

## Review Article

# Dietary lipids, modulation of immune functions, and susceptibility to infection

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**ABSTRACT:** *The integrated action of several polyunsaturated or monounsaturated fatty acids on the immune system includes the alteration of different immune functions in both humans and animals. Several mechanisms have been proposed to explain the action of several dietary lipids on the immune system, such as alteration of membrane fluidity, eicosanoid synthesis, formation of lipid peroxides, regulation of gene expression, apoptosis, modification of antigen presentation, or modulation of intestinal microbiota. Thus, these actions acquire a significant importance in the application of these fatty acids in the diminution of inflammatory disorders. However, the immunomodulatory capacity of n-3 or n-9 fatty acids produces an alteration of host resistance against infectious microorganisms. The papers that describe these activities refer for the most part to the impact of n-3 polyunsaturated fatty acids on the immune system and infection with a pathogenic agent. Here, we summarize the main studies related to the administration of dietary lipids and susceptibility to infection. (Nutritional Therapy & Metabolism 2008; 26: 97-108)*

**KEY WORDS:** *Fish oil, Dietary lipids, Host resistance, Immune system, Infection, Olive oil*

## INTRODUCTION

Nutritional status may exert a strong effect on immune system functions. Thus, it is commonly established that many infectious diseases in human populations are associated with a nutritional deficiency, which generates a suppression of immune response. Therefore, it is obvious that the interactions between certain nutrients and immunity exert a crucial role that should be analyzed from a biological and a clinical point of view. Indeed, different nutrients (macronutrients and micronutrients) are closely related to the modulation of immune response and to the increase or reduction of susceptibility against infectious microorganisms (1). In recent years, a large number of studies have been conducted to investigate the relevance of certain fatty acids in the alteration of immune system functions in both humans and animals.

This assertion has been demonstrated in numerous experimental studies, which have reported the influence of dietary lipid manipulation upon the immune system. Starting from this hypothesis, in the 1980s, an epidemiological study revealed a low incidence of autoimmune diseases in Greenland Eskimos, who consume in their diets a great amount of fish oil (2). The beneficial as-

pects of dietary lipids (particularly unsaturated fatty acids) on the reduction of several parameters that participate in the immune response have been studied in a great number of clinical trials carried out in patients suffering from autoimmune and inflammatory diseases. As a result, early studies have highlighted the importance of n-3 polyunsaturated fatty acids as possible therapeutic substances capable of reducing the incidence of inflammatory disorders in humans (3). Autoimmune diseases such as rheumatoid arthritis, psoriasis, or systemic lupus erythematosus are characterized by the production of an inflammatory response due to a marked increase of proinflammatory cytokines. In recent years, numerous epidemiological studies have widely described the reduction in the incidence of rheumatoid arthritis in populations who consume fish oil or olive oil in their diets, which are related to the prevention of inflammatory disorder incidence, although these events occur after a prolonged ingestion of these fats (4-7).

In this review, we summarize the effects of dietary lipids on the immune functions and the mechanisms responsible for these alterations. Similarly, we analyze the clinical consequences derived from dietary lipid administration, and the adverse effects that several dietary lipids may exhibit as a direct consequence of an im-

munosuppressive process. We focus on the role of dietary lipids as immunosuppressor nutrients and the impact of these diets on host resistance to infectious agents. Readers should keep in mind the fact that the studies described deal for the most part with biological and experimental observations, whose clinical relevance and translation into strong clinical implications are not totally elucidated and require further assessment.

## THE IMMUNE RESPONSE TO INFECTION

The immune system constitutes an integrated defense network that comprises 2 separate but interacting and interdependent types: (i) the innate, natural, or non-specific immune system and (ii) the acquired, adaptive, or specific immune system. Taking into account the diversity of pathogens, it is likely that nutritional modulation (including alteration of immune functions by fatty acids) will not affect host defense against all infectious microorganisms in the same manner.

### Innate immunity

Overall, the innate immunity constitutes the first line of defense (early phase) against pathogens. The innate arm of immunity prevents the entry of infectious agents into the body, it plays a crucial role in the early control of pathogenic infectious agents as well as in the initiation and subsequent course of the acquired immunity, and it represents an important mechanism whereby infectious agents are eliminated by phagocytosis, complement activation, or toxic factors released from phagocytic or natural killer (NK) cells. Innate immunity comprises physical barriers, soluble factors, and phagocytic cells. On the basis of this preliminary concept, it is important to highlight that innate immune response represents an important mechanism which rapidly eliminates infectious agents through different mechanisms such as phagocytosis or engulfment of infectious agents or direct destruction by the production of complement or toxic substances released from phagocytic cells or NK cells. In fact, innate immunity is the most efficient mechanism to eliminate intracellular growth pathogenic agents. Innate resistance does not distinguish among microorganisms and does not change in intensity upon re-exposure.

### Acquired immunity

Acquired immunity is carried out by T (cell-mediated immunity) and B lymphocytes (humoral immunity), which recognize the antigens on the cell surface

and synthesize antibodies, respectively. Antibodies can neutralize microorganisms (extracellular growth microorganisms) by binding to them and preventing their attachment to host cells. Nevertheless, some bacteria (for instance *Listeria*, *Salmonella*, *Shigella*, *Legionella*, etc) and particularly viruses are able to enter into the cell (intracellular growth microorganisms). These pathogens escape humoral immunity and are dealt with by a cell-mediated system conferred by T lymphocytes, which may be divided into 2 types: T lymphocytes expressing CD4 receptor (helper/inducer T lymphocytes) and T lymphocytes expressing CD8 receptor (cytotoxic T lymphocytes). Host defense against intracellular pathogens is commonly related to activation of phagocytes and the generation of CD8 T lymphocytes able to kill pathogen-infected host cells.

On the other hand, acquired immunity requires the identification of molecules from an invading agent. The recognition of antigens is carried out by B lymphocytes (which produce antibodies) and T lymphocytes which recognize the antigens on the surface of cells. Intracellular infections are communicated to T lymphocytes by the expression of peptide fragments along with proteins of the major histocompatibility complex (MHC). Thus, maturation and expansion of T lymphocytes is an essential process for destroying invading organisms. The link of peptide (antigen) and MHC is identified by T lymphocytes. There are 2 types of MHC molecules: MHC class I and MHC class II. MHC class I binds intracellular peptides (from viruses or intracellular growth bacteria) and is subsequently recognized by T lymphocytes expressing CD8 receptor (cytotoxic/suppressor T lymphocytes) which leads to the destruction of the infected cell. MHC class II binds peptides from foreign agents that have been phagocytosed by macrophages or by antigen-presenting cells (extracellular antigens) and is recognized by T lymphocytes expressing CD4 receptor (helper/inducer T lymphocytes) which leads to activating T cell-mediated response.

## MECHANISMS OF ACTION WHEREBY FATTY ACIDS MODULATE IMMUNE SYSTEM

Several potential mechanisms have been proposed to explain the immunomodulatory effects of dietary lipids on immune system functions. The biological consequences that appear as a result of these changes are still unclear, but it is probable that the alteration observed by lymphocyte population enhance the host susceptibility against opportunistic infections.

## Alteration of membrane fluidity

Fatty acids constitute important structural components of the plasma membrane. Changes in the fatty acid composition modify cell membrane fluidity by the administration of certain dietary lipids (8). Unsaturated fatty acid diets increase the fluidity of the plasma membrane, whereas saturated fatty acid diets reduce the fluidity of the cell membrane. As a direct result, numerous cellular functions may be affected, such as intercellular interaction, receptor expression, or signal transduction. Thus, the binding of numerous cytokines to their respective receptors placed in the membrane surface may depend on fatty acid structure (9). Similarly, the expression of MHC class II molecules and intercellular adhesion molecule-1 (ICAM-1) is altered after dietary lipid administration, which leads to a significant inhibition of antigen-presenting function (10, 11).

Currently, the study of membrane lipid microdomains, so-called rafts, is acquiring considerable importance, to explain the modulatory mechanisms of certain fatty acids on T cell signal transduction (12, 13). Membrane lipid rafts may be defined as specialized regions within plasma membrane composed of high concentrations of cholesterol and sphingolipids (sphingomyelin and glycolipids) and a polar region that contains saturated fatty acid residues. Thus, initiation and propagation of cell signaling events taking place in immune cells occur in these regions. Different proteins involved in T cell signaling are concentrated in rafts, and alterations of raft lipid fatty acyl composition is a crucial event that has a role in the inhibitory effects of polyunsaturated fatty acids on T cell activation and in the modulation of immune system functions by certain dietary lipids (14).

The evaluation of how dietary lipids affect the organization of cell membranes will enable us to develop better dietary strategies for the application of some dietary lipids in the prevention and treatment of diseases.

## Eicosanoid synthesis

Eicosanoids or bioactive lipid mediators comprise an important family of oxygenated derivatives of dihomo- $\gamma$ -linolenic acid, arachidonic acid, or eicosapentaenoic acid (EPA) that act as a second group of chemical messengers within the immune system. The most important eicosanoids are prostaglandins (PG), thromboxanes (Tx), leukotrienes (LT), hydroperoxyeicosatetraenoic acids (HPETEs), hydroxyeicosatetraenoic acids (HETEs), and lipoxins, as well as newly identified families of lipid mediators generated from  $n$ -3 polyunsaturated fatty acids, called resolvins (Fig. 1). Two enzymes

acquire a great importance in the biosynthesis of eicosanoids: (i) cyclooxygenase, which produces the PG and Tx, and (ii) lipoxygenase, which produces the HPETEs, HETEs, lipoxins, and resolvins. In general, eicosanoids have numerous functions and, in particular, the most important are focused on their participation as inflammatory regulators and on the modulation of immune system (15). The administration of diets containing fish oil (which are mainly composed of EPA or docosahexaenoic acid [DHA]) to both humans and animals produces a significant reduction in the amount of arachidonic acid in the phospholipid membrane of cells that participate in the immune functions. This event modifies the production of different eicosanoid types, and therefore, immune system functions are also altered. In general, eicosanoids derived from  $n$ -3 polyunsaturated fatty acids are less reactive than those derived from  $n$ -6 polyunsaturated fatty acids. Thus, 3-series PG ( $\text{PGE}_3$ ) and 5-series LT ( $\text{LTB}_5$ ) (both derived from eicosapentaenoic acid) are more potent than eicosanoids derived from arachidonic acid (2-series PG [ $\text{PGE}_2$ ] and 4-series

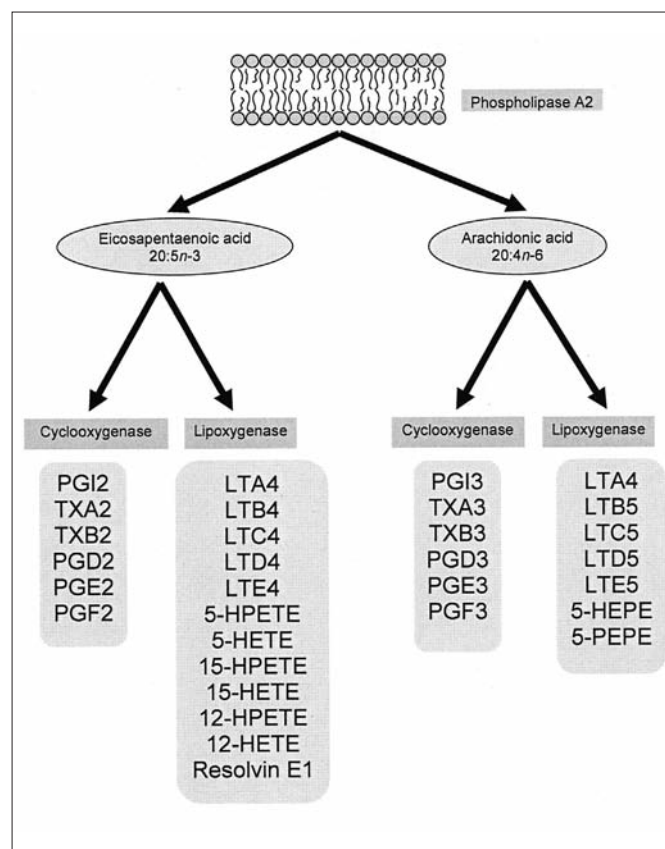


Fig. 1 - Eicosanoid synthesis from eicosapentaenoic acid (20:5n-3) and arachidonic acid (20:4n-6).

LT [LTB<sub>4</sub>] in inhibiting lymphocyte proliferation (16). In addition, prostaglandins inhibit production of interleukin-1 (IL-1) and tumor necrosis factor (TNF), whereas leukotrienes increase NK cell activity, IL-1 production by macrophages, and interferon- $\gamma$  (IFN- $\gamma$ ) production by lymphocytes (17, 18). Therefore, fatty acids derived from fish oil may inhibit the metabolism of arachidonic acid by 2 pathways: (i) reduction of substrate availability, because the administration of *n*-3 polyunsaturated fatty acids results in a significant decrease in the amount of arachidonic acid in the plasma membrane of immune system cells, and (ii) competition with arachidonic acid to serve as a substrate for both cyclooxygenase and lipoxygenase activities.

### Oxidative alteration

Lipid peroxidation modifies the expression of surface molecules (8). This fact may be related to the suppression of human leukocyte antigen (HLA-DR) expression due to free radical production (19). The antioxidant nutrient status of the subjects is of crucial importance in the determination of the effects of polyunsaturated fatty acids on immune system functions, because the incorporation of polyunsaturated fatty acids into plasma membrane increases lipid peroxidation, as well as the requirements for antioxidant substances that protect plasma membrane from lipid peroxidation. In fact, the immunosuppression attributed to certain dietary lipids might be in part associated with an increase of lipid peroxidation, and consequently a substantial reduction of antioxidants (particularly vitamin E). Antioxidants from extra-virgin olive oil have received particular attention for their protective effects against the damage from biological oxidants. Among the antioxidant agents that constitute olive oil are hydroxytyrosol, oleuropein, and caffeic acid. These compounds are capable of scavenging free radicals and of breaking peroxidative chain reactions (20).

### Regulation of gene expression

Fatty acids affect cell responses through direct action on the intracellular signaling pathways, by acting as ligands for nuclear receptors. Thus, recent studies have indicated that the modulatory properties of *n*-3 polyunsaturated fatty acids are due in part to a reduction in the activity of nuclear factor  $\kappa$ B (NF- $\kappa$ B), which is an important transcription factor involved in the promotion of several proinflammatory cytokines, cyclooxygenase, and adhesion molecules (21). Other transcription factors, including peroxisome proliferator-activated receptors (PPARs), have also been proposed as participating in the

expression of inflammatory genes (22), as well as in the modulation of different types of cytokines such as IL-2 and IFN- $\gamma$  (23). PPARs can bind to DNA sequence elements and are involved in the regulation of inflammatory processes by modulating the expression of target genes.

### Apoptosis

Apoptosis has been defined as an essential mechanism in which the activation of catabolic processes and enzymes occurs before cytolysis, thereby facilitating the recognition, uptake, and digestion of the apoptotic cell by phagocytes. Different studies performed by *in vitro* assays or by administration of dietary lipids in both animals and humans have described an important role for several fatty acids in the induction or inhibition of apoptosis. Thus, polyunsaturated fatty acids such as eicosapentaenoic acids, docosahexaenoic acids, saturated fatty acids such as palmitic acid, or fats such as fish oil administered in the diet have been defined as substances capable of inducing cell death via a mitochondrial process, or by down-regulation of Bcl-2 (an antiapoptotic protooncogene product) (24-26). In addition, another possibility that explains in part the induction of apoptosis by long-chain *n*-3 polyunsaturated fatty acids is the direct action of these substances on the cells and by activation of the caspase cascade through cytochrome *c* release coupled with a modulation of mitochondrial membrane depolarization (27). Recent studies have also determined the crucial importance of dietary fatty acids in the reduction of Bcl-2 expression as well as an increase of Fas ligand (Fas-L) expression. Therefore, when the concentration of polyunsaturated fatty acids augments, Bcl-2 expression is reduced, and cell death occurs (26). More recently, a novel mechanism has been proposed to establish a relationship between fatty acids and apoptosis. This mechanism suggests that *n*-3 fatty acids modulate T cell-mediated immunity by selective deletion of Th1-like cells, while maintaining or increasing the Th2-mediated humoral immune response (28). While *n*-6 polyunsaturated fatty acids are involved in apoptosis induction, acting on mitochondrial depolarization and oxygen radical production, oleic acid is less toxic and is involved in caspase-3 activation (29).

### Antigen presentation

The expression of MHC class II antigen-presenting molecules on peripheral blood monocytes or dendritic cells was significantly diminished after the administration of a diet containing fish oil (11, 30). Similarly, the expression of MHC class I antigen-presenting molecules was decreased with a treatment *in vitro* of B lymphocytes in

the presence of arachidonic acid or docosahexaenoic acid. However, MHC class I expression was only restricted to *in vitro* studies. Therefore, it would be necessary to examine these effects in *in vivo* models.

### **Modulation of gastrointestinal microbiota**

The importance of resident intestinal microbiota is crucial to preventing infections caused by potential pathogens. Several studies have determined that high concentrations of polyunsaturated fatty acids exert an important effect on gastrointestinal microbiota, showing that they inhibit the growth and mucus adhesion of lactobacilli (31), whereas low concentrations of  $\gamma$ -linolenic acid and arachidonic acid promoted the growth and mucus adhesion of *Lactobacillus casei*. Long-chain polyunsaturated fatty acids, by enhancing the adhesion of probiotic organisms to the gut mucosal cells, may increase the development of gut-associated lymphoid tissue by direct interaction between the probiotics and the lymphoid tissue and by the ability of long-chain polyunsaturated fatty acids and probiotics to augment certain growth factors such as transforming growth factor- $\beta$  (TGF- $\beta$ ) and various cytokines (32).

### **DIETARY LIPIDS AND INFECTION**

Nutrient intake may frequently be considered as a critical determinant of immunocompetence because of the impact of certain micronutrients and macronutrients on immune system functions (33). Many investigations have reported the modulatory role exerted by certain fatty acids on the immune system and the clinical benefits of dietary lipid supplementation with fish oil or olive oil in both humans and animals. As a result, diets containing fish oil or olive oil have been applied in the resolution, or at least in the attenuation, of diseases characterized by an overactivation of immune system (6), because unsaturated fatty acids (mainly *n*-3 or *n*-9 fatty acids) reduce the levels of many biological mediators associated with the promotion of the inflammatory events that participate in an inappropriate immune response. Different studies have supported this statement by showing that *n*-3, *n*-6, or *n*-9 fatty acids exert immunomodulatory effects (34, 35). On the other hand, human clinical trials have been less conclusive. Nonetheless, the reported reduction of immune response caused by the administration in the diet of these fats may exert a detrimental effect on the host resistance, and therefore, they may impair cellular immunity to pathogenic agents (36).

For obvious reasons, the altered resistance to infec-

tious microorganisms has been analyzed in animal models in which the administration of diets containing fish oil generally reduces the clearance of bacteria from liver or spleen and diminishes significantly survival during the course of an experimental infection with different types of pathogens. As a consequence, the elimination of microbial agents (bacteria, fungi, viruses, or parasites) is more difficult (reviewed in (37)). Different reports have described the clinical consequences of dietary supplementation with *n*-3 polyunsaturated fatty acids, which are characterized by suppressing immune system functions. Nevertheless, the studies focused on the action promoted by fatty acids in immune system functions, and the modulation of host resistance to infectious microorganisms has generated many discrepancies that may be directly attributed to different factors, such as type and amount of diet consumed, time of feeding before the challenge with the microorganism, and the type, dose, and route of infection (38). The main studies investigating the impact of dietary lipids (particularly *n*-3 polyunsaturated fatty acids) on the host immune resistance are summarized in Table I.

Administration of *n*-3 polyunsaturated fatty acid is related to reduction of the proinflammatory biological mediator induced by *Escherichia coli* lipopolysaccharide (LPS). These alterations may exert beneficial effects because *n*-3 polyunsaturated fatty acid intake, either via parenteral emulsion or dietary administration, increased the survival of guinea pigs after LPS injection, exerting a protective effect (40).

### **Bacteria**

Other observations have concluded that the effects of diets containing fish oil are mediated through altered production of leukotrienes, when mice were infected with a gram-negative bacterium such as *Klebsiella pneumoniae* (63). In fact, the administration of fish oil diets exerts beneficial effects on survival of mice after experimental infection with *K. pneumoniae* (46, 51, 62), but adverse effects were reported after infection with *Streptococcus pneumoniae* (62).

*Listeria monocytogenes*, a gram-positive pathogen which serves as an important model for understanding host immune resistance against intracellular bacteria, has been used in numerous investigations associated with fatty acid and infection. An early study reported no differences in the susceptibility to this pathogen of animals fed fish oil diets (42), whereas other investigations found a reduction of host resistance to *L. monocytogenes* infection due mainly to a suppression of macrophage functions, impairment of specific immunity, and persistence of this microorganism in the liver

**TABLE I - CHRONOLOGICAL DATA DEMONSTRATING THE EFFECT OF DIETARY LIPIDS ON HOST IMMUNE RESISTANCE AGAINST INFECTIOUS MICROORGANISMS**

Microorganisms	Treatments	Species	Time (weeks)	Results	References
<i>Listeria monocytogenes</i>	Diet high in lard, cholesterol, and sucrose.	C57BL/6 mice	26	Impairment of specific immunity to <i>L. monocytogenes</i> infection. Persistence of <i>L. monocytogenes</i> in livers.	(39)
<i>Escherichia coli</i> lipopolysaccharide (LPS)	Safflower oil (10%) or fish oil (10%) emulsions	Guinea pigs	24, 48 hours	Increase of survival to endotoxin in animals treated with parenteral fish oil	(40)
<i>Listeria monocytogenes</i>	High-fat diet	ddN mice	1-2	Reduction to <i>L. monocytogenes</i> resistance. Suppression of macrophage functions.	(41)
<i>Pseudomonas aeruginosa</i> , <i>Listeria monocytogenes</i> , <i>Candida albicans</i> , murine cytomegalovirus	Diet containing melted beef tallow (46%) or fish oil	(NZBxNZW) F1 mice	4	No differences in the susceptibility of animals. No association with an increased risk of infection.	(42)
<i>Pseudomonas aeruginosa</i>	Diets containing 10% and 40% safflower oil or MaxEPA	Balb/c mice	2-3	The group fed fish oil diet had significantly higher mortality than those fed safflower oil	(43)
<i>Pseudomonas aeruginosa</i> , <i>Salmonella typhimurium</i>	Diets containing either coconut oil, olive oil, safflower oil or fish oil	CF1 mice	3	No changes observed on survival among different sources of fat. Manipulation of dietary fat does not affect outcome from infection	(44)
<i>Salmonella typhimurium</i>	Diets containing corn oil (20%), hydrogenated coconut oil (20%), or fish oil (20%)	Swiss Webster mice	4	Reduction of survival in mice fed fish oil. A diet rich in fish oil decreases host resistance to infection	(45)
<i>Klebsiella pneumoniae</i> , <i>Plasmodium berghei</i>	Diets containing fish oil (14%), corn oil (15%), or palm oil (15%)	Swiss mice	6	Increase of survival after challenge and resistance to infection. Indomethacin treatment did not alter the outcome in the two infection	(46)
<i>Mycobacterium tuberculosis</i>	Diets containing different concentrations of <i>n</i> -3 and <i>n</i> -6 polyunsaturated fatty acids	Guinea pigs	13	Increase in the number of bacteria from spleen of animals fed <i>n</i> -3 polyunsaturated rich diets	(47, 48)
<i>Salmonella typhimurium</i>	Diets containing corn oil (20%), menhaden fish oil (17% + 3% corn oil)	Mouse	≈1	Reduction of Kupffer cell phagocytosis by fish oil. Diminution of CD18 expression in splenocytes	(49)
Human immunodeficiency virus	Bars containing fish oil or safflower oil	Human	6	Reduction of CD4 cell counts after treatment with fish oil	(50)
<i>Klebsiella pneumoniae</i>	Diets containing fish oil or olive oil	NMRI mice	6	Increase of survival in the group fed a fish oil diet	(51)
<i>Listeria monocytogenes</i>	Diets containing lard (20%), soybean oil (20%), or menhaden fish oil (17% + 3% corn oil)	C3H/Hen mice	4	Reduction of survival in the groups fed soybean and fish oil diets. Reduction of bacteria counts from spleen of mice fed fish oil, but no differences in bacteria counts from liver	(52)
<i>Eimeria tenella</i> , <i>Eimeria maxima</i>	Diets containing menhaden oil (5%), medium-chain triglyceride oil (5%), or flaxseed oil (15%)	Chickens	3	Suppression of <i>E. tenella</i> development, whereas fish oil diet is not beneficial in the reduction of <i>E. maxima</i> infection. This fat may exacerbate lesions at high parasite doses	(53)
Influenza virus	Diets containing fish oil (17% + 3% sunflower oil) or beef tallow (17% + 3% sunflower oil)	Balb/c mice	2	Delay in viral clearance and reduction of IFN- $\gamma$ production, IgG and IgA synthesis	(54)
<i>Listeria monocytogenes</i>	Diets containing lard (20%), soybean (20%), or fish oil (20%)	C3H:HeN Mice	4	Reduction of both IL-12 and IFN- $\gamma$ production during the early phase of a <i>Listeria</i> infection	(55)

TABLE I - Continued

Microorganisms	Treatments	Species	Time (weeks)	Results	References
<i>Listeria monocytogenes</i>	Diets containing olive oil (20%), fish oil (20%), or hydrogenated coconut oil (20%)	Balb/c mice	4	Reduction of survival in mice fed a fish oil diet. Increase of bacteria counts from spleen	(56)
Herpes simplex virus type I (HSV-1)	Diets containing corn oil (5.7% + 14.3 hydrogenated vegetable oil) or fish oil (20%)	Balb/c mice	2	Increase of progression of herpes stromal keratitis	(57)
<i>Listeria monocytogenes</i>	Diets containing 200 g/kg olive oil, fish oil or hydrogenated coconut oil	Mouse	4	Increased invasion and adherence of <i>L. monocytogenes</i> to splenic cells	(58)
<i>Listeria monocytogenes</i>	Diets containing 200 g/kg olive oil, fish oil, or hydrogenated coconut oil, and treated with NAC	Balb/c mice	4	Administration of NAC exerts a moderate detrimental effect after challenge with <i>L. monocytogenes</i>	(59)
<i>Trichinella spiralis</i>	Diets containing fish oil (19%)	Rats	9	Reduction in the number of adult worms and larvae and increase of both IFN- $\gamma$ and IL-4 production	(60)
<i>Listeria monocytogenes</i>	Diets containing 200 g/kg olive oil, fish oil or hydrogenated coconut oil	Balb/c mice	4	Production of IL-12 was reduced, but IL-4 production was increased after <i>L. monocytogenes</i> infection	(61)
<i>Klebsiella pneumoniae</i> , <i>Streptococcus pneumoniae</i>	Diets containing fish oil (10%) or corn oil (10%)	Mice	6	Beneficial effects of fish oil on survival after infection with <i>K. pneumoniae</i> , but detrimental effects on survival were observed with <i>S. pneumoniae</i>	(62)
<i>Klebsiella pneumoniae</i>	Diets containing fish oil or corn oil and treated with 5-lipoxygenase (5-LO) inhibitor	Mice	6	Survival of mice was increased after fish oil administration, but the neutralization of leukotrienes eliminates the beneficial effects	(63)
Induction of polymicrobial sepsis by cecal ligation and puncture	Diets containing fish oil (7%) + soybean oil (3%)	ICR mice	3	Increase of the inflammatory reaction and neutrophil infiltration into tissues. Fish oil augments Th2-type response.	(64)
<i>Listeria monocytogenes</i>	Diet containing olive oil, fish oil, or hydrogenated coconut oil, and treated with cyclophosphamide	Balb/c mice	4	Increased resistance to infection in immunosuppressed animals	(65)
<i>Pseudomonas aeruginosa</i>	Diets containing <i>n</i> -3 polyunsaturated fatty acids (36.5%) or <i>n</i> -6 polyunsaturated fatty acids (32.2%)	C57BL/6 mice	5	Reduction of mortality in <i>n</i> -3 group and increase of distal alveolar fluid clearance as wells as the inflammatory response	(66)
Reovirus	Diets containing 10 g/kg corn oil + 60 g/kg high oleic acid safflower oil or 10 g/kg corn oil + 60 g/kg DHA-enriched fish oil	Mice	4	Reduction of virus clearance from the intestinal tract, whereas DHA did not affect immunoglobulin production	(67)
Hepatitis C	Capsules. 1,800 mg/day of EPA	Human	48	Prevention of a decrease in the lymphocyte counts	(68)

DHA = docosahexaenoic acid; EPA = eicosapentaenoic acid; NAC = N-acetyl-L-cysteine.

(39, 41). Other more recent studies have demonstrated a significant reduction of survival rates in hosts to *L. monocytogenes* infection after feeding experimental mice with a diet containing fish oil (52, 56). These mice were inoculated with a lethal dose of a virulent *L. monocytogenes* strain, a facultative intracellularly growing

bacterium. After the administration of this diet, different results were observed. Bacterial clearance from liver or spleen was increased in these animals (52, 56), bactericidal activity of peritoneal cells was significantly altered (69), and cytotoxic effects due to bacterial infection were increased (58), whereas the susceptibility of cells

to adhesion or invasion by *L. monocytogenes* infection was substantially modified (58). These observations indicate an ineffective capacity of the immune system from animals fed a diet containing fish oil to destroy and eliminate the infectious agents (52, 56, 58, 69). A recent investigation has contributed to explaining in part the reasons for which *n*-3 polyunsaturated fatty acids reduce host defense against *L. monocytogenes*. Thus, consumption of EPA or DHA (both contained in fish oil) impairs the production of IL-12 and IFN- $\gamma$ , cytokines that play an essential role in the innate and adaptive responses of host immune system (70). Hence, the reduction of IL-12 levels may explain the impaired bacterial clearance from spleen and the reduction of mouse survival of *L. monocytogenes* infection (55). Another possible explanation for the reduction of host resistance is based on the inhibition of MHC class II expression (called Ia in mice) that is reduced in mice fed a fish oil diet and infected with *L. monocytogenes* (71). Similarly, our research group and others have described a reduction of survival in the animals fed a fish oil diet as well as a diminution of bacteria counts from spleen (52, 56) after challenge with *L. monocytogenes*. As mentioned above, this outcome may be promoted not only by a reduction of IL-12 and IFN- $\gamma$  production, but also by an increase of IL-4 synthesis during the early phase of *L. monocytogenes* infection (55, 61). However, the mortality of animals was not increased in mice fed an olive oil diet after the exposure to this bacterium (56, 59). Indeed, the adherence and invasion of this pathogen to splenic cells were increased after the administration of a fish oil diet (58), and the combination of this dietary lipid with an antioxidant agent such as N-acetyl-L-cysteine (NAC) produced an adverse effect, leading to a reduction of survival and to an increase of viable bacteria from the spleen (59). The administration of diets containing fish oil in immunosuppressed models treated with a neutrophil-depleting antibody (RB6-8C5) has demonstrated that *n*-3 polyunsaturated fatty acid-mediated reduction of host resistance to *L. monocytogenes* is independent of neutrophil activity (72). In addition, *n*-3 polyunsaturated fatty acids contribute to aggravating the susceptibility against *L. monocytogenes* infection of immunosuppressed animals, which have been treated with cyclophosphamide (a neutropenic agent) (65). Therefore, the results obtained in animal models clearly indicate that the administration of diets containing fish oil may exert an important immunosuppressive effect in patients at risk of sepsis (65, 72).

The exposure of guinea pigs to *Mycobacterium tuberculosis* produced similar results, and, an increase in the number of bacteria from spleen was described, when animals were fed a diet containing fish oil (47, 48).

The action of *Pseudomonas aeruginosa*, a pathogen involved in a large number of nosocomial infections, has also been evaluated in different studies. Evidence from several findings have indicated that diets containing fish oil reduce mortality rates of hosts from this pathogen (66), whereas other investigations have reported no differences in the susceptibility of animals to this microorganism (42, 44) or a significant reduction of mouse survival when fed a fish oil diet after the challenge (43).

In spite of the fact that *Salmonella typhimurium* has not been related to changes in survival after the administration of *n*-3 polyunsaturated fatty acids (44), other authors have found substantial differences in survival of animals fed a diet containing fish oil. Thus, mice fed *n*-3 polyunsaturated fatty acids showed an increase in mortality and diminished bacterial clearance, when this pathogen was administered by an oral route (45).

## Viruses

Experimental observations with viruses have also demonstrated that influenza virus infection in animals fed fish oil diet delays the clearance due to an impairment of primary virus-specific T cell cytotoxicity, but has no effect on NK cytotoxicity (54, 73). The infection in an animal model with ocular herpes simplex virus type 1 (HSV-1) has promoted the development of more severe lesions in mice fed a fish oil diet. Taking into account that the susceptibility of certain strains of mice to HSV-1 stromal keratitis is related to hyperresponsiveness of T lymphocyte to HSV-1 antigens, it is probable that the activation of T lymphocytes observed in the fish oil-fed group could be responsible for the reported exacerbation of this disease (57). However, other early studies have reported that the administration of *n*-3 polyunsaturated fatty acids did not affect survival after a lethal infection with murine cytomegalovirus (42). The infection of mice fed a diet containing DHA with an enteric reovirus produced a reduction of clearance of the virus from the intestinal tract, although the level of immunoglobulin A at 6 or 8 hours of infection was not modified (67). Finally, a recent investigation has reported that EPA supplementation does not reduce lymphocyte counts in patients suffering from hepatitis C receiving a combinatory therapy of pegylated interferon (PEG-IFN) and ribavirin (68).

## Parasites

A study established that a fish oil diet is efficient in the elimination of *Eimeria tenella*, whereas this fat is not beneficial in the reduction of *Eimeria maxima* infection. In fact, fish oil may exert adverse effects, because

it exacerbates lesions at high parasite doses (53). The effect of dietary lipids on host resistance to infection has also been explored in models infected with parasites such as the etiological agent of malaria, *Plasmodium berghei*. The administration of a diet containing fish oil did not lead to decreased resistance to infection. This event was associated with an enhanced *ex vivo* production of proinflammatory cytokines, IL-1 and TNF, by peritoneal cells, whereas the reduction of prostaglandin synthesis did not appear to play an important role during the course of *P. berghei* infection (46).

Nevertheless, a reduction in the number of both adult worms and larvae from *Trichinella spiralis* was observed in rats fed a diet supplemented with fish oil (60).

## CONCLUDING REMARKS

Despite extensive investigations during the last 30 years into the effects promoted by dietary lipids on the immune system of both humans and animals, recent advances have revealed numerous discrepancies supported by experimental and clinical data. These investigations have corroborated that the action of certain dietary lipids on immune system functions depends on different factors, such as type of microorganism, class of fatty acid, concentration, methodology of the study, dose, or route of infection. Therefore, in the light of current experimental observations, it is clear that certain fatty acids modulate the immune system in both animals and humans, and various immunological parameters are considerably altered. Thus, it is generally accepted that lymphocyte proliferation, cytokine synthesis, NK cell activity, or adhesion molecules are affected after the administration of diets containing *n*-3 polyunsaturated fatty acids or *n*-9 monounsaturated fatty acids. As a direct consequence of these events, certain fatty acids have been applied in the reduction of inflammatory disorders, which are characteristics of autoimmune diseases. Nevertheless, the immunosuppression carried out by certain unsaturated fatty acids (particularly long-chain *n*-3 polyunsaturated fatty acids, the most immunosuppressive fatty acids) may lead to a significant increase of susceptibility to different infectious microorganisms, or in other words, to a loss of host immune resistance against viruses, bacteria, or parasites. In contrast, other studies have suggested that long-chain *n*-3 polyunsaturated fatty acids improve the immune resistance, and therefore significantly reduce the susceptibility of both animals and humans to infection. Therefore, it is clear that future investigations should be focused on the relationship between certain fatty acids and the potential

consequences in the clinical application of these nutrients, because several parenteral lipid emulsions (administered to patients at risk of sepsis) are currently applied in clinical nutrition as a potential alternative to others which have classically been used. Nowadays, the administration of an olive oil-containing emulsion (ClinOleic or SMOFLipid) appears to be more beneficial to immune system functions than soybean oil-based emulsions, because it does not alter inflammatory cytokine production. Despite optimistic results, the effect of olive oil-containing emulsion needs to be corroborated by more, randomized clinical trials. Similarly, enteral immunonutrient mixtures (which include arginine, nucleotides, and long-chain *n*-3 polyunsaturated fatty acids) have been applied in surgical and critically ill patients. Nevertheless, the efficacy of these immunonutrient mixtures remains controversial, particularly in critically ill patients. Cautious use of these new lipid emulsions is essential to establish the impact of these lipid emulsions on the immune system.

## ABBREVIATIONS

DHA, docosahexaenoic;  
EPA, eicosapentaenoic acid;  
Fas-L, Fas-ligand;  
HETE, hydroxyeicosatetraenoic acid;  
HPETE, hydroperoxyeicosatetraenoic acid;  
HSV-1, herpes simplex virus-1;  
ICAM-1, intercellular adhesion molecule-1;  
IFN, interferon;  
IL, interleukin;  
LT, leukotrienes;  
LPS, lipopolysaccharide;  
MHC, major histocompatibility complex;  
NAC, N-acetyl-L-cysteine;  
NF- $\kappa$ B, nuclear factor kappa B;  
NK, natural killer;  
PEG-IFN, pegylated interferon;  
PPAR, peroxisome proliferator-activated receptor;  
PG, prostaglandins;  
TGF, transforming growth factor;  
TNF, tumor necrosis factor;  
TX, thromboxanes.

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