ELSEVIER

Journal of Hepatology 47 (2007) 718–725

Journal of Hepatology

www.elsevier.com/locate/jhep

Review

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

Ashraf Mohammad El-Badry, Rolf Graf, Pierre-Alain Clavien*

Swiss HPB (Hepato-Pancreatico-Biliary) Centre, Department of Visceral and Transplant Surgery, University Hospital Zurich, Ramistrasse 100, CH-8091, Zurich, Switzerland

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

Associate Editor: C.P. Day

☆ The authors declare that they have nothing to disclose concerning funding or conflict of interest.

* Corresponding author. Tel.: +41 44 255 3300; fax: +41 44 255 4449.

E-mail address: Clavien@chir.unizh.ch (P.-A. Clavien).

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

0168-8278/$32.00
doi:10.1016/j.jhep.2007.08.005

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

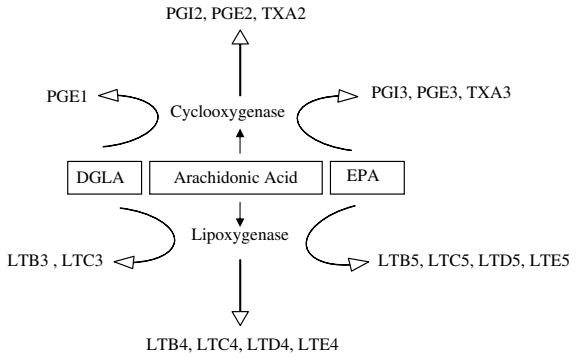

Fig. 1. Eicosanoid synthesis from dihomo-γ-linoleic acid (DGLA), arachidonic acid and eicosapentaenoic acid (EPA). LT, leukotriene; PG, prostaglandin; TX, thromboxane (modified from: Simopoulos AP. World Rev Nutr Diet 2003;92:1–22).

eicosanoids derived from dihomo-γ-linolenic acid can overcome the effects of the proinflammatory arachidonic acid-derived eicosanoids [20]. Nevertheless, in the presence of large amounts of dietary *n*-6 PUFAs, the eicosanoids derived from arachidonic acid are synthesized in larger quantities than those from eicosapentaenoic acid. The arachidonic acid-derived eicosanoids are biologically active even in small quantities. In high concentrations they contribute to the formation of thrombi and the development of inflammatory disorders [19]. Dietary supplementation with eicosapentaenoic and docosahexaenoic acids is associated with a reduced production of thromboxane A2 (TXA2), a potent platelet aggregator and vasoconstrictor, and leukotriene B4 (LTB4), a powerful inducer of inflammation and leukocyte chemotaxis and adherence. Concomitantly TXA3, a weak platelet aggregator and vasoconstrictor is increased. Moreover, they increase concentrations of PGI3, without decreasing PGI2 (both PGI2 and PGI3 are active vasodilators and inhibitors of platelet aggregation) and increase concentrations of LTB5, a weak inducer of inflammation and chemotaxis. Thus, high intake of *n*-6 PUFAs shifts the physiological state to one that is proinflammatory and prothrombotic with increases in blood viscosity, vasospasm, and vasoconstriction. In contrast, *n*-3 PUFAs yield antiinflammatory, antithrombotic, vasodilatory and hypolipidemic properties [19,21–24]. In addition, *n*-3 PUFAs have a negative regulatory influence on hepatic lipogenesis [25].

2. What is the contribution of PUFAs to the development of fatty liver?

Inadequate dietary intake of α-linolenic acid, an imbalance with linoleic acid or defective desaturation and elongation are known factors that influence metabolism of *n*-3 PUFAs. In the presence of one or more of these factors, production of α-linolenic acid long chain derivatives is decreased [10]. *n*-3 PUFAs impact on hepatic lipid homeostasis through their actions on the transcription factors and enzymes which have a major role in fatty acid metabolism and fat accumulation in the liver. For instance, *n*-3 PUFAs downregulate the transcription factor sterol regulatory element binding protein-1 (SREBP-1) [25,26] and decrease the DNA binding of nuclear factor-Y (NF-Y) [27]. SREBP-1 upregulates lipogenic genes, e.g., fatty acid synthase (FAS) and stearoyl Co-A desaturase-1(SCD-1) and therefore promotes triglyceride accumulation in the liver [28]. The availability of NF-Y is crucial for transcription of FAS [27]. Moreover, mutating NF-Y inhibits the SREBP-1-mediated suppressive effect of *n*-3 PUFAs on FAS [29]. On the other hand, *n*-3 long chain PUFAs up-regulate peroxisomal proliferator activated receptor-α (PPAR- α) [26] which stimulates hepatic fatty acid oxidation [30] and increases transcription of fatty acid degradation genes, e.g., mitochondrial carnitine palmitoyl transferase-1 (CPT-1) and peroxisomal acyl-CoA oxidase (ACO) [26,30]. PPAR-α activation increases the secretion of apolipoprotein B-100 (apo B-100), the main structural protein of the very low density lipoprotein and upregulates the expression of liver fatty acid binding protein (LFABP) which is essential for the secretion of apo B-100 [31,32]. Therefore, reduced availability of *n*-3 long chain PUFAs favors fatty acid and triglyceride synthesis over fatty acid degradation, and ultimately results in fat accumulation in the liver (Fig. 2). Since enhancement of triglyceride deposition in the liver correlates with increased fat droplet size [33] it is reasonable to suggest that the reduction of hepatic content of *n*-3 PUFAs and/ or interference with their beneficial biological effects by a high *n*-6: *n*-3 PUFAs ratio might be implicated in the development of macrosteatosis.

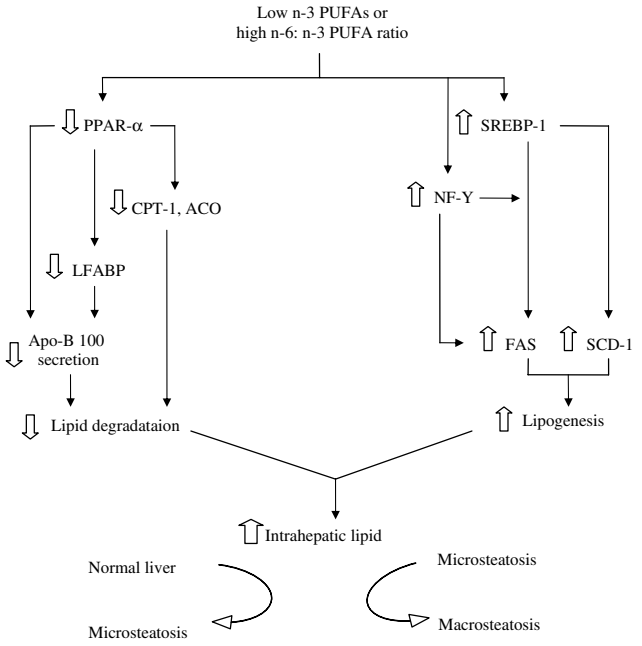

Fig. 2. PUFA-mediated lipid accumulation in the liver which possibly influences the histological pattern of hepatic steatosis. ACO, acyl-CoA oxidase; apo B-100, apolipoprotein B-100; CPT-1, carnitine palmitoyl transferase-1; FAS, fatty acid synthase; NF-Y, nuclear factor-Y; PPAR-α, peroxisome proliferator activated receptor-α; SCD-1, stearoyl Co-A desaturase-1; SREBP-1, sterol regulatory element binding protein-1.

3. How do PUFAs influence micro- versus macrosteatosis?

Steatosis is characterized qualitatively into two categories, micro- and macrovesicular steatosis [34]. The histological lesion in microsteatosis consists of fatty microvesicles, measuring less than 1 μm and filling the hepatocyte cytoplasm, while the nucleus remains cen-

trally located. In contrast, in macrosteatosis hepatocytes contain one single large vacuole of fat, which displaces the nucleus to the periphery of the cell [34,35]. High degrees of macrovesicular change in hepatocytes are known risk factors for complications after liver resection or transplantation. Grafts with severe macrosteatosis are associated with a significant risk of primary poor function [36,37] whereas a safe use of grafts containing high degrees of microsteatosis has been reported [38].

Our mouse models of fatty liver have not disclosed a pure pattern of micro- or macrosteatosis. A mixture of both histological forms with predominance of one pattern was found in each model [39] and correlated with the *n*-6: *n*-3 PUFA ratio [40]. Urena et al. [41] reported in a study on microscopic observations of 83 donor livers that there are two types of steatotic patterns, a high-grade microsteatosis and combined micro- and microsteatosis with no pure macrosteatosis. Singer et al. [42] further demonstrated that a link may exist between *n*-3 PUFAs and hepatic steatosis. They reported increased fat droplet size in fatty livers of diabetic patients in association with reduced hepatic content of eicosapentaenoic acid, and vice versa.

Macrosteatosis constitutes a feature of nonalcoholic fatty liver disease which is characterized by the accumulation of triglycerides in the liver together with reduced hepatic content of *n*-3 long chain PUFAs and an abnormally high *n*-6: *n*-3 PUFA ratio [43,44]. On the other hand, microvesicular steatosis was originally described in association with conditions which share a number of biochemical and a limited number of clinical features such as acute fatty liver of pregnancy, Reye's syndrome and valproate toxicity. These conditions are typically listed as "microvesicular fat diseases". In many instances the primary defect in microsteatosis is a mitochondrial malfunction including inhibition of the mitochondrial beta oxidation of fatty acids [35].

Alwayn et al. [45] showed in ob/ob mice that *n*-3 PUFA supplementation results in conversion of hepatic macro- to microsteatosis with change of *n*-6: *n*-3 PUFA ratio to approach that of lean livers. Similarly, in a rat model of fatty liver, dietary supplementation with eicosapentaenoic acid significantly reduced intrahepatic lipid accumulation and decreased the percentage of large fat droplets [46]. We investigated the influence of *n*-3 PUFAs on histological type of steatosis in two mouse models of fatty liver. C57/Bl6 mice fed a choline deficient diet were used as a model of microvesicular steatosis. Of note, the choline deficient diet is supplemented with methionine; therefore we did not observe manifestations of steatohepatitis. Ob/ob mice were used as a model of predominantly macrovesicular hepatic steatosis [40]. Lean and microsteatotic livers disclosed almost identical *n*-6: *n*-3 PUFA ratio of 4:1, whereas those with macrosteatosis had a ratio of 9:1. A second group of ob/ob mice was supplemented with dietary *n*-3 PUFAs and compared with control diet fed group. Dietary *n*-3 PUFA resulted in normalization of *n*-3: *n*-6 PUFA ratio, reduced intrahepatic lipid content and the extent of macrosteatosis [40]. Araya et al. [44] reported in a study on 19 patients with nonalcoholic fatty liver disease that liver phospholipids contained higher *n*-6 and lower *n*-3 long chain PUFAs with a significantly raised *n*-6: *n*-3 PUFA ratio in comparison with normal livers. Only one uncontrolled study has shown that prolonged supplementation of patients with nonalcoholic fatty liver disease with *n*-3 PUFAs improves biochemical and ultrasonographic features of liver steatosis. Patients treated with *n*-3 PUFAs had significantly decreased serum transaminases and triglycerides in comparison with controls. Circulating arachidonic acids and *n*-6:*n*-3 PUFA ratio were also reduced in treated patients. Ultrasonography demonstrated improvement of liver echotexture after *n*-3 PUFA supplementation whereas no significant changes occurred in controls [47].

4. Do PUFAs impact on hepatic microcirculation and ischemia/reperfusion injury?

Steatosis of the liver is common in Western countries. We found variable degrees of hepatic steatosis in approximately 50% in a series of patients scheduled for hepatectomy [48]. Hepatic steatosis was reported in 25% of donors scheduled for liver transplantation [49]. Transplantation of steatotic livers is associated with a high risk of primary dysfunction and nonfunction [50–53]. Although hepatic steatosis is an established and highly prevalent risk factor for surgery, little is known about the mechanisms of injury related to steatosis. In animal experiments, steatosis is associated with decreased adenosine triphosphate (ATP) production and a disturbance of sinusoidal flow. Further contributing factors may include Kupffer cell dysfunction and leukocyte adhesion [34].

Our group demonstrated significantly higher hepatocyte damage in the macrosteatotic livers after ischemia/reperfusion which was related to a reduced intrahepatic and portal vein perfusion [39]. In a rat model of hepatic steatosis, Kurihara et al. [46] reported that eicosapentaenoic acid supplementation improves blood flow in the liver via reduction of TXA2 synthesis and enhancement of deformability of red blood cells.

Fish oil, which contains *n*-3 long chain PUFAs, reduced hepatic reperfusion injury in a low flow, reflow perfusion model in the rat. Following reperfusion, the rise of portal pressure was markedly minimized with significant reduction in trypan blue distribution time indicating improved microcirculation [54]. A controversy is raised from the study of Lo et al. [55] which stated that dietary supplementation of rats with fish oil does not attenuate hepatic injury after warm ischemia/reperfusion.

Fish oil was administered for a short period of 5 days. Since *n*-3 PUFA content in the liver was not documented, it is unclear whether *n*-3 PUFAs were adequately accumulated in the liver.

We recently studied the impact of dietary supplementation with *n*-3 PUFAs on ischemia/reperfusion injury in a model of macrosteatosis in the mouse liver [40]. We demonstrated significant baseline microcirculatory defects associated with macrosteatosis as evidenced by reduced functional sinusoidal density in comparison with lean and microsteatotic livers. After warm ischemia/reperfusion, we observed significantly more pronounced hepatic damage in macrosteatotic compared with lean and microsteatotic livers. Dietary supplementation of ob/ob mice with *n*-3 PUFAs resulted in amelioration of microcirculation before ischemia and a dramatic improvement after reperfusion [40].

5. How do eicosanoids influence hepatic ischemia/reperfusion injury?

Eicosanoids are derived from dihomo-γ-linolenic, arachidonic and eicosapentaenoic acids (Fig. 1). These long chain PUFAs are released from cell membranes by the action of phospholipase A2. The availability of free dihomo-γ-linolenic, arachidonic and eicosapentaenoic acids is the rate-limiting step in the synthesis of the corresponding eicosanoid derivatives. These precursors are converted to eicosanoids by the cyclooxygenase and the lipoxygenase enzymatic pathways. The major products of the cyclooxygenase pathway are prostaglandins and thromboxanes while leukotrienes are synthesized by lipooxygenases [2,3]. Derangement of omega-6:omega-3 PUFA ratio could influence the synthesis of various eicosanoids.

Prostaglandin E1 (PGE1) confers protection after reperfusion through a variety of mechanisms including improvement of liver perfusion [56], inhibition of leukocyte adhesion and reduction of expressing the intracellular adhesion molecule-1 (ICAM-1) on the vascular endothelium [57]. PGE1 decreased the oxidative stress-induced hepatocyte injury in cultured rat hepatocytes treated with *tert*-butyl hydroperoxide [58]. Further, PGE1 protected cultured human liver sinusoidal endothelial cells from apoptosis through inhibiting the release of inducible nitric oxide synthase and matrix metalloproteinases [59]. In a model of warm ischemia/ reperfusion in dogs, PGE1 ameliorated hepatic injury through enhancement of prostacyclin (PGI2) production and suppression of thromboxane A2 (TXA2) [60]. In another model of hepatic ischemia/reperfusion injury in the rat, intraportal infusion of PGE1 dramatically improved portal venous flow and peripheral liver tissue blood flow [61]. Furthermore, PGE1 was also able to improve survival in a canine model of ischemia/reperfusion injury [62]. The beneficial effects of PGE1 in ameliorating hepatic microcirculation after reperfusion were documented in a model of cirrhotic liver in the rats [63].

The release of another protective prostaglandin, PGE2 from Kupffer cells, the major cellular source of PGs, is temporarily suppressed after ischemia/ reperfusion, possibly contributing to hepatocyte damage after reperfusion [64]. An interaction has been observed between tumor necrosis factor-α (TNF-α) and PGE2. TNF-α increases the production of PGE2 from macrophages, which in turn inhibits TNF-α synthesis (negative loop) [65,66].

The pivotal role of TXA2 in hepatic ischemia/reperfusion injury has been reported in many studies. In a rat model of ischemia/reperfusion, selective TXA2 synthase inhibitor and specific TXA2 receptor antagonist protected the sinusoidal lining cells, ameliorated liver necrosis, blunted serum transaminase levels, restored hepatic tissue blood flow and improved survival [67]. In humans, circulating TXB2 levels, a metabolite of TXA2, were remarkably increased during hepatic resection [68]. In dogs, a significant rise in plasma levels of TXB2 was observed within 24 h after hepatectomy and was associated with insufficient blood flow in the portal vein and hepatic tissue. Administration of TXA2 synthase inhibitor dramatically improved the 2-week survival rate after hepatectomy [69]. Intravenous administration of TXA2 synthase inhibitor intraoperatively in humans reduced the plasma TXB2 levels and concomitantly reduced serum AST levels [70]. In their experiments on canine liver, Kitagawa et al. [71] concluded that the spleen contributes to TXA2 hypersecretion during hepatectomy since the levels of TXB2 were significantly higher in the splenic vein compared to the levels in the mesenteric vein. It was documented in the same experiment that splenic macrophages produce more TXA2 after major hepatectomy compared with controls. Further, combined splenectomy and hepatectomy prevented remnant hepatic dysfunction. In a model of pig liver allotransplantation, pretreatment with TXA2 synthase inhibitor resulted in remarkable reduction in the serum levels of TXA2, providing a better graft function and survival rate after liver transplantation [72].

Another prostaglandin, PGI2, triggers several biological effects opposing those of TXA2. Both PGI2 and TXA2 are produced by the action of cyclooxygenase after ischemia/reperfusion injury. PGI2 reduces platelet aggregation and leukocyte adhesion to the endothelial surface [73,74]. In a rat model of hepatic ischemia/reperfusion, a prostacyclin analogue significantly reduced the microcirculatory defect after reperfusion, lessened adherent leukocytes and improved flow velocity [74].

The contribution of leukotrienes to hepatic ischemia/reperfusion injury is an issue requiring further clarifica-

tion. For instance, leukotriene B4 (LTB4) is known to be associated with liver injury like hepatitis and cirrhosis [75]. However, there are only a few studies about its role in hepatic ischemia/reperfusion injury. In rats, LTB4 inhibition had no effect on neutrophil accumulation and hepatocellular injury in spite of increased LTB4 after ischemia/reperfusion [76]. In another model of ischemia/reperfusion in rats, cysteinyl leukotrienes are generated during reperfusion with concomitant development of hepatic edema and enhanced hepatocyte damage. However, LTB4 was not increased despite a significant neutrophil infiltration [77].

6. Conclusions and perspectives

The current trend of consuming diets deficient in *n*-3 PUFAs with high *n*-6:*n*-3 PUFA ratio may contribute to many disease processes. The liver is one of the organs that might be influenced by derangement of *n*-6:*n*-3 PUFA ratio. In mice, *n*-3 PUFAs alleviate liver inflammation and reduce fat content in steatotic livers. Pretreatment with *n*-3 PUFAs significantly decreases the extent of microcirculatory failure which follows ischemia/reperfusion injury and protects against hepatocellular damage in the macrosteatotic mouse liver. Similar protection was reported in lean livers of mice pretreated with pharmacologic agents that modulate the levels of eicosanoids. In humans, the impact of *n*-3 PUFAs on hepatitis, fatty liver, hepatic microcirculation and ischemia/reperfusion injury should be thoroughly investigated.

References

[1] Lee S, Gura KM, Puder M. Omega-3 fatty acids and liver disease. Hepatology 2007;45:841–845.

[2] Bezard J, Blond JP, Bernard A, Clouet P. The metabolism and availability of essential fatty acids in animal and human tissues. Reprod Nutr Dev 1994;34:539–568.

[3] Stulnig TM. Immunomodulation by polyunsaturated fatty acids: mechanisms and effects. Int Arch Allergy Immunol 2003;132:310–321.

[4] Das UN. Biological significance of essential fatty acids. J Assoc Physicians India 2006;54:309–319.

[5] Borkman M, Storlien LH, Pan DA, Jenkins AB, Chisholm DJ, Campbell LV. The relation between insulin sensitivity and the fatty-acid composition of skeletal-muscle phospholipids. N Engl J Med 1993;328:238–244.

[6] Hamamoto I, Nemoto EM, Evans RW, Mischinger HJ, Fujita S, Murase N, et al. Rat liver lipids during ex vivo warm and cold ischemia and reperfusion. J Surg Res 1993;55:382–389.

[7] McDonald MI, Graham I, Harvey KJ, Sinclair A. Antibacterial activity of hydrolysed linseed oil and linolenic acid against methicillin-resistant staphylococcus aureus. Lancet 1981;2:1056.

[8] Bomba A, Nemcova R, Gancarcikova S, Herich R, Pistl J, Revajova V, et al. The influence of omega-3 polyunsaturated fatty acids (omega-3 pufa) on lactobacilli adhesion to the intestinal mucosa and on immunity in gnotobiotic piglets. Berl Munch Tierarztl Wochenschr 2003;116:312–316.

[9] Schmocker C, Weylandt KH, Kahlke L, Wang J, Lobeck H, Tiegs G, et al. Omega-3 fatty acids alleviate chemically induced acute hepatitis by suppression of cytokines. Hepatology 2007;45:864–869.

[10] Simopoulos AP. Importance of the ratio of omega-6/omega-3 essential fatty acids: evolutionary aspects. World Rev Nutr Diet 2003;92:1–22.

[11] Brenner RR. Nutritional and hormonal factors influencing desaturation of essential fatty acids. Prog Lipid Res 1981;20:41–47.

[12] Narce M, Asdrubal P, Delachambre MC, Gresti J, Poisson JP. Influence of spontaneous hypertension on *n*-3 delta-6-desaturase activity and fatty acid composition of rat hepatocytes. Mol Cell Biochem 1995;152:7–12.

[13] Nakamura MT, Tang AB, Villanueva J, Halsted CH, Phinney SD. Selective reduction of delta 6 and delta 5 desaturase activities but not delta 9 desaturase in micropigs chronically fed ethanol. J Clin Invest 1994;93:450–454.

[14] Lopez Jimenez JA, Bordoni A, Hrelia S, Rossi CA, Turchetto E, Zamora Navarro S, et al. Evidence for a detectable delta-6-desaturase activity in rat heart microsomes: aging influence on enzyme activity. Biochem Biophys Res Commun 1993;192:1037–1041.

[15] Medeiros LC, Liu YW, Park S, Chang PH, Smith AM. Insulin, but not estrogen, correlated with indexes of desaturase function in obese women. Horm Metab Res 1995;27:235–238.

[16] Gonzalez S, Nervi AM, Peluffo RO. Effects of estradiol and environmental temperature changes on rat liver delta 6 microsomal desaturase activity. Lipids 1986;21:440–443.

[17] Marra CA, de Alaniz MJ, Brenner RR. Effect of various steroids on the biosynthesis of arachidonic acid in isolated hepatocytes and HTC cells. Lipids 1988;23:1053–1058.

[18] Liu YW, Medeiros LC, Revesz E, O'Dorisio TM. Desaturation function does not decline after menopause in human females. Horm Metab Res 2000;32:26–32.

[19] Simopoulos AP. Essential fatty acids in health and chronic diseases. Forum Nutr 2003;56:67–70.

[20] Fan YY, Chapkin RS. Importance of dietary gamma-linolenic acid in human health and nutrition. J Nutr 1998;128:1411–1414.

[21] Goetzl EJ. Oxygenation products of arachidonic acid as mediators of hypersensitivity and inflammation. Med Clin North Am 1981;65:809–828.

[22] Samuelsson B. Arachidonic acid metabolism: role in inflammation. Z Rheumatol 1991;50:3–6.

[23] Sinclair S, Levy G. Eicosanoids and the liver. Ital J Gastroenterol 1990;22:205–213.

[24] Bogatcheva NV, Sergeeva MG, Dudek SM, Verin AD. Arachidonic acid cascade in endothelial pathobiology. Microvasc Res 2005;69:107–127.

[25] Sekiya M, Yahagi N, Matsuzaka T, Najima Y, Nakakuki M, Nagai R, et al. Polyunsaturated fatty acids ameliorate hepatic steatosis in obese mice by SREBP-1 suppression. Hepatology 2003;38:1529–1539.

[26] Levy JR, Clore JN, Stevens W. Dietary *n*-3 polyunsaturated fatty acids decrease hepatic triglycerides in Fischer 344 rats. Hepatology 2004;39:608–616.

[27] Teran-Garcia M, Adamson AW, Yu G, Rufo C, Suchankova G, Dreesen TD, et al. Polyunsaturated fatty acid suppression of fatty acid synthase (FASN): evidence for dietary modulation of NF-Y binding to the Fasn promoter by SREBP-1c. Biochem J 2007;402:591–600.

[28] Yahagi N, Shimano H, Hasty AH, Matsuzaka T, Ide T, Yoshikawa T, et al. Absence of sterol regulatory element-binding protein-1 (SREBP-1) ameliorates fatty livers but not obesity or insulin resistance in Lep(ob)/Lep(ob) mice. J Biol Chem 2002;277:19353–19357.

[29] Teran-Garcia M, Rufo C, Nakamura MT, Osborne TF, Clarke SD. NF-Y involvement in the polyunsaturated fat inhibition of fatty acid synthase gene transcription. Biochem Biophys Res Commun 2002;290:1295–1299.
[30] Kersten S, Seydoux J, Peters JM, Gonzalez FJ, Desvergne B, Wahli W. Peroxisome proliferator-activated receptor alpha mediates the adaptive response to fasting. J Clin Invest 1999;103:1489–1498.
[31] Linden D, Lindberg K, Oscarsson J, Claesson C, Asp L, Li L, et al. Influence of peroxisome proliferator-activated receptor alpha agonists on the intracellular turnover and secretion of apolipoprotein (Apo) B-100 and ApoB-48. J Biol Chem 2002;277:23044–23053.
[32] Carlsson L, Linden D, Jalouli M, Oscarsson J. Effects of fatty acids and growth hormone on liver fatty acid binding protein and PPARalpha in rat liver. Am J Physiol Endocrinol Metab 2001;281:E772–E781.
[33] Takahashi K, Hakamada K, Totsuka E, Umehara Y, Sasaki M. Warm ischemia and reperfusion injury in diet-induced canine fatty livers. Transplantation 2000;69:2028–2034.
[34] Selzner M, Clavien PA. Fatty liver in liver transplantation and surgery. Semin Liver Dis 2001;21:105–113.
[35] Hautekeete ML, Degott C, Benhamou JP. Microvesicular steatosis of the liver. Acta Clin Belg 1990;45:311–326.
[36] Urena MA, Ruiz-Delgado FC, Gonzalez EM, Segurola CL, Romero CJ, Garcia IG, et al. Assessing risk of the use of livers with macro and microsteatosis in a liver transplant program. Transplant Proc 1998;30:3288–3291.
[37] Nocito A, El-Badry AM, Clavien PA. When is steatosis too much for transplantation? J Hepatol 2006;45:494–499.
[38] Fishbein TM, Fiel MI, Emre S, Cubukcu O, Guy SR, Schwartz ME, et al. Use of livers with microvesicular fat safely expands the donor pool. Transplantation 1997;64:248–251.
[39] Selzner N, Selzner M, Jochum W, Amann-Vesti B, Graf R, Clavien PA. Mouse livers with macrosteatosis are more susceptible to normothermic ischemic injury than those with microsteatosis. J Hepatol 2006;44:694–701.
[40] El-Badry AM, Moritz W, Contaldo C, Tian Y, Graf R, Clavien PA. Prevention of reperfusion injury and microcirculatory failure in macrosteatotic mouse liver by omega-3 fatty acids. Hepatology 2007;45:855–863.
[41] Garcia Urena MA, Colina Ruiz-Delgado F, Moreno Gonzalez E, Jimenez Romero C, Garcia Garcia I, Loinzaz Segurola C, et al. Hepatic steatosis in liver transplant donors: common feature of donor population? World J Surg 1998;22:837–844.
[42] Singer P, Honigmann G, Schliack V. Decrease of eicosapentaenoic acid in fatty liver of diabetic subjects. Prostaglandins Med 1980;5:183–200.
[43] Sanyal AJ. Mechanisms of disease: pathogenesis of nonalcoholic fatty liver disease. Nat Clin Pract Gastroenterol Hepatol 2005;2:46–53.
[44] Araya J, Rodrigo R, Videla LA, Thielemann L, Orellana M, Pettinelli P, et al. Increase in long-chain polyunsaturated fatty acid *n*-6/*n*-3 ratio in relation to hepatic steatosis in patients with non-alcoholic fatty liver disease. Clin Sci (Lond) 2004;106:635–643.
[45] Alwayn IP, Andersson C, Zauscher B, Gura K, Nose V, Puder M. Omega-3 fatty acids improve hepatic steatosis in a murine model: potential implications for the marginal steatotic liver donor. Transplantation 2005;79:606–608.
[46] Kurihara T, Adachi Y, Yamagata M, Abe K, Akimoto M, Hashimoto H, et al. Role of eicosapentaenoic acid in lipid metabolism in the liver, with special reference to experimental fatty liver. Clin Ther 1994;16:830–837.
[47] Capanni M, Calella F, Biagini MR, Genise S, Raimondi L, Bedogni G, et al. Prolonged *n*-3 polyunsaturated fatty acid supplementation ameliorates hepatic steatosis in patients with non-alcoholic fatty liver disease: a pilot study. Aliment Pharmacol Ther 2006;23:1143–1151.
[48] Petrowsky H, McCormack L, Trujillo M, Selzner M, Jochum W, Clavien PA. A prospective, randomized, controlled trial comparing intermittent portal triad clamping versus ischemic preconditioning with continuous clamping for major liver resection. Ann Surg 2006;244:921–928, discussion 928–930.
[49] Miki C, Iriyama K, Mirza DF, Mayer AD, Buckels JA, Suzuki H, et al. Postperfusion energy metabolism of steatotic graft and its relation to early graft viability following liver transplantation. Dig Dis Sci 1998;43:74–79.
[50] Marsman WA, Wiesner RH, Rodriguez L, Batts KP, Porayko MK, Hay JE, et al. Use of fatty donor liver is associated with diminished early patient and graft survival. Transplantation 1996;62:1246–1251.
[51] Clavien PA, Harvey PR, Strasberg SM. Preservation and reperfusion injuries in liver allografts. An overview and synthesis of current studies. Transplantation 1992;53:957–978.
[52] Strasberg SM, Howard TK, Molmenti EP, Hertl M. Selecting the donor liver: risk factors for poor function after orthotopic liver transplantation. Hepatology 1994;20:829–838.
[53] D'Alessandro AM, Kalayoglu M, Sollinger HW, Hoffmann RM, Reed A, Knechtle SJ, et al. The predictive value of donor liver biopsies for the development of primary nonfunction after orthotopic liver transplantation. Transplantation 1991;51:157–163.
[54] Zhong Z, Thurman RG. A fish oil diet minimizes hepatic reperfusion injury in the low-flow, reflow liver perfusion model. Hepatology 1995;22:929–935.
[55] Lo CJ, Terasaki M, Garcia R, Helton S. Fish oil-supplemented feeding does not attenuate warm liver ischemia and reperfusion injury in the rat. J Surg Res 1997;71:54–60.
[56] Iwata K, Shimazu M, Wakabayashi G, Ohshima A, Yoshida M, Kitajima M. Intraportal perfusion of prostaglandin E1 attenuates hepatic postischaemic microcirculatory impairments in rats. J Gastroenterol Hepatol 1999;14:634–641.
[57] Natori S, Fujii Y, Kurosawa H, Nakano A, Shimada H. Prostaglandin E1 protects against ischemia-reperfusion injury of the liver by inhibition of neutrophil adherence to endothelial cells. Transplantation 1997;64:1514–1520.
[58] Kishimoto S, Sakon M, Umeshita K, Miyoshi H, Taniguchi K, Meng W, et al. The inhibitory effect of prostaglandin E1 on oxidative stress-induced hepatocyte injury evaluated by calpain-mu activation. Transplantation 2000;69:2314–2319.
[59] Yang H, Majno P, Morel P, Toso C, Triponez F, Oberholzer J, et al. Prostaglandin E(1) protects human liver sinusoidal endothelial cell from apoptosis induced by hypoxia reoxygenation. Microvasc Res 2002;64:94–103.
[60] Hanazaki K, Kuroda T, Kajikawa S, Amano J. Prostaglandin E1 reduces thromboxane A2 in hepatic ischemia-reperfusion. Hepatogastroenterology 2000;47:807–811.
[61] Hossain MA, Hamamoto I, Wakabayashi H, Goda F, Kobayashi S, Maeba T, et al. Experimental study of the effect of intraportal prostaglandin E1 on hepatic blood flow during reperfusion after ischaemia and hepatectomy. Br J Surg 1999;86:776–783.
[62] Totsuka E, Sasaki M, Takahashi K, Toyoki Y, Seino K, Chiba S, et al. The effects of intraportal prostaglandin E1 administration on hepatic warm ischemia and reperfusion injury in dogs. Surg Today 1995;25:421–428.
[63] Hossain MA, Izuishi K, Maeta H. Effect of short-term administration of prostaglandin E1 on viability after ischemia/reperfusion injury with extended hepatectomy in cirrhotic rat liver. World J Surg 2003;27:1155–1160.
[64] Quiroga J, Prieto J. Liver cytoprotection by prostaglandins. Pharmacol Ther 1993;58:67–91.
[65] Bachwich PR, Chensue SW, Larrick JW, Kunkel SL. Tumor necrosis factor stimulates interleukin-1 and prostaglandin E2 production in resting macrophages. Biochem Biophys Res Commun 1986;136:94–101.

[66] Kunkel SL, Spengler M, May MA, Spengler R, Larrick J, Remick D. Prostaglandin E2 regulates macrophage-derived tumor necrosis factor gene expression. J Biol Chem 1988;263:5380–5384.
[67] Shirabe K, Kin S, Shinagawa Y, Chen S, Payne WD, Sugimachi K. Inhibition of thromboxane A2 activity during warm ischemia of the liver. J Surg Res 1996;61:103–107.
[68] Shimada M, Matsumata T, Taketomi A, Shirabe K, Yamamoto K, Sugimachi K. The role of prostaglandins in hepatic resection. Prostagl Leukot Essent Fatty Acids 1994;50:65–68.
[69] Iwata M. Pathophysiology of dogs after 84% hepatectomy with emphasis on prostaglandin metabolites and the effect of a thromboxane A2 synthesis inhibitor and a prostaglandin I2 analog. Surg Today 1994;24:1056–1067.
[70] Shirabe K, Takenaka K, Yamamoto K, Kitamura M, Itasaka H, Matsumata T, et al. The role of prostanoid in hepatic damage during hepatectomy. Hepatogastroenterology 1996;43:596–601.
[71] Kitagawa M, Tanigawa K, Iwata M. The role of the spleen, especially regarding changes in both thromboxane A2 and the remnant liver dysfunction after extensive hepatectomy. Surg Today 1999;29:137–142.
[72] Yokoyama I, Kobayashi T, Negita M, Hayashi S, Yasutomi M, Katayama A, et al. Liberation of vasoactive substances and its prevention with thromboxane A2 synthase inhibitor in pig liver transplantation. Transpl Int 1996;9:76–81.
[73] Higgs GA, Cardinal DC, Moncada S, Vane JR. Microcirculatory effects of prostacyclin (PGI2) in the hamster cheek pouch. Microvasc Res 1979;18:245–254.
[74] Chen MF, Chen JC, Chiu DF, Ng CJ, Shyr MH, Chen HM. Prostacyclin analogue (OP-2507) induces delayed ex vivo neutrophil apoptosis and attenuates reperfusion-induced hepatic microcirculatory derangement in rats. Shock 2001;16:473–478.
[75] Hossain MA, Wakabayashi H, Izuishi K, Okano K, Yachida S, Maeta H. The role of prostaglandins in liver ischemia-reperfusion injury. Curr Pharm Des 2006;12:2935–2951.
[76] Hughes H, Farhood A, Jaeschke H. Role of leukotriene B4 in the pathogenesis of hepatic ischemia-reperfusion injury in the rat. Prostagl Leukot Essent Fatty Acids 1992;45:113–119.
[77] Takamatsu Y, Shimada K, Chijiiwa K, Kuroki S, Yamaguchi K, Tanaka M. Role of leukotrienes on hepatic ischemia/reperfusion injury in rats. J Surg Res 2004;119:14–20.