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Role of Fatty Acids in the Resolution of Autoimmune and Inflammatory Diseases

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1. Introduction

The main role of fatty acids is focused on serving as major substrates for energy production; however, fatty acids are also involved in the formation of cellular structures as well as in the transmission of cellular signals. Among the multiple functions attributed to fatty acids are their anti-inflammatory properties. This important characteristic has been applied in the prevention, attenuation or treatment of inflammatory disorders. Based on the previous argument is obvious that several fatty acids (mainly *n*-3 polyunsaturated or *n*-9 monounsaturated fatty acids) are capable of modulating immune system functions. These fatty acids may alter immune response through different mechanisms such as alteration of membrane fluidity, eicosanoid synthesis, oxidative stress, regulation of gene expression, apoptosis or modulation of gastrointestinal microbiota.

Early studies in Greenland Eskimos determined the low prevalence of inflammatory disorders in this population (Kromann et al., 1980). Despite their beneficial effects in the reduction of inflammatory diseases, other studies have demonstrated that the administration of diets containing long-chain *n*-3 polyunsaturated fatty acids may contribute, at least in part, to the reduction of host resistance against infectious agents. In fact, epidemiological investigations described a high incidence of tuberculosis in native Eskimos (Kaplan et al., 1972), who consume a great amount of *n*-3 polyunsaturated fatty acids. These data are clearly illustrative of the potential action of certain fatty acids on the inflammatory response, and of the consequences derived from an excessive immunosuppression.

It is obvious that these fatty acids contained in the diets produce an immune status able to ameliorate inflammatory conditions. Indeed, a growing number of studies using healthy human subjects as well as animal disease models have undoubtedly demonstrated dietary fish oil or olive oil to possess anti-inflammatory properties. For this reason, polyunsaturated or monounsaturated fatty acids have showed beneficial effects in numerous inflammatory diseases characterized by a overactivation of immune system such as asthma (childhood and adult), multiple sclerosis, glomerulonephritis, inflammatory bowel disease (Crohn's disease, ulcerative colitis) and rheumatoid arthritis . Here, we summarize the involvement of fatty acids as anti-inflammatory agents and the action that these fatty acids contained in the human or animal diets exert on the prevention or treatment of autoimmune diseases.

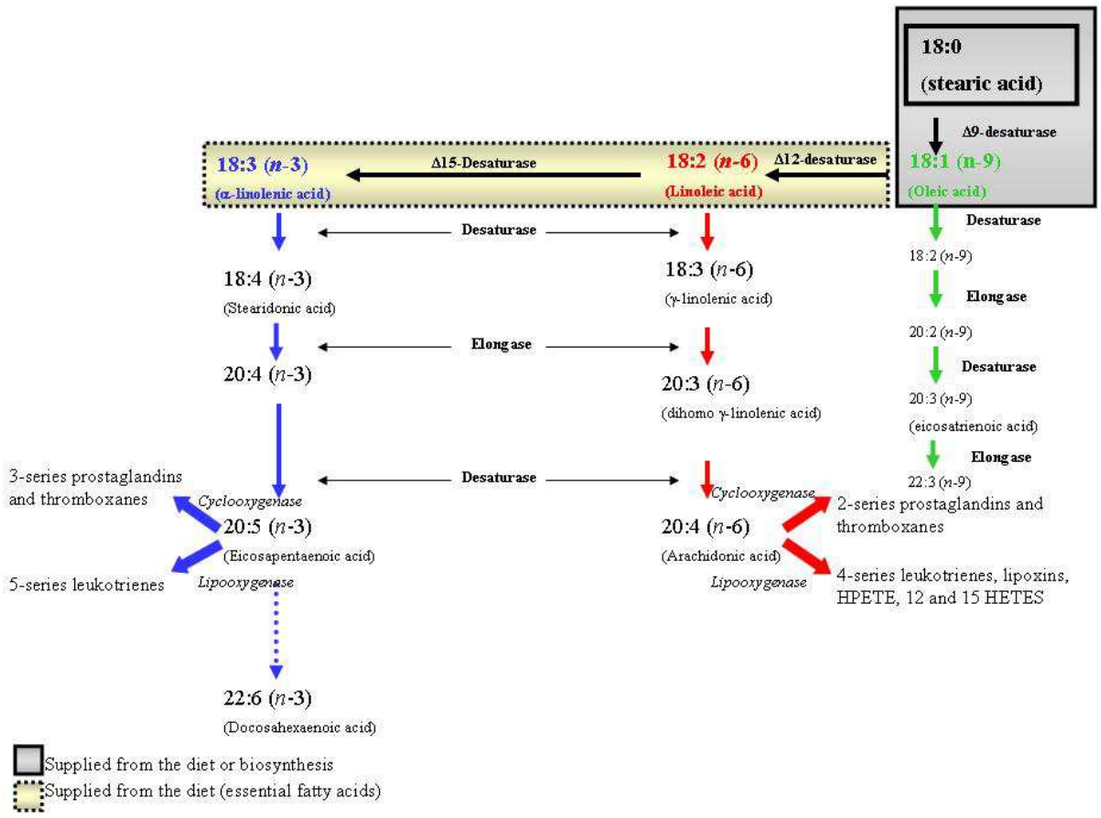

Fig. 1. Different pathways of n-3, n-6 and n-9 fatty acids synthesis. HETEs, hydroxyl-eicosatetraenoic acid; HPETE, hydroperoxy-eicosatetraenoic acids. (Puertollano *et al.*)

2. Fatty acids, inflammation and immune system

Polyunsaturated fatty acids (PUFA) are considered essentials to mammalian cells and should be administered in the diet. These essential fatty acids are divided into two great families: *n-3* series derived from linolenic acid (LNA), and *n-6* series derived from linoleic (LA) acid. Different biochemical processes lead to the production of eicosapentanoic acid (EPA) or docohexaenoic acid (DHA) from LNA, as well as arachidonic acid (AA) from linoleic acid. Likewise, another family of non essential fatty acids such as *n-9* series derived from oleic acid, a monounsaturated fatty acid (MUFA), also seems to play an important role in the immunomodulatory process (Yaqoob, 2002) [Figure 1].

In recent years numerous investigations have examined the mechanisms of action responsible for the modulation of immune system by fatty acids and most of them are in agreement that unsaturated fatty acids are potent immunosupressor especially *n-3* PUFA (reviewed in Puertollano et al., 2008). The main mechanisms of action of fatty acids are schematized in figure 2 and include alterations of immune cells membrane fluidity, eicosanoids synthesis modifications, oxidative alteration, regulation of gene expression and apoptosis mechanisms inducement. Table 1 summarized these mechanisms of actions and others recently proposed such as modulation of gastrointestinal microbiota.

All of these mechanisms of action deal to explain the numerous effects of fatty acids on immune system. It is well known that unsaturated fatty acids are involved on the alteration

of lymphocyte proliferation. In general, administration of high level of fatty acids, and especially *n-3* series, are related with a reduction on lymphocyte proliferation in both animals and human studies (Meydani et al., 1991; Yaqoob et al., 1994; Moussa et al., 2000). This fact can be especially interesting in the amelioration of diseases characterized by overactivation of immune response like autoimmune disorder. In addition fatty acids can modify another lymphocyte functions like cytokine production.

- Eicosanoids production
- Membrane fluidity and lipid rafts
- Oxidative stress
- Signaling transduction
- Gene expression
- Apoptosis
- Ability in antigen presentation
- Modulation of gastrointestinal microbiota

Table 1. Hypothetical mechanisms of dietary lipids on immune functions: factors determining the modulation of immune system.

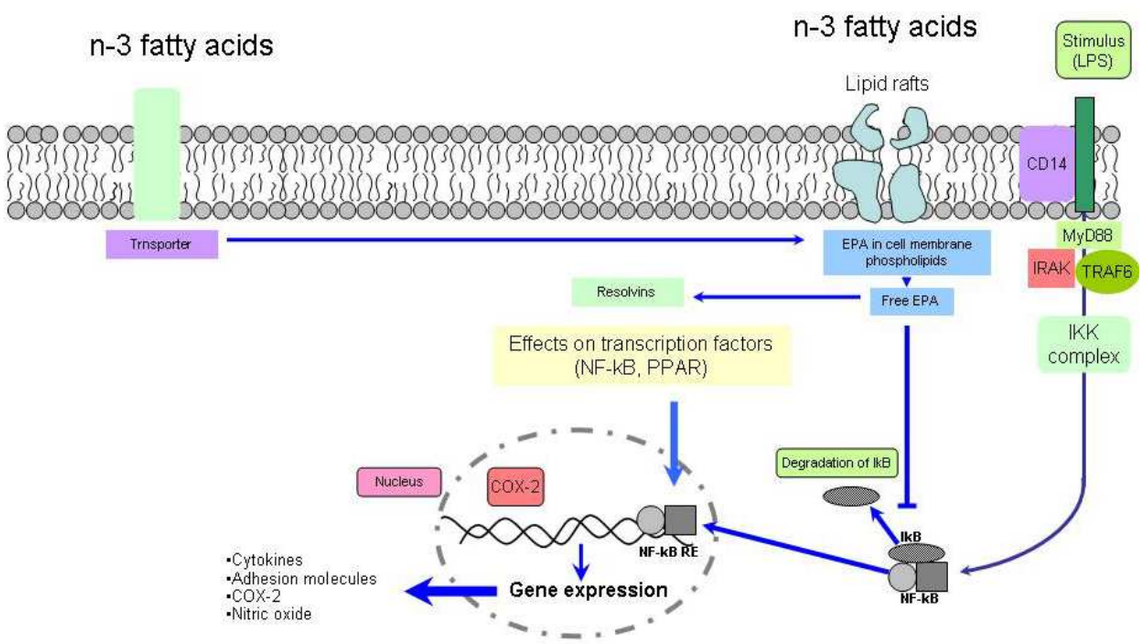

Fig. 2. Schematic diagram of proposed mechanisms of action of *n-3* polyunsaturated fatty acids whereby these fatty acids are involved in the modulation of immune system functions. Abbreviations: CD14, CD14 surface receptor; COX, cyclooxygenase; EPA, eicosapentaenoic acid, IκB, NF-κB inhibitory protein; LPS, lipopolysaccharide; NF-κB, nuclear factor-κB; PPAR, peroxisome proliferator-activated receptor; TLR, Toll-like receptors. (Puertollano *et al.*)

Several studies have demonstrated the immunomodulatory properties of polyunsaturated and monounsaturated fatty acids over reduction of pro and anti-inflammatory cytokines.

In this context interesting investigations indicates that *n-3* PUFA exert a significant inhibition of Th1-type cytokines, whereas they have little effects on Th2-type cytokines (Wallace et al., 2001). In spite of olive oil diets are involved in the reduction of cytokine secretion, their immunosupressant effects are not as potent as those exerted by the administration of a fish oil diet (Puertollano et al., 2004). Fatty acids are able to modify the natural killer (NK) cells activity too. Finally recent studies have proved the action of fatty acids in the expression of adhesion molecules like lymphocyte function antigen-1 (LFA-1) and intercellular adhesion molecule-1 (ICAM-1) (Sanderson et al., 1995; Miles et al., 2001). These facts have been shown in preliminary studies in animal models but it is necessary to confirm it in human studies.

2.1 Dietary lipids and inflammatory response

Inflammation is part of immune response and is a complex process affected by different factors, included mediators generated from fatty acids. Eicosanoids from *n-6* series fatty acids (like prostaglandine E_2 (PGE_2) and leukotriene B_4 (LTB_4) among others) are considered pro-inflammatory mediators while molecules from *n-3* series (like PGE_3 and LTB_5) generally are endowed with lower bioactivity. It is necessary to keep an optimal *n-6*/*n-3* balance to achieve a healthy inflammatory state.

Numerous researches have demonstrated that fish oil rich diet promotes a decrease on inflammatory ecoisanoids production from *n-6* PUFA because of the competition between the two metabolic pathways. In this way *n-3* PUFA supplementation of the human diet is able to decrease production of inflammatory eicosanoids like PGE_2, LTB_4 and thromboxane B_2 (TXB_2) by inflammatory cells (Meydani et al., 1991; Kelley et al., 1999; Trebble et al., 2003; Rees et al., 2006). In addition *n-3* PUFA have other effects over inflammatory response. One of the most important is the generation of resolvins, a group of mediators derived from EPA and DHA that appear to exert potent anti-inflammatory actions (Calder, 2008a). Decreasing antigen presentation via major histocompatibility complex class II (MHC II), inhibiting T-cell reactivity and diminishing inflammatory cytokine production (Calder et al., 2002; Akhtar Khan, 2010; Kim et al., 2010) are others of the anti-inflammatory effects of *n-3* fatty acids. Autoimmunity can be considered as an exacerbated inflammatory response against self structures; therefore *n-3* long chain fatty acids can be useful in the treatment of these diseases.

Oleic acid is the main fatty acid contained in olive oil. Olive oil has traditionally been used as a placebo in the studies investigating the potential action of other dietary lipids on the modulation of immune functions. Thus, MUFA that constitute olive oil were initially considered as neutral fatty acids. Nevertheless different studies demonstrated that olive oil is clearly involved in anti-inflammatory activities and in the modulation of immune response (reviewed in Puertollano et al., 2010). The anti-inflammatory activity of olive oil appears to be associated with the production of the metabolite eicosatrienoic acid from oleic acid (20:3 *n-9*), which is a potent inhibitor of LTB_4 (James et al., 1993). In addition it is possible that beneficial effects of olive oil may be in part due to the presence of natural antioxidants, contributing to an increase in the stability of oil (Linos et al., 1999).

Taken together there is evidence that both *n-3* PUFA and *n-9* MUFA can be useful in treatment of inflammatory disorders associated with autoimmune disease. Table 2 summarizes a list of some of the diseases and conditions with an inflammatory component that could be beneficially affected by *n- 3* and *n-9* series fatty acids.

- Acute cardiovascular events
- Acute respiratory distress syndrome
- Allergic disease
- Asthma (childhood and adult)
- Atherosclerosis
- Cancer cachexia
- Chronic obstructive pulmonary disease
- Cystic fibrosis
- Inflammatory bowel disease (Crohn's disease, ulcerative colitis)
- Lupus
- Multiple sclerosis
- Neurodegenerative disease of ageing
- Obesity
- Psoriasis
- Rheumatoid arthritis
- Systemic inflammatory response to surgery, trauma and critical illness
- Type 1 diabetes
- Type 2 diabetes

Table 2. Inflammatory disorder where fatty acids could be useful. Diseases are listed in an alphabetical order (Adapted from Calder, 2006).

3. Fatty acids and autoimmune disorders

Autoimmunity is the failure of an organism to recognize its own constituent parts as self, which results in immune responses against its own cells and tissues. Autoimmunity involves an inflammatory response against own tissues which are implicated different mechanisms like autoantibodies production, immunocomplex formation and lymphocytes T reactivity. Recently, an important investigation about the implication of fatty acids and dietary lipids in the amelioration of autoimmune diseases has been carried out because of their anti-inflammatory properties (Linos et al., 1999). Below we will summarize the main autoimmune disorder where fatty acids have shown to exert beneficial effects.

3.1 Fatty acids and inflammatory bowel disease

Inflammatory bowel disease (IBD) includes Cronh´s disease and ulcerative colitis which are autoimmune disorders characterized by an exacerbated inflammatory response against innocuous stimulus in gastrointestinal tract. Their pathogenesis is considered to include disorders of the immunomodulation of the bowel mucosa which results in lesions of the epithelium tissue layer caused by activated T cells, mononuclear cells and macrophages. In Crohn's disease the mucosa of the whole alimentary tract from the mouth to the anus can be affected, with maximal manifestation in the ileum and colon, while in ulcerative colitis the mucosa of the colon is mainly affected. In both diseases inflammatory cytokines and eicosanoids like LTB_4 are actively produced in situ (Sharon et al., 1984).

The gastrointestinal system is subjected to sustained exposure to ingested foods throughout the whole life, and this gives rise to interactions between food components and gastrointestinal mucosal cells. Interactions with transporters and transcription factors contribute to the modulation of various responses, including those of cells involved in

inflammatory processes. There are, however, specific chronic diseases of the alimentary tract that are based on inflammatory processes and hence are bound to be susceptible to modulation by dietary FA.

3.1.1 Role of dietary lipids on animal models of IBD

Several studies with animal models of IBD, especially chemical induced colitis, have been developed after the recognition of anti-inflammatory properties of *n*-3 PUFA. Generally researches show that fish oil rich diet are involved in the amelioration of the disease comparing with *n-6* fatty acid oil rich diet. In this way different studies have demonstrated convincingly the reduction on colonic damage and ulceration (Vilaseca et al., 1990; Yuceyar et al., 1999), reduction in cell recruitment and activation (Andoh et al., 2003; Whiting et al., 2005) decreasing levels of LTB_4 and PGE_2 on plasma and gut mucosa (Shoda et al., 1995; Nieto et al., 2002; Hudert et al., 2006) and reduction of pro-inflammatory cytokines (Andoh et al., 2003) in animals fed with *n-3* PUFA rich diet.

The effects of fatty acids on an animal model of Cronh's disease have been proved too. Lately Matsunaga et al. have reported for the first time that *n-3* fatty acids ameliorate the ileum inflammation in a murine model of spontaneous and chronic ileitis that closely resembles human Cronh's disease. Specifically these authors have shown that *n-3* fatty acids diets are capable to decrease the ileum inflammation markers, cells recruitment and infiltration and pro-inflammatory mediators like monocyte chemoattractant protein-1(MCP-1) and IL-6 (Matsunaga et al., 2009).

A number of investigators have studied the effect of olive oil rich diet on animals models of IBD too. In this way Camuesco et al. have reported a lower colonic inflammatory response in rats fed with olive oil-based diet and this anti-inflammatory effect is increased when the olive oil diet is supplemented with a 4% of fish oil (Camuesco et al., 2005). Another study has described a beneficial effect of extra virgin olive oil in colitis associated colon carcinogenesis. A reduction on colonic inflammation, proinflammatory cytokines and less incident and multiplicity of tumours have been reported in rats fed with extra virgin olive oil versus sunflower oil (Sanchez-Fidalgo et al., 2010).

Generally animal models have shown a beneficial effect of *n-3* and *n-9* fatty acids in the development of IBD.

3.1.2 Trials in human patients

The established role of AA derived eicsanoids in pathophysiology of inflammatory bowel diet, and especially and inadequate *n*-6/*n*-3 balance, may play an important role in establishing and perpetuating of the disease. Indeed, multivariate analysis suggested that the recently increased consumption of *n*–6 FA in Japan, resulting in an increased ratio of *n*–6 to *n*–3 PUFA and possibly also elevated AA levels, may be responsible for the increased incidence of Crohn's disease in this country (Shoda et al., 1996).

In recent years some pilot studies have been carried out to analyze the effects of fish oil on IBD patients (reviewed by Calder, 2008a). A number of several randomized, placebo-controlled, double-blind studies on the effects of fish oil (2.7–5.6 g/d) in IBD have reported benefits, including improved clinical scores, mucosal histology, sigmoidoscopic score and lower rates of relapse. In this way an interesting study reported a decreased incidence of relapses in patients with Crohn's disease in remission who received a supplemented of enterically coated fish oil for 1 year; there was a significant reduction in the proportion of

relapse on fish oil group, 28%, compared with placebo group, 69%, over 12 months. In addition this difference was maintained at 12 months, with an incidence of remission of 59% in fish oil group versus 26% in placebo group (Belluzzi et al., 1996). However another studies have not found beneficial effects of *n-3* fatty acids supplementation in IBD patients (Loeschke et al., 1996; Lorenz-Meyer et al., 1996).

Studies about the effect of olive oil in IBD patients are limited and most of them used the olive oil as a placebo because *n-9* MUFA was considered as a neutral fat. Although preliminary studies of Dr. Gassull research group had demonstrated that *n-9* MUFA might be beneficial inducing remission of Crohn's disease (Gonzalez-Huix et al., 1993; Fernandez-Banares et al., 1994). The first multicentre, randomized and double-blind trial to evaluate the influence of fat composition in enteral nutrition have not been successful. Nevertheless the results are not conclusive because of the small sample size (smaller than was initially estimated). The study was prematurely finished and the source of oleic acid used in this trial was synthetic trioleate and not olive oil as in the other studies (Gonzalez-Huix et al., 1993). Olive oil contains polyphenols, another components with a potent antioxidant activity and this fact may contribute to different effects of vegetables oil and even though olive oil and *n-9* MUFA (Owen et al., 2000).

Studies in which olive oil have been used as a placebo have reported contradictory results. Lorenz et al. have shown an increased activity of disease in patients of ulcerative colitis and Crohn's disease supplemented with olive oil as a placebo versus fish oil group (Lorenz et al., 1989; Romano et al., 2005). However others authors have not founds differences between both groups of supplementation (Greenfield et al., 1993; Trebble et al., 2005).

In spite of several favourable studies about the use of fatty acids, and specially fish oil, in the treatment of IBD the evidence of clinical benefits are limited. The soundest result was the potential of *n-3* PUFA to maintain the patients of Crohn's disease in remission (Belluzzi et al., 1996). However, this observation was not confirmed in a recent larger study using a similar protocol (Feagan et al., 2008). One reason why dietary lipids might be more effective in animal models than in human patients is the different dose of assay. In human trials the dose of fatty acids are lower compared with the dose in animals studies (higher compared with habitual human consumption doses).

3.2 Fatty acids and rheumatoid arthritis

Rheumatoid arthritis is a chronic inflammatory autoimmune disease that affects about 1% of adult population and is more frequent in women than men. Rheumatoid arthritis is characterized by joint inflammation, swelling, pain, impaired function, stiffness, osteoporosis, muscle wasting, and the participation of inflammatory cells (macrophages, T lymphocytes, plasma cells infiltrating the synovium). All the mediators of inflammation (cytokines, interleukins and typical pro-inflammatory factors and proteins) are actively produced by synovial cells. COX-2 is over-expressed in the synovium of patients, and its eicosanoid products, in addition to those of the 5-LOX, are found in the synovial fluids (Sano et al., 1992; Sperling, 1995). In addition rheumatoid arthritis is also characterised by signs of systemic inflammation, such as elevated plasma concentrations of some cytokines (e.g. IL-6), acute-phase proteins and rheumatoid factors. The relevance of the pro-inflammatory COX pathway is also underlined by the efficacy of the pharmacological inhibition of this pathway (e.g. by non steroidal anti-inflammatory drugs).

There is evidence that rheumatoid arthritis is less severe in Mediterranean countries where consume of fish oil, fruits and vegetables and olive oil are higher than in other countries (Pattison et al., 2004). This report, joint to the special relevance of COX pathway on the development of the disease, has brought about a great number of studies where the role of dietary lipids in the management of rheumatoid arthritis has been evaluated.

3.2.1 Some studies with animal models

Interest in the use of *n-3* fatty acids in rheumatoid arthritis began in the mid-eighties, following the demonstration in several autoimmune strains of mice that *n-3* fatty acids reduced the severity of diffuse proliferative glomerulonephritis (Simopoulos, 2002). Further studies have shown the efficacy of fish oil in the development of the animal disease. For instance in an early study Leslie et al. shown that fish oil increased the time of onset of arthritis and decreased the incidence and severity of this disease in a murine model of type II collagen-induced arthritis(Leslie et al., 1985). Another researchers have reported a mouse model of rheumatoid arthritis fed with fish oil and have shown a significantly lower serum levels of interleukins IL-6, IL-10, IL-12 and in tumour necrosis factor-α (TNF-α), PGE_2, TXB_2 and LTB_4 compared with levels in mice fed corn oil (Venkatraman et al., 1999). Similarly, EPA and DHA incorporation into macrophage phospholipids via oral administration resulted in a reduction of streptococcal cell wall arthritis in Lew/SSN rats (Volker et al., 2000).

On the other hand it is well known that rheumatoid arthritis is characterized by joint and tissue damage and this damage occurs by a variety of mechanisms, many of which involve reactive oxygen species (ROS). ROS can cause destruction of hyaluronic acid and disruption to collagen, proteoglycans, protease inhibitors, and membrane function, the latter via oxidation of membrane fatty acids. The initiation of rheumatoid arthritis is believed to result in an increase in the concentration of macrophages and neutrophils in the synovial fluid and free-radical-producing enzymes. This leads to high levels of ROS in the joints, which increases and prolongs inflammation and damage (Darlington et al., 2001). Olive oil, and especially extra virgin olive oil, is rich in antioxidants compounds. Taking account the role of ROS in joint and tissue damage on development of rheumatoid arthritis, the effect of olive oil can be especially useful in this kind of disease. Indeed Martinez-Dominguez et al. have shown the efficacy of an olive oil supplemented with polyphenols in animal models of arthritis (Martinez-Dominguez et al., 2001).

3.2.2 Efficacy of fatty acids on human disease

During the 80s and 90s several studies in patients with rheumatoid arthritis showed the beneficial effects of *n-3* PUFA on the development of the disease. Several authors reported that fish oils reduces the production of inflammatory mediators like LTB 4 by neutrophils and monocytes (Kremer et al., 1985; Kremer et al., 1987; Cleland et al., 1988; Tulleken et al., 1990; van der Tempel et al., 1990) and IL-1β by monocytes (Kremer et al., 1990). There is also evidence of reduction in the plasma concentrations of IL-1 (Espersen et al., 1992)and C-reactive protein (Kremer et al., 1985), and normalized neutrophil function (Sperling et al., 1987).

A number of randomized, placebo-controlled, double-blind studies of fish oil treatments have been reported. In different reviews Calder have summarized the results of studies with a dose of fatty acids between 1.6 and 7.1 g/d (average of 3.5 g/day EPA + DHA) and almost

of them reported some benefit (Calder, 2006; Calder, 2008b; Galli et al., 2009). Clinical symptoms were improved, including reduced duration of morning stiffness, number of tender or swollen joints, joint pain, time of fatigue and increased grip strength. Particular relevance has the reduction of the use of anti-inflammatory drugs.

n–3 PUFA may act as anti-inflammatory agents by competition whit AA for incorporation in the eicosanoid pathway. This efficacy of *n-3* PUFA may be achieved in rheumatoid arthritis by simultaneously decreasing of *n*-6 PUFA intake, especially AA. Indeed Adam et al. have shown that a diet supplemented with *n-3*-PUFA and AA restricted is able to ameliorate clinical signs of inflammation like tenders and swollen joints and to decrease the formation of eicosanoids such as leukotrienes and prostaglandins (Adam et al., 2003). This study shows also that intakes of preformed AA, in addition to formation from the precursor LA, may be a factor in the modulation of AA levels in the body, and since LA and AA are provided by quite different sources (seed oils vs. lean meat), this should be taken into consideration in the evaluation of strategies for optimal *n–3* FA intakes.

Several reviews about the role of fish oil in rheumatoid arthritis patients have been carried out and most of them conclude that there was strong evidence about benefits of *n-3* PUFA on the management of this disease (Cleland et al., 2000). These reviews have shown that fish oil is able to improve the signs of the disease like number and severity of tender joint, number of swollen joints, physician and patients´ global assessment and use of anti-inflammatory drugs among others effect (Simopoulos, 2002; Stulnig, 2003; Calder, 2006; Calder, 2008a; Galli et al., 2009). Indeed an editorial comment about the use of fish oil in this disease concluded that dietary fish oil supplements should be regarded as part of a standard therapy for rheumatoid arthritis (Cleland et al., 2000).

With reference to olive oil a study by Linos et al. (Linos et al., 1991) has suggested that a beneficial anti-inflammatory effect of olive oil consumption on rheumatoid arthritis may be possible. In fact, this study compared the relative risk of development of rheumatoid arthritis in relation to lifelong consumption of olive oil in a Greek population and demonstrated that high consumers of olive oil (almost every day throughout life) had four times less risk than those who consumed olive oil less than six times per month on average throughout their lives; by contrast the effect of fish consumption was also tested without statistically significant findings (Linos et al., 1991).

A number of studies that examined the benefits of fish oil in rheumatoid arthritis used an olive oil placebo for the control groups. Kremer et al. evaluated the effect of fish oil supplementation on the progression and severity of the disease using olive oil as a placebo. Unexpectedly clinical evaluation and immunologic test showed similar results in both groups. No explanation of the improvements showed by the olive oil groups was given, although changes in immune function may be responsible (Kremer et al., 1990). A more recent research has reported an improvement in beneficial effect of fish oil when is mixed together olive oil versus a supplementation with only fish oil , suggesting a positive action of olive oil in signs and symptoms of rheumatoid arthritis (Berbert et al., 2005).

Taking together all these results and facts revised in this section, it can be concluded that there are strong evidences to justify the positive effects of fish oil in the management of rheumatoid arthritis. On the other hand, although the results are still preliminary, combination of olive oil and fish oil may be more favorable because of the antioxidant effect of olive oil joint to the anti-inflammatory potential of both oils.

3.3 Fatty acids in systemic lupus erythematosus

Systemic lupus erythematosus (SLE) is a complex autoimmune disease with heterogeneous clinical manifestations and disease course and most of cases occurring in women of childrenbering age. It is characterized by the deregulated innate and adaptive immune pathways and the development of anti-nuclear antibodies (ANA). Mortality of patients with SLE is significatly correlated wiht development of glomerulonephritis. Binding of autoantibodies, specially IgG anti-DNA, and immunecomplex depositions within the kidneys recruits leukocytes and this infiltration results in an inflammatory response that can lead to irreparale renal parenchymal damage (Pestka, 2010).

3.3.1 Studies with animal models

Several studies with animal models of SLE have been carried out about the role of dietary lipids in the development of the disease and generally most of them concluded a beneficial effect of fish oil (reviewed in Pestka, 2010).

Early studies of Prickett and his research group showed that administration of fish oil to young mice induced a reduction on severity and incidence of renal disease and increased the lifespan of NZB/NZW mice (Prickett et al., 1981; Prickett et al., 1982; Prickett et al., 1983), even fish oil was able to reduce the progression of established renal damage in another mouse model of lupus (Robinson et al., 1986). Other studies have reported a link between increased lifespan and reduced renal damage and reductions of anti-DNA autoantibodies and circulating immunocomplexes in NZB/NZW (Alexander et al., 1987).

Subsequently several studies have demonstrated that the amelioration of disease in these animal models were linked with the action of fish oil over eicosanoids metabolism (Kelley et al., 1985; Spurney et al., 1994; Venkatraman et al., 1999).

Results from Fernandes laboratory have reported that DHA, but not EPA, is the most potent *n-3* fatty acid that suppresses glomerulonephritis and extends life span of systemic lupus erythematosus-prone NZB/NZW mice (Halade et al., 2010). In addition the same authors have proved that the beneficial action of fish oil in lupus animal models is increased by caloric restriction (Jolly et al., 1999; Jolly et al., 2001).

3.3.2 Clinical trials

Numerous studies have evaluated the possible beneficial action of fish oil in lupus patients although the results are not so conclusive like animal studies. Indeed two early clinical trials suggested that fish oil supplementation has little value in management of lupus nephritis when it is compared with olive oil (Westberg et al., 1990; Clark et al., 1993). However two double blind studies have reported a benefit in disease criteria and lupus score (Walton et al., 1991; Duffy et al., 2004). More recently investigations have shown that fish oil, and more specifically EPA, may be useful in the amelioration of lupus disease because of the decreasing oxidative stress, improving endothelial functions and conferring cardiovascular benefits (Nakamura et al., 2005; Wright et al., 2008).

In view of the previous reports we can conclude that, in spite of fish oil supplementation may be useful in the amelioration of lupus and prevention of renal disease, new and larger investigations must be carried out to clarify the role of fatty acids in development of this disease.

3.4 Fatty acids and multiple sclerosis

Multiple sclerosis (MS) is a Central Nervous System-specific demyelinating disease and is the most common neurological disorder that occurs in young adults. Although the aetiology

of MS remains unknown there is strong evidence for the presence of autoimmune mechanisms in the disease pathogenesis. Pro-inflammatory cytokines from activated T cells and macrophages have been strongly implicated in the pathogenesis of MS, like the up-regulation of adhesion molecules on endothelial cells and the subsequent infiltration of activated T cells into the Central Nervous System.

An association between dietary fat intake and the incidence of multiple sclerosis was first proposed by Swank in 1950 (Swank, 1950). Some epidemiological studies have been carried out later and the most of them indicate that diets rich in saturated fatty acids are detrimentally associated with MS, while PUFA acid rich diets are beneficially associated with MS. Studies from Harbige laboratory have shown that the relationship between linoleic acid (*n-6*) and dihomo-g-linoleic acid (DGLA), and also between DGLA (*n-6*) and AA is clearly disturbed in MS compared with healthy controls. This may indicate a problem with δ6 and δ5 desaturation and / or a greater requirement for these *n-6* fatty acids in many of the MS patients (Harbige et al., 2007).

3.4.1 Fatty acids in animal models of multiple sclerosis

Experimental autoimmune encephalomyelitis (EAE) is an experimentally induced CD4+ T cell mediated autoimmune inflammatory and demyelinating disease in rodents often used as a useful animal model of MS.

Administration of PUFA can reduce the clinical severity of EAE. Indeed LA supplementation has been shown to reduce the severity of EAE in guinea pigs when it is administered before EAE induction (Meade et al., 1978; Hughes et al., 1980). Harbige et al. also demonstrated that gamma linoleic acid (GLA) supplementation could reduce the severity of both acute EAE and the relapsing phases of chronic. Further analysis revealed an increase in production of transforming growth factor β-1 and PGE_2, both associated with a reduction in the inflammatory response in EAE models (Harbige et al., 1995; Harbige et al., 1997; Harbige et al., 2000).

3.4.2 Clinical trials in human patients

Following the preliminary epidemiological studies by Swank, several researches have attempted the role of PUFA in the development of MS. In this way Millar et al. carried out a double-blind study with LA and olive oil during 24 months. These authors reported an improvement in relapse severity and nonsignificant trends towards lower relapse rates but no difference in disability (Millar et al., 1973). Later, Paty et al. did not find such effects in a similar trial with higher doses of oleic acid as a placebo (Paty et al., 1978). No conclusive data have been found in other trials realized with GLA in combination with LNA (Bates et al., 1977).

However more recently Harbige et al. have reported a randomised double-blind placebo controlled trial to determine the effects of supplementation with selected GLA rich borage oil. Data proved that high dose of this oil reduced the relapse rate and disability progression as measured by EDSS (Expanded Disability Status Scale) and compared with a placebo of polyethylene glycol and with low dose of the same oil (Harbige et al., 2007). Although these data are very positive, the number of patients enrolled in the trial is limited (n=36) and no conclusive statements can be made.

The fish oil action in MS has been investigated too but some studies have not been successful. Two double blind controlled clinical trials have been carried out to evaluate the

effect of fish oil in the disease without significant findings. In these trials olive oil was used as a placebo again and although nonsignificant trends, toward less disability and certain improvements in quality of life, have been found the results are inconclusive (Bates et al., 1989; Weinstock-Guttman et al., 2005). However others researchers have found beneficial effects of fish oil in MS patients. Shinto et al. have reported that *n-3* fatty acids supplementation significantly decreased matrix metalloproteinase-9 (MMP-9) levels in relapsing-remitting MS. This enzyme is thought to have a significant role in the transmigration of inflammatory cells into the central nervous system by aiding in the disruption of the blood brain barrier. In this way the ability of *n-3* fatty acids to decrease the levels secreted by immune cells may be a significant observation in spite of significant changes in quality of life have not been found (Shinto et al., 2009).

Taken over all epidemiological data, animal data and clinical trial we can confirm that PUFA, particularly *n-6* fatty acids, have a role in the pathogenesis and treatment of multiple sclerosis. However different factors must be better controlled in the clinical trials to achieve convincing results, like trials design, sample size and the choice of an appropriate placebo. This last item is of a great important because of olive oil has been used as a placebo in most of the reviewed clinical trials, however experience of our laboratory and others clearly proved the great immunomodulator potential of this fat, usually considered relatively inert (Puertollano et al., 2004; Puertollano et al., 2010). In this way olive oil may be acting in immune system of MS patients and no significant different with *n-3* and *n-6* PUFA can be found.

3.5 Action of dietary lipids in type 1 diabetes mellitus

Type 1 diabetes mellitus (T1DM) is an autoimmune disease characterized by the destruction of insulin-producing beta cells in the pancreatic islets. Dietary factors have been implicated in the aetiology of type 1 diabetes as well as in initiating the autoimmune process that leads to clinical disease. Macrophages and T cells, attracted to the islets, secrete soluble mediators such as oxygen free radicals, nitric oxide (NO), and the cytokines IL-1ß, interferon (IFN)-γ and TNF-α. Increasing evidence suggests that these mediators induce apoptosis, the main mode of ß-cell death in the development of T1DM. Fatty acids, because of their properties as anti-inflamatory compounds as well as cell apoptosis modulators, may be useful in the management of T1DM.

3.5.1 Findings from studies in animal models of type 1 diabetes

Earlier investigations suggested that deficiency of essential fatty acids, including *n-6* and *n-3* PUFA, caused a resistance in development of the diabetes in certain animal models (Lefkowith et al., 1990; Wright et al., 1995).

However, in 2001 Krishna Mohan & Das carried out a study to evaluate the effect of supplementation of various PUFA-rich oils on the incidence of alloxan-induced diabetes in experimental animals (Krishna Mohan et al., 2001). These authors have reported that *n-3* and *n-6* fatty acids may prevent alloxan-induced diabetes in experimental animals administered before of the diabetogenic agent and this preventive action may reside in their ability to enhance antioxidant status, suppress cytokine production, and activate PPARs. These researchers have evaluated also the effect of estearic saturated FA, oleic MUFA and *n-6* AA PUFA in the same model finding that only AA was effective (Suresh et al., 2006).

Recently others authors have evaluated the efficacy of a right balance *n-6*/*n-3* PUFA in diet of T1DM model NOD mice finding that low *n-6*/*n-3* ratio delays the onset of diabetes

(Kagohashi et al., 2010b). Other studies from the same laboratory have shown that the most effective strategy in prevention of the disease in the offspring is an adequate dose of *n-6/n-3* PUFA in maternal diet during gestation and lactation (Kagohashi et al., 2010a).

3.5.2 Trials with type 1 diabetes mellitus patients

In 2003 an interesting pilot case-study was carried out in Norway to the attempt to test the hypothesis that cod liver oil, taken either by the mother during pregnancy or by the child during the first year of life, is associated with a lower risk of type 1 diabetes among children. A significant association between the use of cod liver oil during the first year of life and a lower risk of type 1 diabetes was found (Stene et al., 2003). In a similar way, an observational longitudinal study was carried out in U.S.A., the Diabetes Autoimmunity Study in the Young (DAISY). During 13 years a total of 1770 children at increased risk for type 1 diabetes were sudied. Th results revealed that dietary intake of *n-3* fatty acids is associated with reduced risk of islet autoimmunity in children at increased genetic risk for type 1 diabetes. This association is further substantiated by the pilot observation of a higher proportion of *n*-3 PUFA in the erythrocyte membranes (Norris et al., 2007). However the same authors later reported that there was a lack of association between *n-3* PUFA intake and conversion to type 1 diabetes in children with islet autoimmunity (Miller et al., 2011).
In spite of certain positive data in animal models and human patients nowadays we can not confirm a justification for the use of fatty acids in preventing the development of type 1 diabetes mellitus.

4. Conclusions

In the recent years the immunonutrition area has advanced significantly to elucidate the role of the diet in development and function of immune system and to prevent or ameliorate numerous diseases in which immune system is implicated like infections, cancer, inflammatory disease, allergies and autoimmune disorders. Among the diet components, fatty acids (PUFA in particular), are especially interesting by their immunomodulator and anti-inflammatory role.
Autoimmune disorders are a complex group of disease characterized by an exacerbated immune response against self structures and an elevated inflammatory state. Several investigations have shown that fatty acids and especially *n-3* PUFA act as potent anti-inflammatory molecules and even induce a strong immunosupression. For this reason, the use of fatty acids has been considered a good a therapeutic strategy in prevention and treatment of these diseases.
In spite of convincing data from the several studies with animal model, clinical trials have not achieved similar results. Only clear evidence in management of rheumatoid arthritis and in remission maintenance in Crohn's disease patients justifies the use of fish oil, and perhaps in combination with olive oil. However results from studies with other diseases like ulcerative colitis, lupus and multiple sclerosis are promising. Future studies with a better control of placebo, number of enrolled patients and design are necessary to justify of use of fatty acids in this type of immune disorders.
Finally epidemiological studies report that Mediterranean countries with a traditionall diet rich in fruits and vegetables, fish oil and olive oil and poor in saturated fats, have lower levels of inflammatory disease than countries with other type of diet. In the same way countries like Japan with changes in the habitual diet to "western diet" have increased rates

of inflammatory disease. In our opinion the best strategy recommending to population in general, and autoimmune disease patients in particular, is the maintenance of a healthy diet rich in naturals antioxidants (fruit, vegetables, olive oil), moderate consumption of fats and a well balanced of *n-6/n-3* fatty acids.

5. Acknolwegments

To Dr. José Manuel Martínez Martos and Dr. Mª Jesús Ramírez Expósito , from University of Jaén, Div. of Phisiology, for their assistance with the manuscript.

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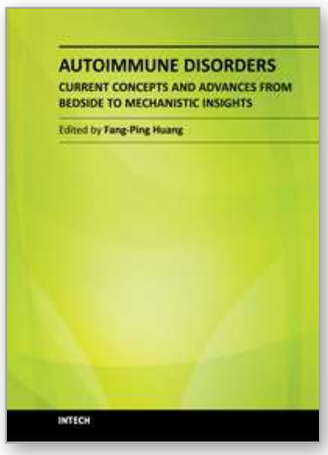

Autoimmune Disorders - Current Concepts and Advances from Bedside to Mechanistic Insights

Edited by Dr. Fang-Ping Huang

ISBN 978-953-307-653-9
Hard cover, 614 pages
Publisher InTech
Published online 14, November, 2011
Published in print edition November, 2011

Autoimmune disorders are caused due to break down of the immune system, which consequently fails in its ability to differentiate "self" from "non-self" in the context of immunology. The diseases are intriguing, both clinically and immunologically, for their diversified clinical phenotypes and complex underlying immunological mechanisms. This book offers cutting-edge information on some of the specific autoimmune disease phenotypes, respective diagnostic and prognostic measures, classical and new therapeutic options currently available, pathogenesis and underlying mechanisms potentially involved, and beyond. In the form of Open Access, such information is made freely available to clinicians, basic scientists and many others who will be interested regarding current advances in the areas. Its potential readers will find many of the chapters containing in-depth analysis, interesting discussions and various thought-provoking novel ideas.

How to reference

In order to correctly reference this scholarly work, feel free to copy and paste the following:

Elena Puertollano, Maŕia A. Puertollano, Gerardo Álvarez de Cienfuegos and Manuel A. de Pablo (2011). Role of Fatty Acids in the Resolution of Autoimmune and Inflammatory Diseases, Autoimmune Disorders - Current Concepts and Advances from Bedside to Mechanistic Insights, Dr. Fang-Ping Huang (Ed.), ISBN: 978-953-307-653-9, InTech, Available from: http://www.intechopen.com/books/autoimmune-disorders-current-concepts-and-advances-from-bedside-to-mechanistic-insights/role-of-fatty-acids-in-the-resolution-of-autoimmune-and-inflammatory-diseases

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