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 suggests 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.

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.
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-linoleic 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[17,19]. 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 atherothrombosis — to emphasize the additional roles of diastolic potential and endothelial function in the pathological process.

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[19,20], alter the production of thromboxane B2 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].

Cancer

Some reports suggest that LA potentiates tumorigenesis 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 C4 and D4 might act as tumour-enhancing agents, and PGE2 in turn may be involved in tumour promotion, prevention 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[225]. In rats, both alpha-linolenic and longer chain omega-3 fatty acids suppressed lymphocyte function both in vivo (graft versus host) and ex vivo[226]. In human studies, women consuming a high omega-6 PUFAs diet had elevated levels of etheno (varepsilon) adducts in DNA which are generated through reaction with lipid peroxidation products[227]. Similar results were found for malonaldehyde adducts[228], while antioxidant vitamin-enriched diets caused a decrease in leukocyte 8-hydroxy-2'-deoxyguanosine (8-OHdG) in normal subjects[229]. Furthermore, increased levels of PGE2 have been associated with aggressive growth patterns of both basal-cell and squamous-cell skin carcinoma in humans[230]. In contrast, factors inhibiting the cyclooxygenase enzyme system, such as indomethacin, piroxicam or the spice curcumin,
have been reported to reduce the incidence of exper-
imental 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 eico-
sanoids 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 pro-
spective 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 con-
trols\[^{38,39}\]. However, in another study, higher linoleate
to arachidonate concentrations were found in gynaeco-
logical 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\[^{45}\], which determines accelerated
atherosclerosis\[^{46}\]. Insulin activates the enzyme phos-
pholipase A\(_2\), which hydrolyses membrane phospho-
lipids to generate free PUFA. These are substrates for
eicosanoid formation via the cyclo-oxgenase and
lipoxygenase pathways, during which processes free
radical are generated which may enhance lipid peroxi-
dation. The roles of free radicals and lipid peroxida-
tion 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 pre-
vented 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 linoleate 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 estab-
lished. 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 cor-
onary 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

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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[10]; the European diet reaches 10–14:1[11], and the Israeli present average ratio is approximately 22–26:1, as can be assumed from studies of subcutaneous fatty acid composition[12]. However, the concept of a omega-6:omega-3 ratio, although discussed extensively[13–14], may not be the best way to describe the relationship[15].

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 integrationist approach to recommend the regular consumption of cold-water fish as part of a balanced diet in which attention is paid to saturated vs unsaturated fatty acids and indices of oxidative stress in human volunteers. Eur J Clin Nutr 1999; 53: 523–8.[16] Berry EM, Dalmaso L, Franceschi S. Synergism between vitamins E and C: biological implications for future research. Int J Cancer 1999; 83: 288.


