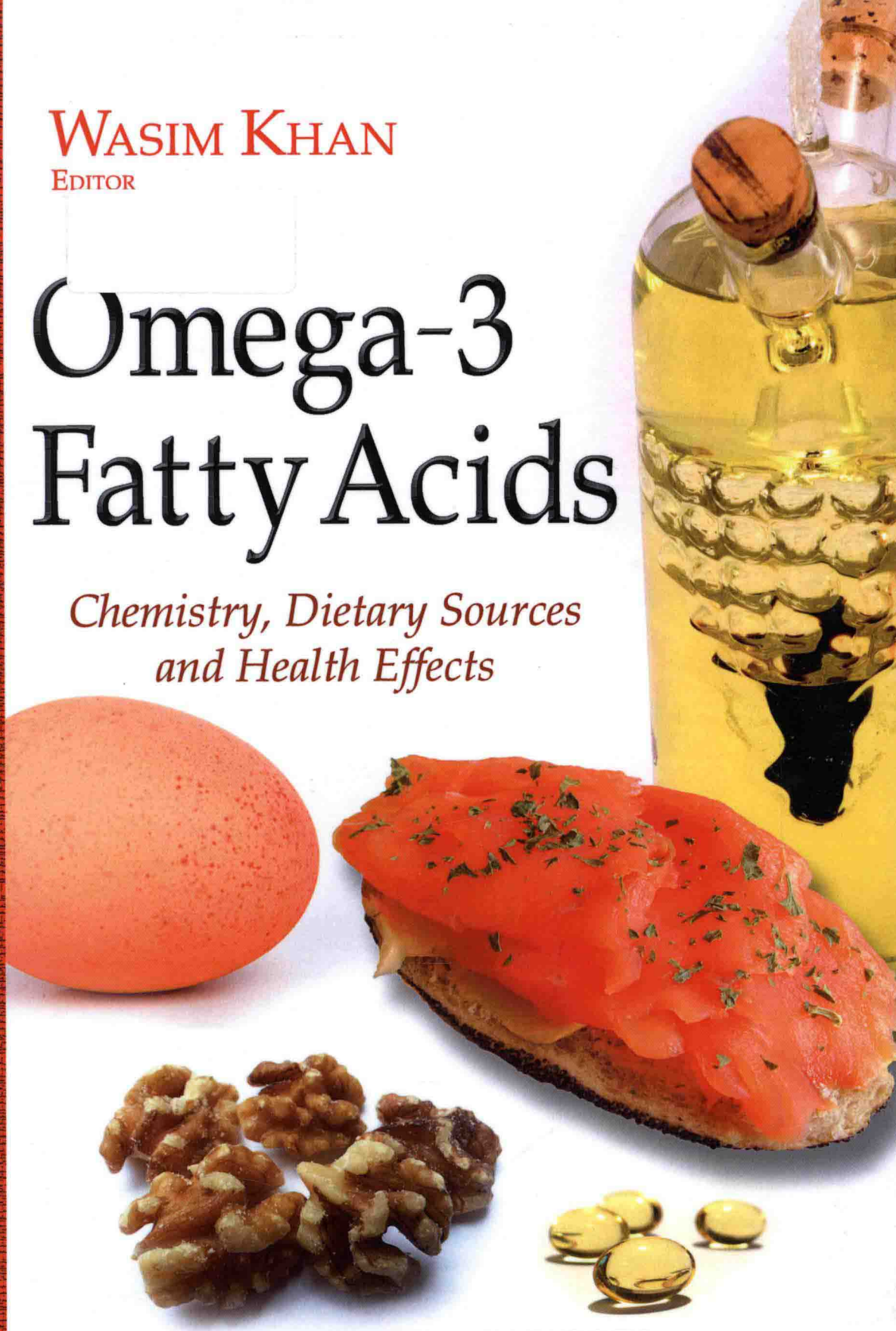
WASIM KHAN
EDITOR

Omega-3 Fatty Acids

Chemistry, Dietary Sources and Health Effects



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OMEGA-3 FATTY ACIDS

CHEMISTRY, DIETARY SOURCES AND HEALTH EFFECTS

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Preface

Hippocrates (460-377B.C), the father of medicine recommended, *"Let thy food be thy medicine and thy medicine be thy food"*. Such an idea reflected the importance of dietary supplements for their therapeutic and preventive bioactive components due to their elevated margin of safety and desired range of efficacy.

The last two decades have witnessed a major drift in the interests of the scientific community towards providing better means to containing the health risks of the human race. The century old chemotherapies against various disorders have never been a success, albeit not a total failure. Such therapies have a major drawback of side effects that give rise to unseen disorders that emerge as a new challenge. In this regard, the concept of foodstuffs as natural medicines i.e. nutraceuticals has become very attractive.

Interest in the omega-3 fatty acids as health-promoting nutrients has increased exponentially in the recent decade. Early clues to the possible importance of unsaturated fatty acids especially polyunsaturated fatty acids (PUFA) came from studies showing that young humans and experimental animals experienced impaired growth when all fatty acids were removed from the diet. Small amounts of ω-3 (α-linolenic acid) or ω-6 (linoleic acid) fatty acids prevented that impaired growth and thus were termed as "essential". Highly unsaturated/polyunsaturated fatty acids (HUFA/PUFA) were relatively found to be several-fold more effective.

Further studies have revealed that ω-3 PUFA have numerous health benefits. ω-3 PUFA especially from fish/marine foods were found to be effective in lowering incidence of various pathologies. This stems from the observations of the difference in prevalence of coronary heart disease and other chronic diseases (including psoriasis, bronchial asthma, diabetes mellitus and thyrotoxicosis) in the Greenland Inuit (Eskimo) population relative to Western populations. ω-3 PUFA (e.g. EPA and DHA) from marine fish and mammals were indicated as the main dietary factor responsible for such differences. The consumption of fish has now been linked with the rate of depression among various populations. In countries where people eat the least fish the rate of depression is highest, and vice versa. This correlation holds true across the world.

The most dramatic change in what we eat has happened in the past century, with industrialization and development of the food industry, the intake of saturated fat, trans fat and especially ω-6 enriched refined oils have enormously increased whereas the consumption of ω-3 PUFA has considerably declined. These dietary imbalances in fat intake, in fact, are

prime cause of modern sufferings like cancer, hypertension, diabetes, depression, cardiovascular and renal disorders.

Sea fish are considered the best sources of omega-3 fatty acids, but consumption of fish is too low to meet the requirements. Efforts to supplement foods with omega-3 fatty acids have had drawbacks mainly due to the "unappealing taste" associated with the oxidation products of PUFA due to the highly labile nature of raw materials. Thus, the scientific community was presented with the difficult challenge of delivering highly unsaturated fatty acid foods that are appealing to taste buds. The stability of omega-3 fatty acids is dictated not only by the number of double bonds present in the molecules but also by the endogenous and exogenous antioxidants employed as well as the system in which they are incorporated. Microencapsulation of products as a means of delivering these highly labile materials to foods has thus been perfected and introduction of PUFA to bread, cereal, and dairy based products and spreads has slowly been taking place. Furthermore, production of omega-3 capsules as well as concentrates and structured lipids containing omega-3 fatty acids has led to a large number of over the- counter supplements and nutraceuticals.

It is the purpose of this book to present a detailed assessment of the current research about the chemistry, nutrition, and health aspects of omega-3 fatty acids and to address stability issues and the potential for their delivery in functional foods. We are highly indebted to participating authors who provided authoritative views and results of their latest investigations on different aspects of omega-3 fatty acids.

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Contents

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Chapter 1

The Link between Omega-3 Fatty Acids and Rheumatoid Arthritis: Properties, Mechanisms and Therapeutic Efficacy

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Abstract

Omega-3 fatty acids (FAs) are long chain polyunsaturated fatty acids characterized by a double (C=C) bond starting after the third carbon atom from the end of the carbon chain. These FAs are known to be primarily abundant in fish and plant oil products. Numerous studies indicate that omega-3 FAs have anti-inflammatory properties and, therefore, might be useful in the management of inflammatory and autoimmune diseases such as Rheumatoid Arthritis (RA). Rheumatoid arthritis (RA) is one of the systemic

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inflammatory disorders that gained widespread importance in every aspect of research due to its controversy of reducing the lifespan of patients from 3 to 12 years. It is a common disorder that affects both men and women at the prime of their lives with extra-articular manifestations that include vasculitis, lung disease, pericarditis, neuropathy, and subcutaneous nodules. This chapter will discuss the pharmacological properties, mechanisms, and therapeutic efficacy of various omega-3 FAs as it relates to RA, as well as the importance of omega-6/omega-3 ratio balance to such disease.

Keywords: Omega-3 fatty acids, rheumatoid arthritis, eicosanoids, inflammation, omega-6/omega-3 ratio

Introduction

Polyunsaturated fatty acids (PUFAs) are known to play critical roles for the proper functioning of the human body. A group of PUFAs called omega-3 fatty acids (FAs) have become important due to its diverse physiological effects in cellular functions and processes. Among all fatty acids, it is these fatty acids, which possess the most immunomodulatory activities. It has been shown through animal experiments and clinical intervention studies that that omega-3 FAs have anti-inflammatory properties, thus, might be beneficial for the management of inflammatory diseases (Simopoulos, 2002).

Although not yet confirmed as an approved health claim, current research suggests that the anti-inflammatory activity of long chain omega-3 FAs may translate into clinical effects (Wall, Ross, Fitzgerald, and Stanton, 2010). As an example, evidence shows that rheumatoid arthritis (RA) sufferers taking omega-3 fatty acids from fish sources have reduced pain compared to those receiving standard non-steroidal anti-inflammatory drugs (NSAIDs) (Ruggiero et al., 2009).

This chapter will discuss the importance of omega-3 fatty acids as it relates to RA. As a starting point in the discussion and to facilitate readers, we briefly discussed the symptoms, causes, and pathogenesis of the disease.

Rheumatoid Arthritis

Symptoms and Causes

Rheumatoid arthritis (RA) is a common chronic inflammatory and destructive arthropathy that cannot be cured and that has substantial personal, social, and economic costs (Choy and Panayi, 2001). It is considered as the most common inflammatory arthritis and is a major cause of disability (Firestein, 2003). The disease is characterized by synovial inflammation and hyperplasia ("swelling"), autoantibody production (rheumatoid factor and anti-citrullinated protein antibody, cartilage and bone destruction ("deformity"), and systemic features, including cardiovascular, pulmonary, psychological, and skeletal disorders (McInnes and Schett, 2011).

A prevalence of 0.5 and 1.0% for the occurrence of RA among several Europeans (Aho, Kaipiainen-Seppanen, Heliovaara, and Klaukka, 1998; Carmona et al., 2002; Cimmino,

Parisi, Moggiana, Mela, and Accardo, 1998; Kvien et al., 1997; Power, Codd, Ivers, Sant, and Barry, 1999; Riise, Jacobsen, and Gran, 2000; Saraux et al., 1999; Simonsson, Bergman, Jacobsson, Petersson, and Svensson, 1999) and North-American (Gabriel, 2001; Gabriel, Crowson, and O'Fallon, 1999) populations has been reported to be relatively constant.

It has also been noted that American-Indians, specifically have the highest recorded occurrence of RA. A high prevalence of RA has been documented in Pima Indians (5.3%) (Del Puente, Knowler, Pettitt, and Bennett, 1989) and in the Chippewa Indians (6.8%) (Harvey, Lotze, Stevens, Lambert, and Jacobson, 1981). In contrast, populations from China and Japan have been reported to have low occurrences (Silman and Pearson, 2002).

RA is known to have been caused by both genetic and environmental factors. Genetically, the role of HLA DRB1 alleles as a risk factor of RA has been established for 25 years. Besides this, the non-MHC genes such as the CYP19, IFN-γ, and other cytokines are known to be genetic risk factors in RA (Silman and Pearson, 2002). Environmental factors also play roles as susceptibility factors for development of RA. In particular, hormonal and pregnancy factors were investigated in association to RA due to the increased risk of RA in females (Silman and Pearson, 2002).

It has been found that in general, male sex hormones, specifically testosterone, are lower in men who have RA (Silman and Hochberg, 2001) whereas the levels of female sex hormones are not different between RA cases and controls (Heikkila et al., 1998). Investigation of pregnancy as a risk factor RA development, on the other hand, led to contradicting results (Silman and Pearson, 2002). Infection is also another environmental factor known to be associated with RA suggesting that exposure to infectious agents such as Epstein-Barr and parovirus maybe triggers for RA (Silman and Pearson, 2002). Further, research shows that Vitamin D deficiency is common in those with RA and may be causally associated (Wen and Baker, 2011).

Pathogenesis

The RA pathogenesis is poorly understood. Approximately half of patients with RA have specific serologic abnormalities several years before the onset of symptoms. IgM rheumatoid factor (IgM-RF) and anti- anti–cyclic citrullinated peptide (anti-CCP) testing with appropriately high specificity may assist in the early detection of RA in high-risk populations (Nielen et al., 2004).

Although widely diverse mechanisms have been responsible for damage in RA, it is unlikely that immune complexes are the underlying cause. The distinguishing feature of RA in a patient constitute self-aggregating complexes of 7s RF while circulating complexes of 19s RF directed against the hinge region of 7s immunoglobulins are considered less specific. Other autoimmune complexes, such as those antibodies mentioned above are considered more specific for RA but have not been fully characterized. The immune complexes together with the neutrophils are essential for RA pathogenesis. The mechanism involve the release of mediators of inflammation and joint destruction (Weissmann, 2004).

Anti-Inflammatory Properties of Omega-3 Fatty Acids

Inflammation is part of the body's immediate response to infection or injury. As a result of an inflammation occurring in uncontrolled or inappropriate manner, excessive damage to host tissues or disease can occur. Rheumatoid arthritis is a chronic inflammatory disease which triggers hyper-expression of cytokines such as tumor necrosis factor α (TNF-α), interleukin 1β (IL-1β) and interleukin 6 (IL-6).

Omega-3 polyunsaturated fatty acids (PUFA) have shown clear evidence of having anti-inflammatory properties through animal experiments and clinical intervention studies. Long-chain omega-3 PUFAs decrease the production of inflammatory eicosanoids, cytokines, and reactive oxygen species and the expression of adhesion molecules. Long-chain omega-3 PUFAs also give rise to a family of anti-inflammatory mediators known as resolvins (P. C. Calder, 2006).

The key relation between PUFAs and inflammation is that eicosanoids, which are among the mediators and regulators of inflammation and they are involved in modulating the intensity and duration of inflammatory responses.

Recent studies have shown that the increased consumption of long-chain omega-3 PUFAs, such as eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) resulted in elevated proportions of those fatty acids in inflammatory cell phospholipids. The inclusion of EPA and DHA into human inflammatory cells is occurring partly at the expense of arachidonic acid (AA) which is usually the major substrate for eicosanoid synthesis. Due to less substrate availability for the synthesis of eicosanoids from AA, a decreased production of prostaglandin E_2 (PGE_2), thromboxane B_2 (TXB_2), leukotriene B_4 (LTB_4), leukotriene E_4 (LTE_4) and 5-hydroxyeicosatetraenoic acid by inflammatory cells have been resulted which in turn reduced the inflammation. EPA can also act as a substrate for cyclooxygenase (COX) and 5-lipoxygenase (5-LOX) resulting eicosanoids that have slightly different structure from those derived from AA, and these are less potent than those formed from AA as inflammatory agents. The reduction in generation of AA derived mediators that associated with the consumption of fish oil had led to the idea that fish oil is anti-inflammatory (P. C. Calder, 2006).

Recent studies have identified a novel group of mediators which are resulted from EPA by COX-2, known as E-series resolvins that showed anti-inflammatory actions (C. N. Serhan, C. B. Clish, J. Brannon, S. P. Colgan, N. Chiang, et al., 2000; C. N. Serhan, C. B. Clish, J. Brannon, S. P. Colgan, K. Gronert, et al., 2000; C. N. Serhan et al., 2002). In addition to EPA, DHA-derived mediators known as D-series resolvins, docosatrienes and neuroprotectins which are resulted by COX-2 activity have also shown anti-inflammatory actions (Hong, Gronert, Devchand, Moussignac, and Serhan, 2003; Marcheselli et al., 2003; Mukherjee, Marcheselli, Serhan, and Bazan, 2004). Apart from these observations, some other studies have shown that the dietary fish oil consumption resulted in decreased leukocyte chemotaxis, decreased production of reactive oxygen species and proinflammatory cytokines, and decreased adhesion molecule expression, which decreased the inflammatory effects (P. C. Calder, 2006).

A dietary supplementation study using 3.1 g of EPA and 14.4 g of DHA has shown a time dependent decrease in chemotaxis of human neutrophils and monocytes toward variety of chemoattractants, including LTB_4, bacterial peptides and human serum. Several studies that included cell culture and animal feeding studies reported decreased production of some adhesion molecules on the surface of monocytes, macrophages or endothelial cells upon exposure to long-chain omega-3 PUFAs. Another supplementation study that provided 3.1 g EPA and 8.4 g DHA has shown decreased production of reactive oxygen species by 30-55%. EPA and DHA are also shown to be capable of inhibiting the production of IL-1β and TNF-α by monocytes and the production of IL-6 and IL-8 by venous endothelial cells (P. C. Calder, 2006).

Fish oil has shown anti-inflammatory effects in several studies which involved patients with rheumatoid arthritis.

Anti-inflammatory effects such as decreased LTB_4 production by monocytes and neutrophils, decreased IL-1 production by monocytes, decreased plasma IL-1β concentrations and serum C-reactive protein concentrations have been reported (Cleland, French, Betts, Murphy, and Elliott, 1988; Espersen, nGrunnet, et al., 1992; Kremer et al., 1985; Kremer et al., 1990; Tulleken, Limburg, Muskiet, and Rijswijk, 1990; H van der Tempel, J E Tulleken, P C Limburg, F A Muskiet, and M H van Rijswijk, 1990). Literature reports on randomized, placebo-controlled, double-blind studies of fish oil in rheumatoid arthritis have shown promising results. Long-chain omega-3 PUFAs used in the dose range of 1.6-7.1 g/d and average of about 3.5 g/d in above studies have shown beneficial effects such as reduced duration of morning stiffness, reduced number of tender or swollen joints, reduced joint pain, reduced time to fatigue, increased grip strength and decreased use of nonsteroidal anti-inflammatory drugs (P. C. Calder, 2006). Furthermore long-chain omega-3 PUFAs may also act as anti-inflammatory agents by competing with arachidonic acid for incorporation in to inflammatory cell membranes and for metabolism by enzymes of eicosanoid synthesis (P. C. Calder, 2006).

Another important anti-inflammatory effect of omega-3 PUFAs is mediated at the level of altered inflammatory gene expression through their effects on transcription factors such as nuclear factor kappa B (NFκB) and peroxisome proliferator-activated receptors (PPARs). NFκB plays a major role in various inflammatory signaling pathways and it controls cytokines such as IL-1, IL-2, IL-6, IL-12, TNF-α and chemokines such as IL-8 and monocyte chemoattractant protein-1. Furthermore NFκB controls adhesion molecules and inducible effector enzymes (Wall et al., 2010). By inhibiting the activity of this pivotal pro-inflammatory transcription factor, NFκB, omega-3 PUFAs help in regulating inflammation. The NFκB pathway includes three major events which are mediated by several proteins and there is evidence that omega-3 PUFAs block each of these three stages independently (Singer et al., 2008). Omega-3 PUFAs and their eicosanoid derivatives act as ligands for PPARs and when activated PPARs bind to the PPAR-response element and repress or induce the transcription of target genes, for example PPARs have shown to inhibit NFκB and therefore it plays a major role in inflammatory processes. EPA and DHA have shown to be down-regulating the lipopolysaccharide –induced activation of NFκB via a PPAR-γ-dependent pathway in human kidney-2-cells (Wall et al., 2010).

Pharmacological Properties of Omega-3 Fatty Acids

Omega-3 FAs includes docosahexanoic acid (DHA), eicosapentanoic acid (EPA), and alpha-linoleic acid (ALA). DHA and EPA are derived from fish or fish oil, while ALA is derived from plants (the main sources are canola and soy bean oils, flaxseeds, and walnut). In the body, ALA can undergo conversion to EPA and DHA, however, this conversion is usually very low. (Burdge, 2004) Omega-3 FA from plant sources may have similar benefits to omega-3 FAs from fish oil, however the benefits are less well-known and only DHA and EPA have the more established benefits.

Regular consumption of fish or fish oil supplement contains omega-3 FAs has been reported to have many beneficial effects and have been used in preventing and managing conditions such as cardiovascular disease (Albert et al., 2002; Hu et al., 2002), diabetes (Brostow et al., 2011; Hendrich, 2010; Storlien et al., 1987), mood change and psychiatric disorder (Magnusson, Axelsson, Karlsson, and Oskarsson, 2000; Peet and Stokes, 2005), cancer chemopreventive agents (Rose and Connolly, 1999), and arthritis (H. van der Tempel, J. E. Tulleken, P. C. Limburg, F. A. Muskiet, and M. H. van Rijswijk, 1990).

The benefits of fish fatty acids on atherosclerosis, which can lead to several serious problems including heart attack, have been postulated since 1940s by Hugh Sinclair (Sinclair, 1956). Several studies on Greenland Eskimos who consume large amount of food which contains high concentration of omega-3 FAs in their diet showed that they have lower rate of coronary heart diseases (CHD) (Bjerregaard and Dyerberg, 1988; Bjerregaard, Mulvad, and Pedersen, 1997; Dyerberg, 1989). Long chain of omega-3 FAs have been shown to decrease triglyceride concentrations, to lower blood pressure, to decrease thrombosis and cardiac arrhythmias, and to increase heart rate variability, where these mechanisms most likely explain the cardiovascular protection by omega-3 FAs (P. C. Calder, 2004).

Omega-3 DHA and EPA have also been studied for their activities in insulin resistance on high-fat feeding in rats, and it is reported that replacement of only 6 percent of omega-6 FAs in diet with omega-3 FAs from fish oil prevented the development of insulin resistance. (Storlien et al., 1987)

Although the benefits of nonmarine omega-3 FAs are less well-known, recent finding by Brostow et al. suggested that omega-3 FAs form nonmarine sources (ALA) play a role in the prevention of type-2 diabetes in Chinese Singaporean (Brostow et al., 2011).

A study by Magnusson et al. suggested that there is a lack of seasonal disorders in Iceland which may be due to the high content of fish in the Icelandic diet (Magnusson et al., 2000). Similar lack of disorders was also observed in Japan which also has a high content of fish in their diet. The mechanism through which EPA and DHA decrease the depressive symptoms is suggested to include the modulation of serotonin turnover, phosphoinositol-mediated signal transduction, and L-type calcium channel regulation (Hibbeln et al., 2000). Peet et al. also reported the importance of the two omega-3 FAs, EPA and DHA, with depression (Peet and Stokes, 2005). EPA, most importantly, is suggested to give benefits in treatment of depression and schizophrenia.

Recent study by MacLennan et al. showed that omega-3 FAs from marine oils may reduce breast cancer risk (MacLennan et al., 2013). In their study, the *fat-1* and MMTV-neu (ndl)-YD5 mouse models were crossed to create a novel double-hybrid mouse used for

investigation of the effect of omega-3 FAs exposure on mammary tumor development. The result from this study provides clear evidence that the size and the number of tumors were significantly decreased in group of mice treated with omega-3 FAs.

In relation to RA, different studies show that omega-3 is responsible in important decrease in the synthesis of leukotriene B_4 (LTB_4) (T. H. Lee, Hoover, and Williams, 1985; Sperling et al., 1987), as well as interleukin-1β (IL-1β) and interleukin-1α (IL-1α), which was associated with clinical improvement in patients with rheumatoid arthritis. Van der Tempel et al. reported that patients with RA treated with fish oil show significant improvement for joint swelling index (decrease of six points in swelling index) and the duration of morning stiffness (decrease by a mean of 35 minutes) (H. van der Tempel et al., 1990).

Meta-analysis study by Fortin et al. also shows that the use of fish oil significantly reduced tender joint count and duration of morning stiffness (Fortin et al., 1995). Espersen et al. reported the effects of dietary supplementation with omega-3 FAs on the level of cytokines and complement activation in plasma from the patients with RA (Espersen, Grunnet, et al., 1992). Their findings suggested that there is a significantly reduced level of plasma IL-1β, as well as a decrease in cytokine productions.

Omega-3 Fatty Acids and RA

Research involving omega-3 fatty acids, eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) in rheumatoid arthritis began in the mid-eighties, following the demonstration in several autoimmune strains of mice [NZB (NZB x NZW) F_1, MRL/1pr, and B x SB/Mpj) that omega-3 fatty acids reduced the severity of diffuse proliferative glomerulonephritis (DPGN) (Simopoulos, 2002). Animal experiments and clinical intervention studies indicate that omega-3 fatty acids have anti-inflammatory properties and, therefore, might be useful in the management of inflammatory and autoimmune diseases. Omega-3fatty acids may be particularly helpful in managing rheumatoid arthritis (RA) because they reduce production of compounds that cause inflammation (inflammation mediators), while increasing the production of biochemicals that hinder inflammation. Studies have reported anti-inflammatory effects of omega-3 fatty acids in patients with RA, such as decreased leukotriene B_4 (LTB_4) production by neutrophils, decreased monocyte production of platelet-activating factor, decreased PGE_2 production by mononuclear cells, decreased plasma of pro-inflammatory cytokine interleukin-1 beta (IL-1,2,6 and 8β) (Darlington and Stone, 2001) concentrations, decreased serum C-reactive protein concentrations, decreased serum pro-inflammatory cytokine tumor necrosis factor-alpha (TNF-α) and soluble receptor activator of NFκB ligand concentrations, and normalization of the neutrophil chemotactic response (Ariza-Ariza, Mestanza-Peralta, and Cardiel, 1998). The suggested mechanism for the improving effects of omega-3 fatty acids (DHA plus EPA) on RA is a decrease in inflammation due to EPA's ability to competitively inhibit omega-6 prostaglandins and thus increase the production of LTB5, a non- inflammatory eicosanoid and decreasing the production of pro-inflammatory eicosanoids (eg. PGE2, thromboxane and LTB4). The result is decreased vasodilation, neutrophil degranulation, vascular permeability and hyperalgesia. This combination effectively decreases swelling, redness and loss of function which are the hallmark signs and symptoms of RA. The authors conclude there is strong and consistent

scientific evidence that omega-3 fatty acid supplementation is effective at reducing inflammation and improving symptoms of RA in randomized controlled trials and that dietary alteration provides an added opportunity to give patients some control over their health and management of their disease. Recently, new substances derived from the omega-3 fatty acids that resolve and protect against inflammation (Ariel, Li, and Wang, 2005; Chiang and Serhan, 2006) aptly called *resolvins* and *protectins*, help provide arthritis relief without the side effects of conventional arthritis drugs and does not seem to suppress the immune system. These are a novel class of bioactive lipid mediators, which are enzymatically biosynthesized in vivo from EPA and DHA. First, from eicosapentaenoic acid called the E-series resolvins (RvEs) and second, docosahexaenoic acid, termed the D-series resolvins (RvDs) and protectin D1 (PD1). These lipid mediators exert anti-inflammatory and pro-resolving properties and are log-orders more potent than their precursors (L. V. Norling and Perrett, 2013). Initial animal studies showed that compared with vegetable oil, mice fed with fish oil delayed the onset (mean 34 vs 25 days), reduced the incidence (69% versus 93%) and severity (mean peak severity score 6.7 vs 9.8) of type II collagen-induced arthritis (Leslie et al., 1985). There are at least 13 double-blind, randomized, placebo- controlled clinical trials that show benefit from fish oil supplements in patients with RA (M.J. James and Cleland, 1997). A common feature of the studies has been a reduction in symptoms and in the number of tender joints. Also, there was a reduction in the dose of analgesic anti-inflammatory drugs. In a subsequent meta-analysis, morning stiffness decreased, as well as the number of tender joints (Fortin et al., 1995). The Japanese population consumes a larger quantity of omega-3 fatty acids in their diet compared to North Americans. A case-controlled study showed that subjects who ate 2 or more fish (omega-3 fatty acid source) meals per week had a 43% reduced risk of developing RA as compared to those who consumed less than one serving of fish per week (Stamp, James, and Cleland, 2005). Cleland compared outcomes among patients with RA who did not consume fish oil supplements and those who did. They found that fish oil users were more likely to reduce use of NSAIDs and were more likely to be in remission (Cleland, Caughey, James, and Proudman, 2006). There have been a number of clinical trials of fish oil in patients with RA. Most of these trials report clinical improvements (e.g. improved patient assessed pain, decreased morning stiffness, fewer painful or tender joints, and decreased use of NSAIDs), and when the trials have been pooled in meta analyses statistically, significant clinical benefit has emerged (Y. H. Lee, Bae, and Song, 2012). Evidence for clinical efficacy of omega-3 PUFAs in RA is robust. A recent study, involved 37 individuals with RA. All the volunteers completed a food frequency questionnaire and kept a daily diary of their food intake for three days. Researchers analyzed levels of adipokines and oxidative stress markers in serum and saliva and found that consuming omega-3 fish oil and monounsaturated fatty acid had a beneficial effect on RA and reduced inflammation (Hayashi et al., 2012). In another study, results of a meta- and mega- analysis involving 10 double-blind, placebo-controlled trials that included 183 patients with rheumatoid arthritis of 10-11 years duration and 187 patients who were treated with placebo, showed that patients who took omega-3 fatty acids (more than 2.7- >6 grams daily for more than 3 months) needed to take less non-steroidal anti-inflammatory drugs to treat their symptoms (M.J. James and Cleland, 1997). In addition, the number of tender and swollen joints, level of morning stiffness, and physical function also showed a trend toward improvement among patients who took omega-3 fatty acids when compared with controls. No statistically significant changes were observed for the other measured indicators of disease severity. Little difference in the magnitude of effect