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Lipoproteins in inflammation and sepsis. II. Clinical aspects

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Abstract *Background:* Systemic inflammation and sepsis are accompanied by severe metabolic alterations, including insulin resistance together with increased levels of triglycerides (TGs) and decreases in high- and low-density lipoproteins. Clinical studies have clearly established a link between lipid metabolism and systemic inflammation. Lipoproteins were shown to neutralize LPS and to exert direct anti-inflammatory actions. High- and low-density lipoproteins are thus thought to be important regulators of the host immune response during endotoxemia, which may also have the potential of improving the care of patients with Gram-negative sepsis. *Discussion:* Nutritional lipids supplied during critical illness have been shown to modulate the host response to inflammation. In particular, inclusion of ω-3 fatty acids seems to have beneficial effects on cellular immunity and helps to maintain the balance between pro- and anti-inflammatory cytokines thereby preventing hyperinflammatory complications. In addition to improvements in the profile of lipid mediators generated, ω-3 fatty acids act as activating ligands of peroxisome proliferator-activated receptors and directly inhibit nuclear factor κB mediated proinflammatory signaling. We present an overview on the alterations in the metabolism of serum lipoproteins during sepsis and present data from clinical studies and discuss the significance of nutritional lipids and their role in immunomodulation with special emphasis on ω-3 fatty acids.

Keywords High-density lipoproteins · Sepsis · ω-3 Fatty acids · Fish oil · Soybean oil · Immunonutrition

Introduction

In recent decades intensive collaborative research in the fields of chronic and acute inflammatory disorders has resulted in a better understanding of the pathophysiology and diagnosis of these diseases. Modern therapeutic approaches, however, remain unsatisfactory, and shock, sepsis, and multiple organ failure (MOF) are still great challenges in intensive care medicine. Clinical studies have established a link between lipid metabolism and systemic inflammation. Insulin resistance together with increased levels of triglycerides (TGs) and decreases in high- (HDL) and low-density lipoproteins (LDL) are prominent features of these metabolic disturbances. Lipoproteins were shown to neutralize lipopolysaccharide (LPS) and to exert direct anti-inflammatory actions, as currently reviewed in detail by Murch and coworkers. Thus HDL and LDL lipoproteins are thought to be important regulators of the host immune response during endotoxemia.:

Recent research in the field of peroxisome proliferator-activated receptors (PPARs) has opened new perspectives in understanding the interplay between inflammation and lipid homeostasis and may offer additional therapeutic opportunities. Key enzymes of cellular lipid metabolism are regulated by PPARs, and LPS as well as inflammatory cytokines downregulated PPAR-isoforms

in liver and heart [1, 2]. In addition, single-nucleotide polymporphisms of the PPAR-δ gene, the predominant PPAR isoform expressed in skeletal muscle, have been demonstrated to be associated with differences in insulin sensitivity by modifying skeletal muscle glucose uptake [3]. However, whether these single-nucleotide polymporphisms are clinically relevant in the context of the systemic inflammation and sepsis has not been determined. In addition to its insulin-sensitizing effect the activation of PPAR-γ was also shown to inhibit nuclear factor (NF) κB induced transcription of proinflammatory genes [4] and a PPAR agonist improved survival in an animal model of endotoxemia [5]. Thus they seem to be attractive therapeutic tools not only in the therapy of type 2 diabetes but also during the systemic inflammation and sepsis.

The first part of this review discusses the changes in lipid metabolism and lipoprotein composition in light of results from clinical studies. As studies in subjects with insulin resistance and type 2 diabetes mellitus also show marked derangements in the regulation of reverse cholesterol transport that can in part be overcome by insulin treatment, we give special emphasis to the recent report by Mesotten and coworkers [6] who demonstrated that the improvements in morbidity and mortality obtained by intensive insulin therapy in critically ill patients are partially attributable to increases in the serum levels of LDL and HDL lipoproteins. The second part of the review discusses the impact of nutritional lipids supplied during critical illness with special emphasis on polyunsaturated ω-3 fatty acids (FA). ω-3 FA have been shown to modulate the host response to inflammation by different mechanisms. In addition to the improvements in the profile of lipid mediators generated, they act as activating ligands of PPARs.

Changes in plasma lipid profile of critically ill patients

During the course of infection significant changes in patients' serum profile of lipids, lipoproteins, and lipoprotein-associated proteins are observed [7, 8, 9, 10]. Whereas moderate (surgical) stress increases TG clearance due to an increased total body fat oxidation, serum TG levels and very low density lipoproteins (VLDL) frequently increase in septic conditions because of reduced TG hydrolysis and fat oxidation. LPS and proinflammatory cytokines such as tumor necrosis factor (TNF) α, interleukin (IL) 1, and IL-6 rapidly induce de novo FA and hepatic TG synthesis [11, 12] which may even result in a fatty liver in severely ill patients. In particular, this was a problem when therapeutic hyperalimentation was common in the care of critically ill patients in the past. At that time nutritional goals were set to limit negative nitrogen balances with up to 4,000 kcal or 1 kg glucose per day. While FA are the primary energy source of hepatocytes, the myocardium, and the skeletal muscle in the critically ill, monitored administration of lipids is crucial in the nutritional care of these patients. Plasma TG levels resulting from lipolysis or from artificial administration further depend on the efficacy by which VLDL TGs are removed from the circulation. Critical determinants of VLDL clearance are the activity of lipoprotein lipase (LPL) and the subsequent tissue uptake of remnant particles. In most surgical patients these mechanisms are not impaired or may even be accelerated and TG levels are normal or lowered [13]. High levels of endotoxin, however, as occurring in severe sepsis depress the activity of LPL leading to elevated TG plasma levels [14]. The increase in free FA induces insulin resistance and thereby contributes to elevated blood glucose levels during systemic inflammation. Diacylglycerol, an intermediate of TG metabolism, leads to sustained activation of protein kinase C (PKC) [15]. This in turn reduces insulin-mediated cellular glucose uptake by interfering with the insulin-receptor signal transduction cascade ultimately leading to reduced translocation of glucose transporter 4 (GLUT 4) to the cell surface [16, 17]. In addition, activated PKC reduced the amount of NF-κB inhibitory protein α, the physiological inhibitor of NF-κB activation [17]). Thus, increased plasma TG levels are critical determinants of inflammation-induced insulin resistance and are capable of amplifying the proinflammatory response.

In contrast to the elevations in plasma TG levels, total cholesterol, HDL and LDL cholesterol, HDL and LDL, are reduced in serum of patients with sepsis [7, 8, 18, 19, 20]. These changes occur early during the course of systemic inflammation with cholesterol content in LDL and HDL decreasing within hours and are attributed to the effects of LPS and cytokines (Fig. 1a). Whether cytokines directly inhibit enzymes involved in cholesterol synthesis is currently unknown. On the side of cholesterol catabolism it is noteworthy that LPS and cytokines inhibit both the classical and the alternative pathways of cholesterol excretion [21, 22].

During infection and inflammation there are also important changes in lipoprotein composition (Table 1), especially in the case of HDL that markedly affect HDL metabolism itself [7, 10, 23]. Normal HDL contains the apoproteins apolipoprotein (apo) A-I and apoA-II and associated enzymes and transport proteins that are essential for reverse cholesterol transportlike lecithin cholesteryl acyltransferase (LCAT), cholesteryl ester transfer protein (CETP), and phospholipid transfer protein (PLTP). HDL also carries antioxidative proteins such as paraoxonase, platelet-activating factor acetylhydrolase, protectin, transferrin, and clusterin which serve to protect membranes by scavenging radicals and inhibiting oxidation processes.

Acute-phase HDL is smaller in size and contains less esterified cholesterol, and apoA-I is replaced by serum amyloid A (SAA). SAA also displaces paraoxonase decreasing the antioxidative capacity of HDL [25, 26,

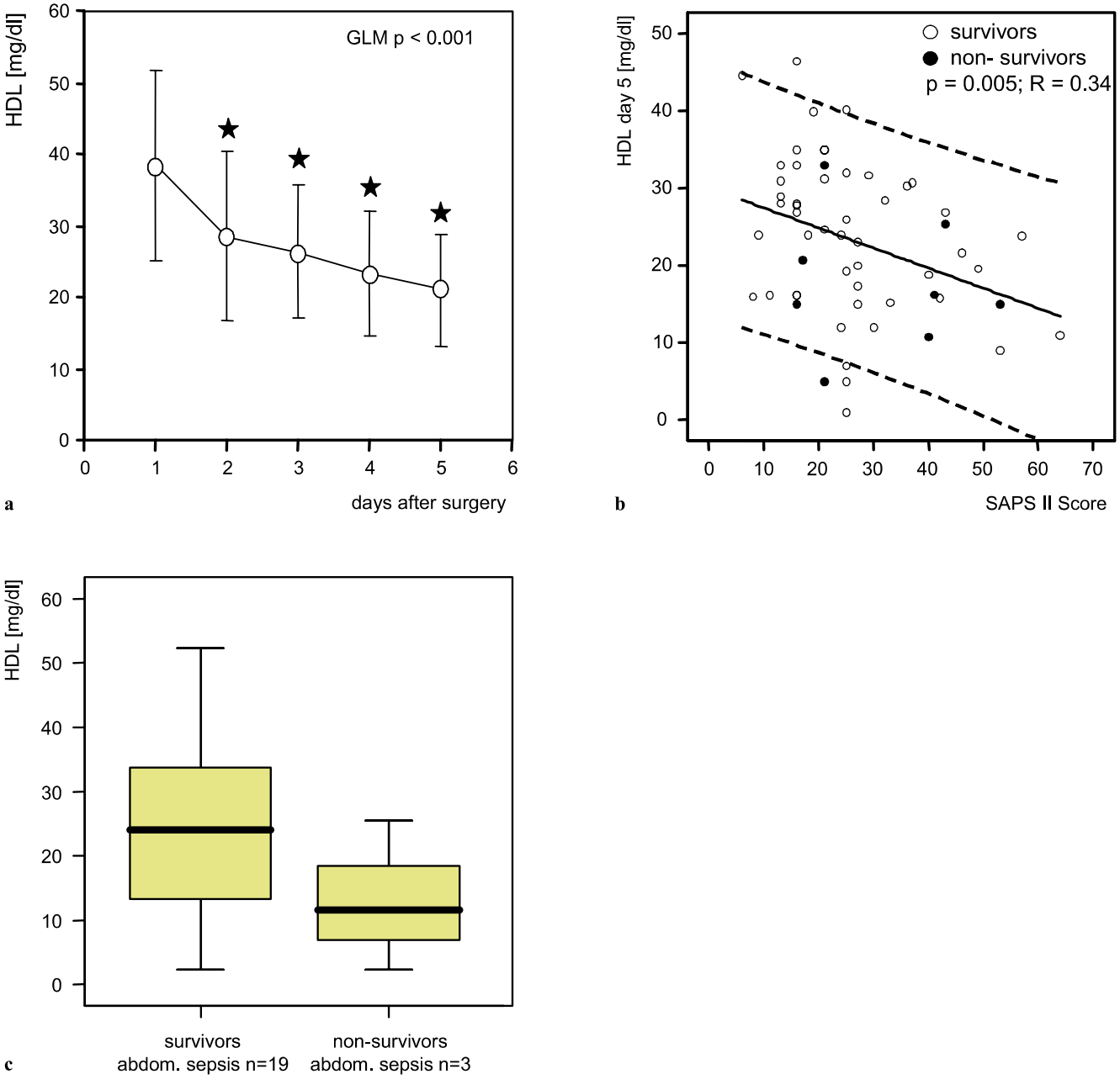

Fig. 1 **a** HDL levels (mean ± SD) in 83 severely ill patients after surgery; *$p < 0.05$ vs. day 1 (Bonferroni's adjusted GLM). SAPS II distribution see **b**. **b** Scatter plot of the SAPS II score vs. HDL on postoperative day 5; $p = 0.005$ (Spearman's rank correlation); *dotted line* individual 95% confidence interval. **c** *Open circles* Survivors; *closed circles* nonsurvivors. HDL levels in survivors and nonsurvivors in the subgroup with abdominal sepsis. (Data taken from [38], in parts unpublished)

27]. In addition, reductions in HDL-associated LCAT [28] and CETP [29] occur while apoE-containing HDL and PLTP activity were increased in serum from patients with a systemic inflammatory response, despite reduced PLTP mass [8, 9, 27]). The increased PLTP activity together with enhanced HDL TG and reduced LCAT and CETP content were shown to promote HDL conversion to pre-β-HDL with low content of esterified cholesterol and shedding of small apoA-I containing particles [8, 26]. Overexpression of human PLTP in mice has been demonstrated to enhance liver cholesteryl ester content and excretion of bile acid [30]. Finally, the inflammation-induced reduction in LPL activity also contributes to the fall in HDL cholesterol [31] as reduced amounts

Table 1 Factors, mechanisms and consequences in distinct settings

	Mechanisms	Effects	References
Moderate stress			
TG	Total body fat oxidation ↑ TG clearance ↑	TG levels ↔/↓	[7, 8, 9, 10]
VLDL	LPL activity ↔/↑ Hepatic VLDL output ↑ Uptake of remnant particles ↔/↑	VLDL ↑	[13]
Septic state			
TG, VLDL	Cytokines (TNF-α, IL-1, IL-6) LPL activity ↓ TG hydrolysis ↓ Fat oxidation ↓	De novo fatty acid and hepatic TG synthesis ↑, VLDL secretion ↑, ↑ fatty liver	[7, 8, 9, 10, 11, 12, 14, 15]
Free FA	TG synthesis ↑	Free FA ↑→ diacylglycerol ↑→ PKC ↑ PKC ↑→ GLUT-4 translocation to cell surface ↓ PKC ↑→ IκB-α ↓→ NF-κB ↑ → cellular insulin-mediated glucose uptake ↓, proinflammatory action	[15, 16, 17]
HDL, LDL	LPS, cytokines	Cholesterol synthesis ↓, LPL activity ↓, apoA-I ↓, apoA-II ↓, LCAT ↓, CETP ↓, PLTP mass ↓, PLTP activity ↑ → plasma HDL and LDL ↓ → conversion of HDL to pre-β-HDL (low in esterified cholesterol) → reverse cholesterol transport ↓ → HDL carrier function for antioxidative proteins ↓	[7, 8, 18, 19, 20, 21, 22, 25, 26, 27, 31, 32, 33, 34, 35, 36, 37]

of free cholesterol are provided to be incorporated into HDL.

In critically ill patients reductions in lipoprotein content were shown to be correlated with the severity of disease [32] and low cholesterol levels were associated with higher mortality [33] and infectious complications [34]. Reduced HDL levels were associated with poor clinical outcome in critically ill [35, 36] and burn patients [37] and negatively correlated with the length of stay in the ICU and serum concentrations of the proinflammatory cytokines TNF-α and IL-6 [36]). Our own observations (Fig. 1a–c) showed significant reduction in HDL levels in severely ill patients over time, an inverse correlation between plasma HDL and the severity of disease and lower levels of HDL in patients with sepsis who died [38]. Reductions in apoA-I serum levels were associated with systemic inflammatory response syndrome exacerbations in surgical ICU patients [39] and increased mortality in patients with severe sepsis [36]. However, these data do not allow determining whether the changes in plasma cholesterol and lipoproteins simply reflect the severity of inflammation, whether they are an epiphenomenon of other regulatory processes, or whether they are directly causative in modifying the host response to inflammation and have a direct influence on mortality. To clarify these questions data from in vitro cell culture experiments and studies in animal models of acute inflammation and sepsis are indispensable.

Impaired insulin signaling is a major feature of the metabolic disturbances during systemic inflammation and sepsis. In addition to the actions of counterregulatory hormones and catecholamines, also increased plasma TGs and free FA impair insulin signaling as outlined above.

As septic patients type 2 diabetics are characterized by increased plasma TG levels, reduced HDL content, and insulin resistance. In both sepsis and type 2 diabetes mellitus PLTP activity is elevated [8, 9, 40]. From studies in patients with type 2 diabetes mellitus it is known that insulin regulates serum lipoprotein levels. Insulin reduced plasma TG levels and lowered PLTP activity [40]. However, the latter effect was blunted under conditions of insulin resistance indicative of impaired insulin action.

Hyperglycemia per se has been demonstrated to affect reverse cholesterol transport. In vitro net cholesterol transport from fibroblasts to severely hyperglycemic plasma was impaired and the effect was reversed when blood glucose was lowered by insulin [41]. However, supraphysiological concentrations of insulin were also shown to decrease reverse cholesterol transport [42]. On the other hand, cell membrane cholesterol depletion reduced the effect of insulin on gene transcription and cell surface expression of GLUT 4 and impaired cellular glucose uptake in adipocytes [43]. Whether insulin regulates the expression of other gate-keeper proteins of cholesterol trafficking such as ATP-binding cassette transporter 1 and the scavenger receptor class B type I is currently unknown, and further research is warranted.

The importance of tight glycemic control by intensive insulin treatment in postoperative ICU patients was recently demonstrated in the randomized controlled trial of intensive insulin therapy by Van den Berghe and coworkers [44]. In a subgroup analysis of the same trial

Mesotten and coworkers analyzed patients with prolonged critical illness and an ICU stay of more than 7 days [6]. In this patient group intensive insulin treatment not only normalized blood glucose levels but also modified the serum levels of circulating lipids. In conventionally treated patients TGs increased on day 8 compared to day 1. This increase was not observed in the intensive insulin treatment group. In this group serum TG levels were significantly reduced as early as day 1. Notably, intensive insulin treatment did not affect serum TG in nonsurvivors.

Intensive insulin treatment also affected the serum levels of LDL and HDL lipoproteins. While in both treatment groups HDL levels decreased over time, this decrease was less severe in the intensive insulin treatment group. LDL serum levels were decreased on day 1 and increased on day 8. Again, patients with intensive insulin treatment exhibited higher LDL serum levels on day 8 than conventionally treated patients. While there was a nearly linear correlation between serum TGs and mortality, there seemed to be cutoff levels for both LDL (20 mg/dl) and HDL (15 mg/dl) below which mortality strongly increased. Multivariate regression analysis showed the effect of intensive insulin therapy to be independent of glycemic control and TG levels, but in part this was attributable to the effects of intensive insulin treatment on HDL and LDL serum levels.

Higher insulin dosing, possibly reflecting the severity of insulin resistance, was an independent risk factor for morbidity and mortality. Whether genetic polymorphisms, for example, in the skeletal muscle PPAR-δ determining insulin sensitivity, as recently reported by Vättinen and coworkers [3], contribute to this phenomenon is unknown. Future work in this field will probably enhance our understanding of the underlying mechanisms and help to identify specific at-risk patient subgroups and hopefully allow us to direct therapeutic strategies according to the patient's individual risk profile.

Modulation of LPS-induced inflammation by lipoproteins and apoproteins

The protective roles of lipoproteins in neutralizing LPS have been extensively studied and also direct anti-inflammatory actions such as reductions in cellular adhesion molecule and inducible nitric oxide synthase expression were reported and are reviewed in detail by Murch and coworkers in this issue.

Complexes of LPS with lipoproteins were shown to have little or no stimulatory effect on cytokine production either in vitro or in vivo [36, 45, 46, 47]. Notably, LPS-neutralization efficiency varies for lipopolysaccharides derived from different bacterial species [47]. Kitchens and coworkers [48] showed that lipoproteins are essential for the release of bound LPS from cell membranes, and that HDL is the main lipoprotein involved. Only small amounts of LPS were bound to LDL and even less to VLDL. Soluble CD14 (sCD14) accelerated the release of cell-bound LPS while lipopolysaccharide binding protein (LBP) had only a minor effect and PLTP did not affect LPS binding to HDL [49]. A role for LDL/VLDL and apoB apoprotein in binding LPS in serum has been established by Vreugdenhil and coworkers [50]. They demonstrated that the LBP in serum from both healthy individuals and patients with sepsis is bound mainly on apoB apoprotein present in LDL and VLDL and enhanced LPS binding to these lipoproteins. They also determined a tenfold higher affinity of LBP for apoB than for apoA-I. In addition to these findings, Levels and coworkers [32] reported that in plasma and lymph from patients with systemic inflammatory response syndrome and multiorgan failure, the LPS distribution shifted mainly toward LDL and not VLDL. In summary, these studies suggest that there are at least two different mechanisms of LPS neutralization, i.e., binding of free LPS in serum to apoB-containing LDL and, to a lesser extent, also VLDL lipoproteins, on the one hand, and release of cell-bound LPS from monocytes by HDL and sCD14, on the other. Interestingly, serum from patients with sepsis and severe sepsis induced a higher rate of LPS-release from monocytes than serum from normal individuals or patients with systemic inflammatory response syndrome. This occurred despite reduced HDL lipoprotein levels and was significantly correlated with the serum levels of sCD14 and other acute-phase proteins such as serum amyloid A, LBP, and serum phospholipase A_2 [49]. However, while these mechanisms are thought to prevent an exaggerated host response to LPS and are considered to be protective, the role of sCD14 is uncertain as high blood levels of sCD14 were associated with mortality in patients with Gram-negative sepsis [51].

Substitution of lipoproteins by infusion of reconstituted HDL (rHDL) has been proposed as therapeutic option. In animal models of endotoxemia the administration of rHDL decreased mortality [52, 53]. In humans the infusion of rHDL blunted endotoxin-induced procoagulant activation without adverse side effects [54]. However, the safety of rHDL administration is a concern as infusion of higher doses of rHDL has been demonstrated to promote growth of *Candida albicans* ex vivo [55] although the clinical significance of this finding is currently unknown.

One ongoing worldwide multicenter trial recruiting more than 1,800 patients with Gram-negative sepsis is attempting to establish the therapeutic efficacy of intravenous lipid administration on LPS neutralization. The proposed mechanism of action is to expand the phospholipid surface on plasma lipoproteins, for example, HDL and thereby facilitating LPS neutralization. Similar to rHDL, soy bean oil emulsions (ω-6 FA) have been claimed to be associated with infectious complications in a meta-analysis by Heyland et al. [56]. Thus the concept of administration of soybean oil as well as of rHDL seems to be double edged and must be considered cautiously, in particular in patients with suspected infection. In this

regard, lipid emulsions with a reduced content of ω-6 FA in favor of medium chain TG, olive oil, or fish oil rich in ω-3 FA may be the better choice. Recently Lekka and coworkers [57] reported that total parenteral nutrition with medium-chain and long-chain TGs aggravated lung inflammation and deteriorated gas exchange in patients with acute respiratory distress syndrome. However, the adverse effects observed in their study may at least in part be due to to the rapid infusion rate used. From animal experimental data it seems that the inclusion of ω-3 FA may be useful in attenuating lipid induced pulmonary inflammation in acute lung injury [58, 59]. In recent years apolipoprotein mimetic peptides have been developed. Based on the observation that infusion of apoA-I is protective against LPS in mice [52], Gupta and coworkers [60] studied the effects of an apoA-I mimetic peptide (L-4F) on LPS-induced inflammatory responses in vitro and in vivo. They observed reductions in monocyte adhesion to endothelial cells and reduced expression of inflammatory cytokines and adhesion molecules. They further elucidated the mechanisms involved and demonstrated that L-4F reduces the association of LPS with LBP and consecutive adhesion of the LPS-LBP complex with endothelial cell surface receptors. In addition to their effectiveness in reducing atherosclerosis as shown previously [61], apolipoprotein mimetic peptides may therefore offer a therapeutic potential in modulating the host response to LPS.

Although the LPS-neutralizing effects of lipoproteins and apolipoprotein mimetic peptides are well characterized, the significance of these mechanisms in the context of bacterial infections is not as clear. Flegel and coworkers [47] demonstrated that the LPS-neutralizing capacity of lipoproteins is not correlated with the inhibition of cytokine release induced by whole Gram-negative bacteria in vitro. Thus the efficacy of therapeutic approaches aiming at neutralizing LPS by the use of lipoproteins and apolipoprotein mimetic peptides must be evaluated carefully in the clinical setting.

Modulation of LPS-induced inflammation by oxidized phospholipids

While quantities of phospholipids present in lipoproteins do not significantly change during inflammation, they are qualitatively altered by oxidation. Increased oxidative stress during systemic inflammation and a decrease in the antioxidative capacity due to decreases in paraoxonase activity in HDL particles contribute to oxidation of phospholipids. In addition, oxidized phospholipids are also released by necrotic and apoptotic cell death [62]. Oxidated phospholipids have been demonstrated to exert proinflammatory effects and to induce IL-8 and monocyte chemotactic peptide 1 expression in endothelial cells [63]. They are considered to mediate chronic inflammatory processes and thereby to contribute to the pathogenesis of atherosclerosis. In the context of acute bacterial inflammation, however, it is important to note that oxidized phospholipids inhibit LPS-mediated induction of NF-κB and consecutive gene expression [64, 65, 66]. This inhibition seems to involve at least two different mechanisms dependent on the cell type under investigation. Bochkov and coworkers [67] reported that oxidation products of 1-palmitoyl-2-arachidonoyl-*sn*-glycero-3-phosphorylcholine (ox-PAPC) inhibit LPS induction of E-selectin in human umbilical vein endothelial cells, and that ox-PAPC prevents binding of LPS to immobilized LBP and CD14. From these data they concluded that ox-PAPC extracellularly sequester LPS and prevent activation of the LPS receptor complex. However, in a recent report Walton and coworkers [68] reported that ox-PAPC do not prevent LPS binding to Toll-like receptors (TLRs) in human aortic endothelial cells. In their study the inhibitory effect of ox-PAPC on LPS-mediated signal transduction was due to inhibition of ligand activation of TLR 2 and 4. They provided evidence that ox-PAPC prevent effective recruitment of some of the components of the LPS receptor complex to the lipid rafts/caveolae thereby preventing LPS-mediated signal transduction. In the context of systemic inflammation and sepsis these findings have two implications. First, the inhibition of the primary host response to LPS can result in protection from septic shock. However, it can also lead to impaired bacterial elimination resulting in enhanced susceptibility to bacterial infections. In addition, due to their chronic proinflammatory effects oxidized phospholipids may also contribute to the clinical course of protracted sepsis.

Modulation of LPS-induced inflammation by polyunsaturated fatty acids: therapeutic potential

ω-3 FA were shown to modify the serum lipid profile and to exert beneficial cardiovascular effects. They seem to be capable of lowering the plasma-TG levels, while HDL slightly increases, and LDL and cholesterol remain constant or even decrease slightly [69, 70, 71]. In addition to their impact on the development of atherosclerosis, ω-3 FA, as with eicosapentaeonic acid (EPA) and docosahexaeonic acid (DHA) are also recognized to modulate the systemic inflammatory response. As a result, improved outcome was observed in a broad range of diseases ranging from chronic disorders to critical care conditions. Reduction in tumor risk, however, could not be substantiated [72]. Experimental data demonstrate that ω-3 FA attenuate an overwhelming inflammatory reaction [73], ameliorate host defense [59, 73], and improve splanchnic blood flow and gut barrier function [74] in septic states. Diets enriched with ω-3 FA result in a change in the ω-3/ω-6 ratio in the membranous fatty acid composition of multiple cells [75, 76, 77] in favor of pentaenoic acids. In states of inflammation EPA is released from cellular

membrane sources to compete with arachidonic acid for enzymatic metabolism producing less inflammatory and chemotactic derivatives. The EPA-derived metabolites have a lower biological activity [78, 79] than the analogous arachidonic acid derivatives. In addition, the generation of proinflammatory PAF is reduced by EPA via interference with the PAF precursor pool [80, 81].

Recent data suggest that in the context of LPS-induced inflammation ω-3 FA exhibit beneficial effects beyond their modulatory effect on the profile of inflammatory lipid mediators. Lee and coworkers [82, 83, 84] demonstrated that saturated fatty acids promote the activation of general proinflammatory pathways such as NF-κB and cyclooxygenase 2 expression (Fig. 2). They function as ligands for TLRs and activate TLR4 as well as dimers of TLR2 with TLR6 or TLR1 while polyunsaturated FA were inhibitory. ω-3 FA also affect proinflammatory signal transduction cascades downstream of TLR receptor signaling. ω-3 FA, as with EPA and DHA and their derivatives, are kown natural ligands of PPARs. In human kidney cells Li and coworkers [85] demonstrated that the EPA and DHA inhibit LPS-induced NF-κB activation via PPAR-γ.

On the other hand, improved production of cytokines, increases in cell-mediated immunity, and opsonization index, and an increase in antigen-induced lymphocyte generation were induced by diets enriched in ω-3 FA [86, 87, 88, 89]. In clinical studies enteral nutrition with diets containing fish oil had restorative effects on the depressed cellular immunity of patients with critical illness and after major abdominal surgery [90, 91]. While these studies did not demonstrate a significant decrease in infectious complications or mortality, a prospective study in burn patients demonstrated that a diet containing fish oil significantly reduced wound infection, shortened hospital stay, and reduced mortality than standard enteral nutrition [92].

Most recently Pontes–Arruda reported improved survival in septic patients after ω-3 FA treatment [93].

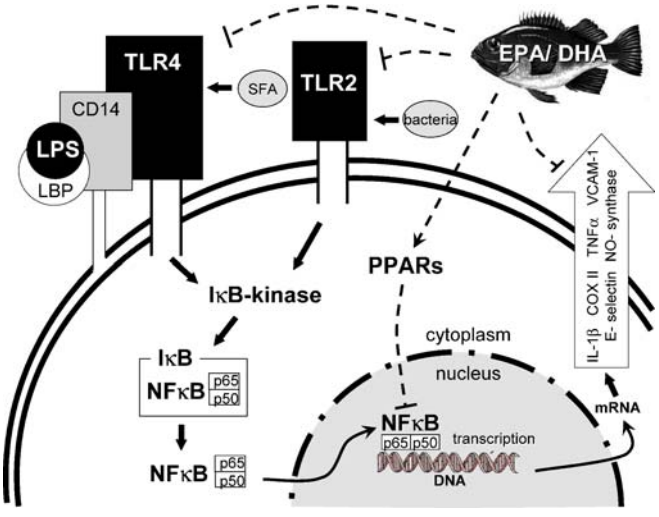

Fig. 2 Effects of *ω*-3 FA on the Toll-like receptor (*TLR*) nuclear factor κB (*NFκB*)-axis. While TLR-4 communicates the presence of a Gram-negative infection to the inner cell, TLR-2 reports the presence of Gram-positive bacteria. Saturated fatty acids (SFA) may likewise activate the TLR-4 cascade. Via inhibitory factor κB (*IκB*) kinase the blockade the function of IκB is postponed and NFκB may translocate into the nucleus to promote transcription of inflammatory genes. Consequently inflammatory receptors, enzymes, and cytokines are expressed; *ω*-3 eicosapentaenoic acid (*EPA*) and docosahexaenoic acid (*DHA*) may competitively interfere with this sequence on various levels of the cascade. *LBP* Lipopolysaccharide-binding protein; *LPS* lipopolysaccharide; *PPARs* peroxisome proliferator-activated receptors

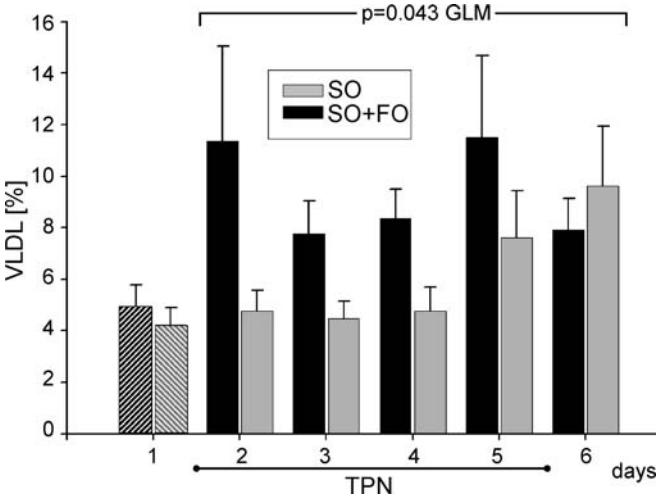

Fig. 3 Levels of VLDL (means ± SEM) after major abdominal cancer surgery followed by total parenteral nutrition (*TPN*) supplemented with soybean oil (*SO*; 1 g/kg per day; *gray columns* *ω*-6) or with SO 0.8 g/kg per day and a fish oil (0.2 g/kg per day *black columns* *ω*-3 supplement); *hatched columns* baseline before TPN

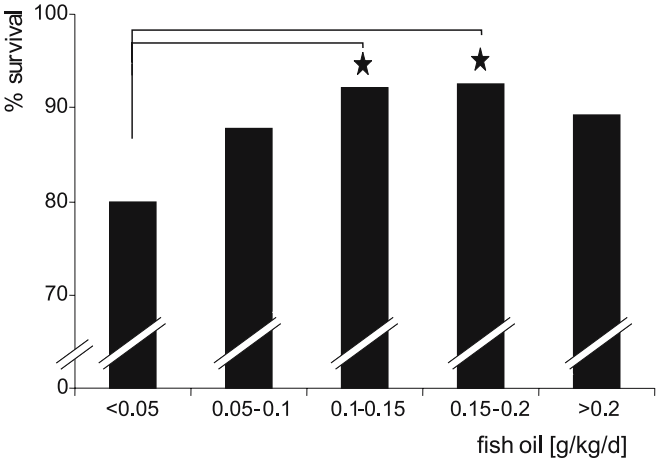

Fig. 4 Fish oil dose-related survival in the percentage of 661 ICU patients receiving total parenteral nutrition for at least 3 days (sepsis any cause $n = 292$; postoperative $n = 255$; others $n = 114$) significant differences from Tukey post hoc multiple comparison CANOVA with covariates age, Simplified Acute Physiology Score (*SAPS*) II score, and daily calorie intake, as indicated; $*p < 0.05$

Following major abdominal surgery we found that even short-term intravenous administration of ω-3 FA improves liver function without untoward effects on platelet function and coagulation [94]. Moreover, ω-3 FA helped to maintain the balance between pro- and anti-inflammatorycytokines, thereby preventing hyperinflammatory complications. Improved liver function in the group receiving a daily fish oil supplement of 0.2 g/kg resulted in significantly higher levels of VLDL than to sole soy bean oil infusion (Fig. 3). Because VLDL may likewise serve as an LPS scavenger, fish oil supplementation should be considered for this purpose rather than plain soybean oil which prolongs bacterial elimination compared to fish oil [59]. Beneficial effects of fish oil on outcome were confirmed in 661 patients who received fish oil infusion. Fish oil dose-dependently lowered the occurrence of comorbid infection and length of hospital stay and improved survival (Fig. 4) [38]. In a multifactor regression model the two main factors contributing to the length of stay were the amount of soybean oil (+1.6 d/100 g) and the delay in nutrition onset (+1.42 d/day of delay). These findings clearly point out the immunological impact of lipids in addition to being simple components of nutrition. Moreover, in line with the most recent guidelines of the German Society of Nutrition Medicine, these data show that the administration of soybean oil (ω-6 FA) should be limited to its essential dose. A combination of medium-chain TG, olive oil, and fish oil should then complete the lipid component of nutrition to cover 30–40% of daily nonprotein calorie load.

Conclusion

Recent clinical studies have established a link between lipid metabolism and systemic inflammation. Lipoproteins were shown to neutralize LPS and consequently blunt its proinflammatory effects. Thus HDL and LDL lipoproteins are important regulators of the host immune response during endotoxemia. In line with this exogenous administration of lipoproteins may have beneficial therapeutic effects in the course of Gram-negative sepsis. To what extent this concept in fact improves clinical outcome needs to be confirmed in further studies.

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