oil, which entirely prevented the arrhythmia[24].

These studies show the difficulties of making generalizations on specific fatty acid actions when considering the multiple pathogenetic mechanisms involved in atherosclerosis. This applies equally to carcinogenesis.

Cancer

Some reports suggest that LA potentiates tumourigenesis by providing structurally and functionally essential fatty acids for the growth of dividing cells, and by serving as precursor for eicosanoid metabolites of arachidonic acid (AA). Leukotrienes C_4 and D_4 might act as tumour-enhancing agents, and PGE_2 in turn may be involved in tumour development, promotion and immunosuppression (summarized in Reference 6). This reduces macrophage tumouricidal activity and inhibits interleukin-2 production, which activates the natural killer cell and cytotoxic T cell activity. Omega-6 fatty acids may down-regulate the surface expression of CD4 and CD8 in mice lymphocytes[25]. In rats, both alpha-linolenic and longer chain omega-3 fatty acids suppressed lymphocyte function both in vivo (graft versus host) and ex vivo[26]. In human studies, women consuming a high omega-6 PUFA diet had elevated levels of etheno (varepsilon) adducts in DNA which are generated through reaction with lipid peroxidation products[27]. Similar results were found for malonaldehyde adducts[28], while antioxidant vitamin-enriched diets caused a decrease in leukocyte 8-hydroxy-2′-deoxyguanosine (8-OHdG) in normal subjects[29]. Furthermore, increased levels of PGE_2 have been associated with aggressive growth patterns of both basal-cell and squamous-cell skin carcinoma in humans[30]. In contrast, factors inhibiting the cyclooxygenase enzyme system, such as indomethacin, piroxicam or the spice cumin,

have been reported to reduce the incidence of experimental colonic cancers[31]. Similarly, blocking the lipoxygenase pathway with esculetin suppressed PC3 prostate cancer cells or mastocytoma cells in culture[32]. Certain tumours also augment the formation of eicosanoids by enhancing phospholipase A_2 activity via epidermal or transforming growth factors. The AA thus released enters the AA cascade as a precursor for eicosanoids via cyclooxygenase and lipoxygenase enzyme systems, or to tumours for their own production of prostaglandins[33].

Translating these animal and experimental studies into the clinical situation requires knowledge of the long-term habitual diet. The evidence required to link diet and disease may be assessed at a number of different levels. Work in cell culture (in vitro 'feeding') and animals may suggest possible biological mechanisms for findings from epidemiological/geographical studies. However, these relationships suggest association rather than causality, which is also the limitation of case-control retrospective studies. Cohort studies are prospective and more reliable. However, dietary studies are notoriously difficult to evaluate because of the extended time-scale of the exposure and the lack of suitable instruments for assessing the long-term habitual dietary intake in the absence of objective biomarkers. An example of such confusion is provided in the field of carcinoma of the breast, where most animal and case-control studies suggest a relationship between fat and cancer[34], while cohort studies (meta-analysis) fail to do so[35]. An answer, therefore, has to await a long-term dietary intervention randomized control trials with all their difficulties of compliance[36]. However, work on animals suggests an alternative explanation, in that it is total energy intake which is of more relevance than the type or quantity of fat ingested[37].

A possible way to study the association between fat and cancer is through the use of adipose tissue fatty acid composition. Since the omega-6 and omega-3 fatty acids are essential, their presence must be entirely derived from the diet. We have conducted studies in small groups of patients. In patients with cancer of the breast and colon no significant differences were found in the LA content of storage fat between cases and controls[38,39]. However, in another study, higher linoleate to arachidonate concentrations were found in gynaecological tumours[40], perhaps indicating decreased insulin sensitivity[41]. In healthy subjects, more 'abnormal' in vitro immune function test results occurred at both extremes of LA dietary intake, 12·7% and 21·5%[42].

Insulin resistance

Omega-6 fatty acids may increase the secretion of insulin, and/or reduce insulin catabolism[43], causing impaired insulin action[44] and leading progressively to insulin resistance[4], which determines accelerated atherosclerosis[45]. Insulin activates the enzyme phospholipase A_2, which hydrolyses membrane phospholipids to generate free PUFA. These are substrates for eicosanoid formation via the cyclo-oxygenase and lipoxygenase pathways, during which processes free radical are generated which may enhance lipid peroxidation. The roles of free radicals and lipid peroxidation in cancer aetiology[47] and atherosclerotic processes have been documented extensively. The same relationships hold for eicosanoids formed from dietary omega-6 lipids affecting thrombosis, vasospasm, arrhythmia and chronic inflammatory processes[48]. In the absence of adequate insulin activity there is a relative decrease in the conversion of LA to AA[41]. Studies have shown that AA is inversely related to both Hb A1c concentrations, as well as to the degree of diabetic complications[49]. There is also a correlation between AA and insulin sensitivity in muscle biopsies[50]. In summary, there appears to be a reciprocal relationship between insulin and the omega-6 fatty acid pathway; these fatty acids impair insulin activity which in turn regulates their metabolic conversions.

The optimal omega-6:omega-3 ratio

The hyperinsulinaemia and insulin resistance which may be aggravated by a high omega-6 intake may be prevented by fish oils containing omega-3 fatty acids[51]. A number of studies link a high dietary omega-6:omega-3 ratio with an increased risk of diabetes, cardiovascular disease and pathophysiological mechanisms impairing insulin activity. Omega-3 fatty acids alleviate many of the metabolic abnormalities associated with the insulin-resistance syndrome — obesity[52], hypertension[53], and hypertriglyceridaemia (summarized in Reference 54). The competition between the two pathways of essential fatty acids is very difficult to untangle biologically. Thus it is not known with any confidence in what proportions C20 and C22 long-chain fatty acids will be produced from a given mixture of linoleic and alpha-linolenic acids fed to any animal[7]. Also, the efficiency of the conversion in man of the C18 precursors (linoleate and alpha linolenate) to the long-chain highly unsaturated omega-6 and omega-3 fatty acids needs to be established. This would answer the question whether linseed oil or perilla oil (say) would be adequate substitutes for fish oil in the diet and provide the same biological benefits.

Epidemiological evidence for the use of the ratio is provided by Raheja and colleagues[55]. They reported a sharp increase in the prevalence of NIDDM and coronary artery disease in the upper socio-economic classes in India after the adoption of diets high in total fat, with high concentrations of omega-6 fat and a high omega-6:omega-3 ratio in lipids. There are, however, other confounding explanations to the increase in these 'self-inflicted' (or 'diaetagenic', from the Greek word for life-style) diseases related to, say, obesity and physical activity. Another example is the low incidence of breast cancer observed in Greenland Inuits despite eating a relatively high-fat diet, and also in Japanese women on

their traditional diet, which contains fats derived from marine sources, rich in omega-3 PUFAs. Thus, the ratio of the two fatty acids in the diet may be important and it would seem to be on the increase when compared with the diet of the past. Mesolithic men had a diet ratio of omega-6:omega-3 of 1–4:1[56]; the European diet reaches 10–14:1[57], and the Israeli present average ratio is approximately 22–26:1, as can be assumed from studies of subcutaneous fatty acid composition[39]. However, the concept of a omega-6:omega-3 ratio, although discussed extensively[6,56], may not be the best way to describe the relationship[8].

The above considerations suggest that a reductionist (single nutrient) approach to nutritional recommendations may not be appropriate when considering fatty acids. They have to be considered in terms of their biological function in relation to other nutrients (integrationist approach)[58] — the omega-3 fatty acid series and relevant antioxidants. Therefore, it may not be possible, at present, to give dietary advice other than to recommend the regular consumption of cold-water fish as part of a balanced diet in which attention to lifestyle and the quantities eaten are of far more importance than the type of fatty acid consumed.

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