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Review

Omega 3 – Omega 6: What is right for the liver?☆

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Linoleic and α-linolenic acids are the fatty acids designated as "essential" since they are not synthesized by mammalian cells and must be provided in the diet. The recent dietary shift towards the consumption of *n*-6 (omega-6) at the expense of *n*-3 (omega-3) polyunsaturated fatty acids (PUFAs) is thought to be a primary cause of many diseases related to the Western diet. The body converts linoleic acid to arachidonic acid and derives eicosapentaenoic acid from α-linolenic acid. Ideally the effects of these fatty acids and their eicosanoid derivatives are tailored to the specific biological needs of the body. The balance between *n*-3 and *n*-6 PUFAs is essential for metabolism and maintenance of the functions of both classes. The availability of *n*-3 long chain PUFAs plays a major role in regulating both fat accumulation and its elimination by the liver. Derangement of hepatic *n*-6:*n*-3 PUFA ratio impacts on the histological pattern of fatty liver through modulation of the amount of intrahepatic lipids. Moreover, the influence of PUFAs and their eicosanoid products on hepatic microcirculation and ischemia/reperfusion injury has been demonstrated in many studies. This concise review article will focus on the role of PUFAs and eicosanoids in hepatic steatosis, microcirculation and ischemia/reperfusion injury.

***Keywords*: Omega-3 fatty acids; Fatty liver; Macro- and microvesicular steatosis; Ischemia/reperfusion; Eicosanoids**

1. What are essential and polyunsaturated fatty acids?

Fat is increasingly recognized as a central feature of many biological processes. Dietary fat may influence a variety of physiological events in the human body and thereby could impact on the pathogenesis of various diseases [1]. Properties of fat are influenced by fatty acid components. Fatty acids are categorized into either saturated or unsaturated, respectively, depending on absence or presence of a carbon-to-carbon double bond. Unsaturated fatty acids are further divided into 2 subgroups: monounsaturated fatty acids containing only one double bond and polyunsaturated fatty acids (PUFAs) which harbor two or more double bonds [2]. Common monounsaturated fatty acids include palmitoleic and oleic acids. PUFAs are classified according to the original fatty acids from which they are synthesized into two distinct families, namely *n*-6 (omega-6) PUFAs, which derive from linoleic acid and *n*-3 (omega-3) PUFAs, which come from α-linolenic acid (Table 1) [3]. Contrary to other fatty acids, linoleic and α-linolenic acids cannot be synthesized *de novo* by mammalian cells; therefore they are termed "essential" and must be obtained in adequate amounts from diet. The main sources of linoleic acid include cereals, eggs, animal fat, whole-grain breads and sunflower and corn oils. α-Linolenic acid is present in abundant amounts in leafy green vegetables, walnuts and canola, flaxseed and rapeseed oils. Marine foods represent good sources for the *n*-3 long chain PUFAs such as eicosapentaenoic and docosahexaenoic acids [2,4].

Essential fatty acids constitute an important component of all cell membranes and influence membrane

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Abbreviations: DNA, deoxyribonucleic acid; LT, leukotriene; PG, prostaglandin; PUFA, polyunsaturated fatty acid; TNF, tumor necrosis factor; TX, thromboxane.

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Table 1
Fatty acids

Category	Trivial name	Omega-references
Saturated FAs	Lauric acid	12:0
	Myristic acid	14:0
	Palmitic acid	16:0
	Stearic acid	18:0
MUFAs	Palmitoleic acid	16:1 ω-9
	Oleic acid	18:1 ω-9
n-6 PUFAs	Linoleic acid[a]	18:2 ω-6
	γ-Linolenic acid	18:3 ω-6
	Dihomo-γ-linolenic acid	20:3 ω-6
	Arachidonic acid	20:4 ω-6
n-3 PUFAs	α-Linolenic acid[a]	18:3 ω-3
	Eicosapentaenoic acid	20:5 ω-3
	Docosahexaenoic acid	22:6 ω-3

Any fatty acid (FA) has a carboxylic acid at one end and a methyl group with its carbon atom named omega (ω), the last letter of the Greek alphabet, at the other end. The omega reference system defines first the number of carbon atoms and the number of double bonds, separated by (:). When the closest double bond to the omega carbon is e.g. 3 carbon atoms away, the fatty acid is called omega (ω) or (*n*)-3.
[a] Essential fatty acid, MUFAs, monounsaturated fatty acids; PUFAs, polyunsaturated fatty acids (modified from: Stulnig TM. Int Arch Allergy Immunol 2003;132:310–321).

fluidity and the behavior of membrane-bound enzymes and receptors [4]. Borkman et al. [5] demonstrated in a group of patients undergoing coronary bypass surgery as well as in healthy controls that variations in insulin sensitivity are related to differences in the cell membrane content of long chain PUFAs within skeletal muscle phospholipids. In rats, activation of phospholipase A2, e.g., by ischemia/reperfusion induces break down of membrane phospholipids and the release of free fatty acids from the cell membrane lipid pool [6]. In turn, certain PUFAs are utilized for the formation of various eicosanoids [3]. Essential fatty acids have antibiotic-like actions; for instance, α-linolenic acid rapidly kills *Staphylococcus aureus* [7]. Moreover, *n*-3 PUFAs modulate the action of probiotics (e.g., *Lactobacillus paracasei*) in the jejunal mucosa of gnotobiotic piglets [8]. PUFAs suppress proinflammatory cytokines such as interleukins, and tumor necrosis factor (TNF) and thus function as endogenous antiinflammatory molecules [3]. Schmocker et al. [9] have recently provided evidence for inflammation-dampening effects of *n*-3 PUFAs in liver of transgenic fat-1 mice. These mice express a *Caenorhabditis elegans* desaturase endogenously; therefore they are able to form *n*-3 PUFAs from *n*-6 PUFAs. Feeding the fat-1 mice a diet rich in *n*-6 and low in *n*-3 PUFAs resulted in significant enhancement of hepatic content of *n*-3 PUFAs, lowering of *n*-6: *n*-3 PUFA ratio and alleviation of chemically induced acute hepatitis compared with their wild type littermates. The decreased inflammatory response in fat-1 mice was associated with significantly reduced hepatic gene expression of TNF-α, interleukin-1β, interferon-γ and interleukin-6.

Linoleic and α-linolenic acids are metabolized to their respective metabolites by alternate desaturation-elongation reactions by the same set of Δ^5 and Δ^6 desaturases and elongases. Depending on the initial substrate (linoleic or α-linolenic acids) different classes of eicosanoids are generated. A simplified overview of eicosanoids' synthesis from PUFAs is shown in Fig. 1 [3,10]. Many factors are involved in the regulation of Δ^5 and Δ^6 desaturase activity. For instance, low Δ^6 desaturase activity was reported in diabetic [11] and hypertensive rats [12]. Other experiments on rats demonstrated that hormones e.g. glucagon, epinephrine, glucocorticoids and thyroxin depress Δ^5 and Δ^6 desaturase activity whereas insulin is a well-known Δ^6 desaturase stimulator [11]. In micropigs, chronic alcohol consumption reduces the actions of both desaturases [13]. Lopez Jimenez et al. [14] demonstrated a reduction of Δ^6 desaturase activity in heart microsomes associated with aging in rats. In humans, obesity decreases the metabolism of essential fatty acids due to reduced activities of desaturases [15]. Studies on animals and humans demonstrated that the gender-related difference in Δ^5 and Δ^6 desaturase activity is possibly mediated by sex hormones [16–18]. Normally, Δ^5 and Δ^6 desaturases and elongases exhibit affinity to metabolize *n*-3 more than *n*-6 PUFAs provided that both exist in the physiological ratio of 1: 1–4 [4,10].

In Western diets, the ratio of *n*-6 to *n*-3 PUFAs ranges from 15–16:1 instead of the presumably healthy range of 1–4: 1 [10]. This imbalance can be corrected by ingestion of eicosapentaenoic and docosahexaenoic acids, which partially replace the *n*-6 PUFAs especially arachidonic acid from cell membranes of platelets, erythrocytes, neutrophils, monocytes and hepatocytes [19]. The Δ^5 and Δ^6 desaturases and elongases tend to metabolize *n*-3 PUFAs and therefore their eicosanoid products are maintained in balance with those derived from *n*-6 PUFAs. The Δ^5 desaturase has a limited activity to convert dihomo-γ-linolenic acid to arachidonic acid. Therefore the synthesis of the antiinflammatory

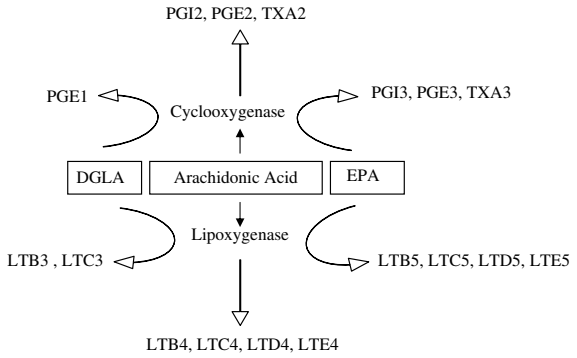

Fig. 1. Eicosanoid synthesis from dihomo-γ-linoleic acid (DGLA), arachidonic acid and eicosapentaenoic acid (EPA). LT, leukotriene; PG, prostaglandin; TX, thromboxane (modified from: Simopoulos AP. World Rev Nutr Diet 2003;92:1–22).