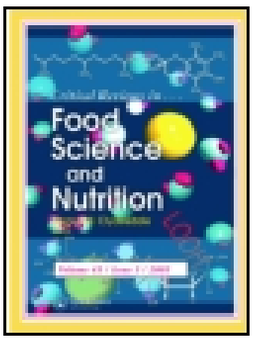

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Anti-inflammatory effects of polyunsaturated fatty acids

Anti-inflammatory effects of omega 3 and omega 6 polyunsaturated fatty acids in cardiovascular disease and metabolic syndrome

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Abstract

A lipid excess produces a systemic inflammation process due to tumor necrosis factor-α, interleukin-6 and C-reactive protein synthesis. Simultaneously, this fat excess promotes the appearance of insulin resistance. All this contributes to the development of atherosclerosis and increases the risk of cardiovascular diseases. On the other hand, polyunsaturated fatty acids (PUFAs), especially eicosapentaenoic acid and docosahexaenoic acid (omega 3), and arachidonic acid (omega 6) have shown anti-inflammatory properties.

Lately, an inverse relationship between omega-3 fatty acids, inflammation, obesity and cardiovascular diseases has been demonstrated. To check fatty acids effect, the levels of some inflammation biomarkers have been analyzed. Leptin, adiponectin and resistin represent a group of hormones associated with the development of cardiovascular diseases, obesity, type 2 diabetes mellitus and insulin resistance and are modified in obese/overweight people comparing to normal weight people. Omega-3 PUFAs have been shown to decrease the production of inflammatory mediators, having a positive effect in obesity and diabetes mellitus type-2. Moreover, they significantly decrease the appearance of cardiovascular disease risk factors. Regarding omega-6 PUFA, there is controversy whether their effects are pro- or anti-inflammatory. The aim of this manuscript is to provide a comprehensive overview about the role of omega-3 and omega-6 PUFAs in cardiovascular diseases and metabolic syndrome.

Keywords

Omega-3 PUFA, Omega-6 PUFA, Inflammation, Cardiovascular disease, Obesity and Type-2 Diabetes Mellitus.

Abbreviations

AF Atrial fibrillation.

AHA American Heart Association.

BMI Body mass index.

CABG Coronary artery bypass grafting.

CAD Coronary artery disease.

CDVs Cardiovascular diseases.

CRP C-reactive protein.

DHA Docosahexaenoic acid.

EPA Eicosapentaenoic acid.

ESC European Society of Cardiology.

IL-6 Interleukin-6.

LPS Lipopolysaccharides.

MI Myocardial infarction.

NF-κB Nuclear factor-κB.

PCI Percutaneous coronary intervention.

POAF Post-operative atrial fibrillation.

PUFA Polyunsaturated fatty acid.

RBC Red blood cell.

TNF-α Tumor necrosis factor-α.

VEGF Vascular endothelial growth factor.

WAT White adipose tissue.

WHO World Health Association.

Introduction

According to World Health Association (WHO), cardiovascular diseases (CVDs) are the leading cause of death worldwide. The main cause for developing CVDs is the fat accumulation in the wall of blood vessels that irrigate the brain or the heart. This phenomenon is known as atherosclerosis. Coronary heart disease can manifest itself as angina pectoris, or acutely, as myocardial infarction, whereas coronary brain disease can trigger stroke. Importantly, the major risk factors of CVDs are obesity, unhealthy diet, non physical activity, smoking and diabetes (Murray et al, 2015).

Obesity is a multifactorial chronic disease characterized by abnormal or excessive fat accumulation that can be harmful to health. In obese subjects, adipose tissue is hypertrophied and it is located predominantly in the waist, surrounding the viscera. This hypertrophy is associated with dyslipemia, insulin resistance, hypertension and metabolic syndrome (Després, 2012). On the other hand, diabetes is a chronic disease arising due to insulin inefficient use, promoting an increase of glucose levels in blood. The result of non-controlled diabetes is a hyperglycemic state that can damage many organs and systems, especially nerves, heart and blood vessels (Alberti et al, 2005). According to WHO, diabetes increases the risk of major ischemic heart disease and stroke. Moreover, about 50% of diabetic patients die of CVDs. Insulin resistance, obesity and inflammation are central components of a group of metabolic abnormalities called metabolic syndrome (Grundy et al, 2004).

Physiological inflammation is a defence mechanism that protects the host from infection and other harmful problems. It is an essential activity to initiate pathogen killing and tissue repair processes to restore tissue homeostasis. Inflammatory responses are normally well regulated to

minimize collateral tissue damage (Calder, 2007). Importantly, chronic inflammation is one of the most important common nexus linking obesity with atherosclerosis. A characteristic of the obese people is a chronic low-grade inflammation state promoted by the release of many inflammatory mediators by adipose tissue and, more importantly, by infiltrating macrophages. Thus, obese people have higher circulating concentrations of many inflammatory markers than lean people do. In addition, it has been observed that healthy eating patterns are associated with lower circulating concentrations of inflammatory markers. Among the components of a healthy diet, whole grains, vegetables, fruits, and fish are all associated with lower inflammation state (Dawson et al, 2014).

Omega fatty acids are polyunsaturated fatty acids with an acid end containing the functional carboxylic acid group and a methyl end, also known as omega end. In omega-3 (ω-3) and omega-6 (ω-6) fatty acids, the first site of desaturation is located after the third and the sixth carbon from the omega end, respectively. Most of these PUFAs are essential; it means that must be supplied through diet because the body is not able to produce them. Dietary sources of ω-3 PUFA include fish oils rich in EPA and DHA, whereas the ω-6 PUFA linoleic acid is mostly found in plants and vegetable oils (Dawson et al, 2014). There are three main types of omega-3 fatty acids proceeding from food: α-linolenic acid, eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA). EPA and DHA are the most important ω-3 PUFAs, modifying gene expression and anti-inflammatory processes (Calder et al, 2008). Regarding omega-6 fatty acids, linoleic acid is the shortest-chained omega-6 fatty acid and is one of the most important polyunsaturated fatty acid being a precursor of arachidonic acid.

Polyunsaturated EPA, DHA and arachidonic acid fatty acids are synthesized by different routes. The EPA and DHA are synthesized from α-linolenic acid (ω-3) and most of the linoleic acid (ω-6) is converted into the body to arachidonic acid (Figure 1). Interestingly, arachidonic acid seems to have critical pro-inflammatory roles because it is converted to omega-6 prostaglandin and omega-6 leukotriene eicosanoids during the inflammatory cascade, while EPA and DHA are precursors of eicosanoids with anti-inflammatory properties. Cells involved in the inflammatory response are typically rich in the ω-6 fatty acid arachidonic acid, but the content of arachidonic acid and the ratio of ω-3 (EPA/DHA) to ω-6 fatty acids can be altered through ingestion of EPA and DHA (Simopoulos, 2008).

Nowadays, there is growing evidence showing that fish oils derived from omega-3 PUFAs have a variety of heart healthy properties like reduction of plasma triglycerides, regulation of blood pressure, reduction of arrhythmias, inflammation, and even improvement of endothelial dysfunction (Mizia-Stec et al, 2011). A large number of trials have shown that the excess body fat in adulthood is associated to adverse levels of adipokines and inflammatory markers as adiponectin, leptin, CRP and IL-6 (Heinonen et al, 2009; Rasmussen-Torvik et al, 2012; Ambeba et al, 2013). Moreover, the longer an individual is obese during adolescence and adulthood, the most adverse level of adipokines and inflammatory markers have at 60 years (Rasmussen-Torvik et al, 2012; Ambeba et al, 2013) (Figure 2). Therefore, preventing the development of overweight and obesity in young adult life or earlier could have significant benefit for the prevention of type 2 diabetes mellitus as well as CVDs.

The objective of this study is to analyze the properties and benefits of omega-3 and omega-6 PUFAs (EPA, DHA and arachidonic acid) as pro and anti-inflammatory substances, and their

effects on inflammation biomarker (IL-6, TNF-α, CRP) and hormone (adiponectin, leptin and resistin) synthesis. We also discuss the effect of these biomarkers and hormones in relation to CVDs and metabolic syndrome.

Methods

Published data for this review were identified by search and selection in PUBMED database and reference lists from relevant articles and reviews about PUFAs and human health. The keywords "PUFAs", "atherosclerosis", "cardiovascular diseases", "diabetes mellitus", "inflammation", "obesity", "metabolic syndrome" and combinations of them were used. The search was narrowed to studies published in English and Spanish, and both conducted in humans, animals or cell lines. Bibliographies of all selected articles and review articles about PUFAs and/or human health were reviewed for other relevant articles.

Inflammation biomarkers and hormones

The pituitary and the hypothalamus regulate several functions of the endocrine system. In the hypothalamus are located some nervous centres that regulates eating habits; specifically in the arcuate nucleus appears the hunger and the satiety centre. The route of information from the endocrine system begins in the hypothalamus, continues with pituitary and with various endocrine glands, and ends with the effector organs. Subsequently, pituitary hormones and hormones acting on the effector organs can be regulated by negative feedback mechanisms (Moreno-Aliaga et al, 2010).

Adipokines are a kind of cytokines produced by adipose tissue with endocrine, paracrine, autocrine and yuxtacrine actions. They are involved in a wide variety of physiological and pathological processes, including immunity and inflammation (Klöting et al, 2014). In obesity,

circulating levels of several pro-inflammatory adipokines are increased while the levels of the anti-inflammatory adipokine adiponectin are reduced, contributing to the chronic inflammatory status. In addition, adipokines have also been implicated in atherosclerosis by increasing the expression of proangiogenic/proatherogenic factors like vascular endothelial growth factor (VEGF) or generating oxygen-derived free radicals (Lau et al, 2005). Furthermore, endothelial cells and hypertrophied adipocytes contribute to this phenomenon as a result of endoplasmic reticulum stress and mitochondrial dysfunction (Tripathi & Pandey, 2012). The main pro-inflammatory adipokines are TNF-α, IL-6, CRP, leptin and resistin, all implicated in endothelial dysfunction (Lovren et al, 2015), whereas adiponectin is the most important anti-inflammatory adipokine. Their role on metabolic syndrome and CVDs will be discussed below (Figure 2).

TNF-α

TNF-α is a cytokine of about 17 kDa released by immune system cells involved in inflammation and in the acute phase reaction (Locksley et al, 2001). Thus, it can be considered as a pro-inflammatory cytokine. The primary role of TNF-α is the regulation of immune cells; however, TNF-α is an endogenous pyrogen, able to induce fever, apoptotic cell death, cachexia, inflammation and respond to sepsis via IL1 & IL6 producing cells. In addition, TNF-α strongly correlates with insulin resistance and with the development of type 2 diabetes mellitus through elevated levels of C-reactive protein and IL-6 (Maury & Brichard, 2010).

IL-6

Interleukin-6 is a 26 kDa glycoprotein secreted by macrophages, T cells, endothelial cells and fibroblasts released in response to TNF-α. It is mainly a pro-inflammatory cytokine. Importantly,

physiological conditions driving upward plasma IL-6 levels are generally associated with elevated C-reactive protein (CRP) concentrations (Liu et al, 2014).

CRP

CRP is a circulating plasma protein with a molecular weight of 100 kDa with increasing levels in response to inflammation. Subjects with elevated plasma CRP concentrations have an increased risk for acute myocardial infarction (Ridker et al, 2002). Moreover, elevated CRP concentration is an independent predictor of coronary heart disease risk (Ridker et al, 2004). It has been proposed as a simple, inexpensive, reliable, and stable marker of inflammatory processes contributing to atherosclerosis.

Leptin

Leptin is a 16 kDa protein produced by adipocytes involved in the regulation of food intake, weight and energy homeostasis. Leptin serum levels increase in the postprandial period and decrease during starvation (Sáinz et al, 2015). Therefore, leptin is secreted when the amount of stored fat in adipocytes increase. This signal informs the hypothalamus that the body has enough reserves and disables appetite (Trayhurn et al, 2006). Leptin exert atherogenic, thrombotic, and angiogenic actions on the vasculature, being an independent coronary disease risk factor (Ntaios et al, 2013). Moreover, leptin has been extensively linked with obesity leading to atherosclerosis, myocardial infarction and stroke (Wolk et al, 2004). Thus, higher levels of circulating leptin are significantly associated with CVDs. In obesity, a reduced capacity for leptin transportation across the blood-brain barrier has been observed (La Cava & Matarese, 2004).

Adiponectin

Adiponectin was firstly identified as ACRP30 (Adipose Complement-Related Protein of 30 kDa) because of its similarity to complement protein. It is a hormone secreted by adipocytes that participates in glucose and fatty acids metabolism (Haluzik et al, 2004). Adiponectin circulating levels are inversely associated to body mass index (BMI); thus, concentrations of adiponectin are reduced in obese, type 2 diabetes mellitus and coronary arterial disease patients (Haluzik et al, 2004). Adiponectin concentration is inversely proportional to visceral fat and considered a cardioprotective cytokine through its antiatherogenic and anti-inflammatory properties. Moreover, circulating low adiponectin levels are considered an independent risk factor for endothelial dysfunction (Okui et al, 2008; Hernández-Romero et al, 2013).

Resistin

Resistin is a cystein rich protein with a molecular weight of 12,5 kDa. This protein is secreted by macrophages in adipose tissue and it is a pro-inflammatory adipokine released in excess in individuals with visceral fat. It seems to play a physiological role in adipogenesis, in the regulation of metabolism and in inflammation (Steppan & Lazar, 2004). A positive correlation between resistin levels and vascular inflammation has been demonstrated in obese humans (Choi et al, 2011). It is important to remark that resistin profoundly upregulates the expression of TNF-α and IL-6 in human peripheral blood cells (Bokarewa et al, 2005).

Effects of PUFAs on adipokines and metabolic syndrome

The effect of PUFAs in regulating some adipokines is scientifically demonstrated by several studies. An *in vitro* study showed the effects of EPA and DHA on the modulation of IL-6 and TNF-α in macrophages treated with lipopolysaccharides (LPS) (Mullen et al, 2010). IL-6

secretion was attenuated in cells treated with DHA compared with EPA-treated cells, whereas EPA-treated cells secreted significantly less TNF-α compared to control and DHA-treated cells. This data suggests that DHA is more potent than EPA in reducing the secretion of IL-6, whereas EPA appeared to have more effect at modulating TNF-α (Mullen et al, 2010).

In another *in vitro* study, the effects of ω-3 and ω-6 PUFAs on adiponectin and leptin secretion were investigated in adipocytes (Romacho et al, 2015). Adipocytes were incubated for 24h with EPA, DHA, or arachidonic acid combined with DHA at different concentrations. Omega-3 PUFAs EPA and DHA increased adiponectin secretion after 24 hours of incubation, whereas they did not exert any significant effect on leptin secretion. The ω-6 PUFA arachidonic acid did not significantly enhance adiponectin or leptin secretion. It was determined whether a ω-3/ω-6 combination could modulate adiponectin synthesis and secretion, and it was observed that the combination DHA/arachidonic acid significantly upregulated adiponectin secretion. However, only DHA alone and in combination with arachidonic acid exerted a potent anti-inflammatory effect in physiological conditions reflected by a decrease of tumor necrosis factor-α (TNF-α) levels (Romacho et al, 2015). These results confirmed previous observations obtained in adipocytes demonstrating anti-inflammatory properties of ω-3 PUFAs in adipose tissue (Siriwardhana et al, 2012). In this study, differential effects of EPA (ω-3 PUFA) on expression and secretion of IL-6 was determined. Increasing EPA levels significantly diminished IL-6 and other adipokine levels. Importantly, it was tested whether nuclear factor-κB (NF-κB), a pro-inflammatory transcription factor, was involved in regulation of adipokines by PUFAs. EPA significantly inhibited NF-κB activation compared to control. Moreover, EPA attenuated TNF-α and further reduced its secretion in the presence of an NF-κB inhibitor (Siriwardhana et al,

2012). These studies confirmed direct anti-inflammatory effects of ω-3 PUFAs and beneficial effects in adipocyte inflammation and metabolic disorders, such as the metabolic syndrome.

Several *in vivo* studies have been carried out in different animals to analyze the effect of ω-3 and ω-6 PUFAs in adipokines secretion and ultimately, in the regulation of metabolic syndrome and cardiovascular diseases (Figure 2). One recent study conducted in grass carp (*Ctenopharyngodon idellus*) analyzed the effect of a 95-day feeding trial using two diets formulated with either lard oil (as control) or fish oil (supplying ω-3 PUFA as treatment) as the main lipid source (Liu et al, 2014). The expression of the lipolysis-related genes TNFα and leptin among others were evaluated and was significantly higher in the treatment than in the control group ($p<0.05$).

Another *in vivo* study evaluated the chronic regulation of plasma leptin by dietary ω-3 PUFA in insulin-resistant, sucrose-fed rats (Peyron-Caso et al, 2002). Rats were randomly segregated into two groups depending on the type of oil administered. After 6 weeks of fish oil consumption, plasma leptin was 75% ($p<0.05$) greater than in rats fed with control oils. The same result was found when plasma leptin was adjusted by total fat mass, as measured by dual-energy X-ray absorptiometry (Peyron-Caso et al, 2002). Moreover, the fish oil diet increased adipose tissue glucose transporter-4 protein levels and prevented the sucrose-induced elevations in plasma triglycerides and free fatty acids, thus regulating fatty acids metabolism in insulin-resistant rats.

Once it has been accepted that PUFAs are involved in the regulation of lipid metabolism and inflammation processes, several authors have tried to elucidate the optimal dietary ω-6/ω-3 PUFA ratios. Duan and colleagues analyzed the effect of four isoenergetic diets with ω-6/ω-3 PUFA ratios of 1/1, 2.5/1, 5/1 and 10/1 in ninety-six pigs (40). The concentrations of IL-6 and adiponectin of pigs fed the diet with an ω-6/ω-3 PUFA ratio of 1/1 were decreased compared

with those of the other groups ($p<0.05$). However, the concentration of leptin was increased compared with PUFA ratios of 5/1 and 10/1 ($p<0.05$). Additionally, the optimal dietary ratios of ω-6/ω-3 PUFA of 1/1 and 5/1 clearly reduced the expression levels of lipid metabolism-related genes and also significantly suppressed the expression of the inflammatory cytokines IL-1, TNF-α and IL-6 (Duan et al, 2014). These results indicated that the optimal ω-6/ω-3 PUFA ratios of 1/1 and 5/1 exerted more beneficial effects on lipid metabolism and inflammatory system than other ratios.

On the other hand, analysis of the effects of PUFAs on adipokines has also been performed in humans (Kondo et al, 2010). 17 young, non-obese, healthy volunteers from Japan were selected for an 8-week fish-diet intervention (omega-3 PUFA 3.0 g/day) without affecting total energy intake, and serum adiponectin concentration and fatty acid profiles were measured. Interestingly, EPA, DHA and total ω-3 PUFA concentrations changed by sex distinctively. In women, serum EPA, DHA and total ω-3 PUFAs significantly increase ($p<0.001$), however, in men serum EPA significantly increase ($p<0.05$) but DHA and total ω-3 PUFAs did not achieve the statistical significance although a trend towards serum increase could be observed. Regarding serum adiponectin, its concentration in female increased significantly ($p<0.01$) whereas no differences were obtained in males. Moreover, when adiponectin and ω-3 PUFAs changes were calculated subtracting baseline concentration minus serum concentration at week 8, adiponectin was positively correlated with ω-3 PUFAs. Additionally, triglyceride concentration decreased significantly throughout the study with no differences between sexes, although LDL cholesterol concentration did not change (Kondo et al, 2010). Although the size of the study population was really small, the subjects had no co-morbidities and all changes in the parameters analyzed

should be taken into account. Thus, diet supplementation with ω-3 PUFAs may increase serum adiponectin concentrations exerting its anti-atherogenic and anti-inflammatory properties. All these observations highlight the importance of a PUFA-rich diet to significantly decrease unfavourable biomarkers of CVDs and metabolic syndrome. In addition, *in vitro*, *in vivo* and human studies have demonstrated beneficial effects of PUFA ingestion on lipid metabolism and inflammatory system.

Effects of PUFAs on CVDs

The first time that cardiovascular health was associated to PUFAs ingestion was after analyzing the "Inuit diet": Inuit had lower risk of CVDs than the remaining population and this difference was thought to rely on their lifestyle and diet. The main factor associated with this CVD reduction was their high-fish consumption (Bang & Dyerberg, 1980). It was demonstrated, for the first time, the relation between origin marine fat consumption and low risk of CVD. This effect was associated to ω-3 PUFAs (Fodor et al, 2014). Since then, numerous studies have been conducted, attempting to elucidate the effects of ω-3 PUFA on CVD. The Nurse's Health Study followed 84,688 female nurses and found that women with higher consumption of fish and ω-3 PUFAs had a lower risk of CVDs, particularly deaths from CVDs (Hu et al, 2002). Another example was the Japan Public Health Center's (JPHC) study that followed 41,575 participants who were free of a prior diagnosis of CVD for 11 years. The risk of CVD was approximately 40% lower among people eating fish eight times a week than among those eating fish once weekly (Iso et al, 2006). This finding implies that high intake of fish can reduce risk of initial CVD events.

As far as we know, the first randomized controlled trial of dietary fish intake in secondary cardiovascular prevention was the Diet and Reinfarction Trial (DART), which followed 2,033 men diagnosed with a myocardial infarction (MI). The intervention group consumed an average of 200 to 400g of fatty fish weekly, estimated to provide 500 to 800 mg of ω-3 PUFA daily. The study found a reduction of 29% in mortality from all causes and a 16% reduction in risk of ischemic events after 2 years (Burr et al, 1989). This trial suggested that ingestion of fatty fish reduced mortality in men after a MI.

A larger study analyzing the role of ω-3 PUFAs in CVDs was performed by the Gruppo Italiano per lo Studio della Sopravvivenza nell'Infarto Miocardio (GISSI)-Prevenzione. This randomized, double-blind, placebo-controlled trial tested the efficacy of oral administration of ω-3 PUFAs and vitamin E on morbidity and mortality in 11,323 Italian patients with recent myocardial infarction (MI). Post-MI participants were randomly segregated into 4 groups and the follow up was 3 years and a half. The first group was assigned to 300 mg of vitamin E daily; a second group was assigned to 850 mg of EPA/DHA, a third group was assigned to both treatments and a fourth control group received usual care. The results showed that compared to control participants, those taking ω-3 PUFAs, but not vitamin E, showed relative risk reductions of 20% for all deaths, 30% for cardiovascular deaths, and 45% for sudden deaths.

In PREDIMED study, 7,447 participants who were at high cardiovascular risk, but with no cardiovascular disease at enrolment, were divided in three dietary intervention groups: a Mediterranean diet supplemented with nuts, a Mediterranean diet supplemented with extra-virgin olive oil (both supplements rich in ω-3 and ω-6 PUFAs) and a control diet (advice to reduce dietary fat) (Estruch et al, 2013). The first group received approximately 1 litre of extra-virgin

olive oil per week and the second group received 30g of nuts per day. A Mediterranean diet supplemented with either extra virgin olive oil or nuts resulted in a risk reduction of approximately 30% in major cardiovascular events among high risk persons who were initially free of CVD. In conclusion, the risk of major cardiovascular events (MI, stroke or cardiovascular death) was reduced significantly in the two Mediterranean diet groups and these results support the benefits of the Mediterranean diet for prevention of CVDs.

In several studies, the beneficial effect of ω-3 index (EPA+DHA) has been observed. Omega-3 index can be determined analyzing the fatty acid composition of the red blood cells (RBC) membrane. In one of these studies, 334 case patients with primary cardiac arrest were interviewed to quantify the ingestion of dietary PUFAs. In addition, blood samples were extracted to determine red blood cell membrane fatty acid composition. It was found that small increases in ω-3 PUFA levels (the equivalent of one fatty fish meal per week) were associated with a significant reduction (between 50-70%) in the risk of primary cardiac arrest (Siscovick et al, 1995). In another case-controlled study, 768 acute coronary syndrome patients were compared with 768 matched controls (Block et al, 2008). The omega-3 index was 20% lower in patients than in controls ($p<0.001$). It was also observed that patients with the lowest ω-3 PUFA content in RBC membrane had a three-fold increase in developing ACS compared to those with the highest ω-3 PUFA content. In another study, the effects of ω-3 PUFA on plasma adiponectin, leptin and resistin in high risk patients with stable coronary artery disease (CAD) undergoing percutaneous coronary intervention (PCI) were evaluated (Mostowik et al, 2013). This study demonstrates that ω-3 PUFAs added to optimal medical and interventional therapy in patients with stable CAD favourably alters the plasma adipokine profile. It was observed that after 1-

month treatment with ω-3 PUFAs, plasma adiponectin increased, while leptin decreased compared with the control group ($p=0.0042$ and $p<0.001$, respectively), whereas no changes were observed in resistin concentration between groups (Mostowik et al, 2013). Taken together, these studies confirm the importance of ω-3 PUFA content in the prevention of CVDs, such as cardiac arrest, sudden death or ACS.

The protective effects of ω-3 PUFAs against arrhythmia have also been studied. Regarding atrial fibrillation (AF), the most common arrhythmia in clinical practice associated with decreased quality of life, and increased mortality and morbidity from stroke and thromboembolism, there are some controversies about the role of PUFAs with positive and negative results. A recent study developed in Denmark investigated the association between consumption of marine ω-3 PUFAs and development of AF (Rix et al, 2014). A total of 57,053 Danish participants aged 50-64 were enrolled in the Diet, Cancer, and Health Cohort Study between 1993 and 1997. Dietary intake of fish and marine ω-3 PUFAs was assessed by a semi-quantitative food frequency questionnaire. In total, 3,345 incident cases of AF occurred over 13.6 years. Multivariate Cox regression analyses using cubic splines showed a significant U-shaped association between consumption of marine ω-3 PUFA and risk of incident AF, with the lowest risk of AF at a moderate intake of 0.63 g/day. Of note, intake of total fish, fatty fish, and the individual ω-3 PUFA (EPA and DHA) also showed U-shaped significant associations with incident AF (Rix et al, 2014). Similarly, a Finnish prospective study with 2,174 men aged 42-60 with an average follow-up time of 17.7 years, found a significant inverse association between blood serum levels of total fish-derived ω-3 PUFAs with incident AF (Virtanen et al, 2009). In contrast, a very recent prospective, double-blind, placebo-controlled, parallel group study examined the effects

of high-dose marine ω-3 PUFAs added to conventional therapy on the recurrence of AF and on markers of inflammation and oxidative stress (Darghosian et al, 2015). Patients with paroxysmal or persistent AF were randomized to ω-3 PUFAs (4 g/day; n=126) or placebo (n=64) in a 2:1 ratio. The authors found that in patients with paroxysmal or persistent AF, treatment with ω-3 PUFAs 4 g/day did not reduce the recurrence of AF, nor was associated with clinically important effects on concentrations of markers of inflammation and oxidative stress (Darghosian et al, 2015). The same negative results were obtained in a double-blind, randomized, placebo-controlled, parallel-arm study in 337 patients with symptomatic paroxysmal or persistent AF treated with 4 g/day of fish oil within 6 months of enrollment (Nigam et al, 2014).

Several studies, mostly randomized trials, have explored the effect of PUFA supplements on the risk of post-operative AF (POAF) with opposite results. In one study, 160 patients from a randomized, controlled trial were pre-treated with fish oil capsules for 5 days before coronary artery bypass grafting (CABG) surgery and a significant absolute reduction in incidence of POAF by 18% and a significant shorter length of hospital stay by 0.9 day compared to controls was observed without influence of β-blockers use (Calò et al, 2005). A more recent randomized, double blind and placebo controlled trial using ω-3 PUFA plus ascorbic acid and vitamin E supplementation showed a decreasing in POAF development compared with control group (9.7% vs 32%, $p<0.001$) (Rodrigo et al, 2013). Moreover, it was also confirmed that the atrial tissue redox status and inflammation was attenuated while antioxidant potential was increased. In this study, the formulation of the ω-3 PUFA mixture contained EPA and DHA acids in a 1:2 EPA/DHA ratio. Importantly, clinical trials performed with this same EPA/DHA ratio also reported a beneficial effect in POAF prevention (Calò et al, 2005); however, other randomized

placebo-controlled studies that failed to demonstrate a beneficial effect used a formulation containing 1:24 EPA/DHA ratio (Mozaffarian et al, 2012; Savelieva et al, 2010). Moreover, a meta-analysis including all published controlled trials concluded that ω-3 PUFA therapy decreased the risk of developing POAF in post-surgical cardiac patients (Singh et al, 2013). Another study including a total of 198 patients with recent (≤ 3 months) myocardial infarction showed a significant reduction of POAF (Wilbring et al, 2014). Half of the patients were included in the treatment group receiving a daily dose of 2 g omega-3 PUFA, initiated 5 days before surgery. Patients from the treatment group had less frequently postoperative AF (treatment: 31.3% vs. control: 48.0%; $p = 0.017$) with a reduction in relative risk of 34.8% in the treatment group. A more pronounced effect was observed in patients ≤ 70 years ($p = 0.007$). Besides, patients of the treatment group had a shorter intensive care unit stay ($p = 0.001$) (Wilbring et al, 2014). On the other hand, in a large multicentric clinical trial, a total of 1,516 patients scheduled for cardiac surgery in 28 centers in the United States, Italy, and Argentina were enrolled (Mozaffarian et al, 2012). Patients were randomized to receive fish oil capsules (1:24 EPA/DHA ratio) just until hospital discharge or postoperative day 10, whichever came first. In this multinational trial among patients undergoing cardiac surgery, perioperative supplementation with ω-3 PUFAs, compared with placebo, did not reduce the risk of postoperative AF (Mozaffarian et al, 2012).

There are some explanations for the discrepancies across studies. Firstly, food intake questionnaires could not represent accurately fish-derived ω-3 PUFA intake; second, the length of the PUFAs treatment can be different, third, the formulation of the ω-3 PUFA mixture contained EPA and DHA acids can also vary across studies; and finally, the mercury content of

fish. Mercury promotes lipid peroxidation, and exposure increases the risk of cardiovascular disease. However, despite the differences across studies, the importance of PUFAs in the management and prevention of CVDs has been clearly demonstrated and warrant more clinical studies that should be conducted to confirm their clinical applications.

Conclusions

Focusing on the effect of omega-3 PUFAs on inflammatory-related adipokine levels, they may result useful in early nutritional programming, acting as a protective factor against diseases characterized by low degree chronic inflammation, such as obesity, diabetes and metabolic syndrome. Similarly, ω-3 PUFAs may exert a beneficial effect on CVDs. Regarding arachidonic acid (ω-6 PUFA), there is a huge controversy about its anti-inflammatory properties. Therefore, it cannot be concluded if ω-6 PUFAs have anti or pro-inflammatory effects and larger clinical trials should be carried out. Significantly, a number of reports here reviewed have demonstrated the anti-inflammatory role of ω-3 PUFAs and their beneficial effects in cardiovascular diseases and metabolic syndrome. For that reason, and despite the contradictory results, nutritional guidelines in Canada, the United States, and Europe encourage the dietary intake of fish and ω-3 PUFAs as part of a preventive approach towards overall heart health. The American Heart Association (AHA) and the European Society of Cardiology (ESC) recommend eating fish (particularly fatty fish) at least twice weekly.

Disclosure of interests

The authors report no conflicts of interest.

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Table 1. Effects of PUFAs on adipokine levels, metabolic syndrome and CVDs

PUFAs studied	Adipokine analyzed	Effect of PUFAs	Main Findings	References
DHA and EPA	IL-6 and TNF-α in macrophages.	Modulation of inflammation	DHA is more potent than EPA in reducing the secretion of IL-6, whereas EPA appeared to have more effect at modulating TNF-α	Mullen et al, 2010
EPA, DHA, and arachidonic acid	Adiponectin, tumor necrosis factor-α (TNF-α), nuclear factor-κB (NF-κB) and IL-6 in adipocites.	Anti-inflammatory properties	DHA alone and in combination with arachidonic acid exerted a potent anti-inflammatory effect in physiological conditions decreasing tumor necrosis factor-α (TNF-α). EPA significantly diminished IL-6 and inhibited NF-κB activation.	Romacho et al, 2015; Siriwardhana et al, 2012
Fish oil (ω-3 PUFAs) consumption.	Lipolysis-related genes, TNFα and leptin in rats and grass carp.	Regulation of lipid metabolism.	Expression of adipokines was significantly higher in the treatment group (Fish oil).	Liu et al, 2014; Peyron-Caso et al, 2002

Optimal dietary ω-6/ω-3 PUFA ratios	IL-1, IL-6, TNF-α, adiponectin and leptin in pigs.	Beneficial effects on lipid metabolism and inflammatory system.	Optimal dietary ratios of ω-6/ω-3 PUFA of 1/1 and 5/1 reduced expression levels of lipid metabolism-related genes and also significantly suppressed the expression of the inflammatory cytokines IL-1, TNF-α and IL-6	Duan et al, 2014
Fish-diet intervention (omega-3 PUFA 3.0 g/day)	Serum adiponectin, triglycerides and cholesterol profile in human.	Anti-atherogenic and anti-inflammatory properties.	Serum adiponectin increased significantly in females. Triglyceride concentration decreased significantly throughout the study in both sexes.	Kondo et al, 2010
Consumption of fish and ω-3 PUFAs		Reduction of CVDs.	Large clinical trials showed that consumption of fish and ω-3 PUFAs implied a lower risk of CVDs (risk 40% lower) particularly deaths from CVDs. Fatty fish ingestion reduced mortality in men after a MI	Estruch et al, 2013; Iso et al, 2006; Hu et al, 2002; Burr et al, 1989

			(29%).	
Omega-3 index (EPA+DHA)	Plasma adiponectin, leptin and resistin in high risk patients with stable coronary artery disease (CAD)	Prevention of CVDs, such as cardiac arrest, sudden death or ACS	Omega-3 PUFA added to optimal medical and interventional therapy in patients with stable CAD favourably alters the plasma adipokine profile	Mostowik et al, 2013; Block et al, 2008; Siscovick et al, 1995
Dietary intake of fish and marine ω-3 PUFAs		Reduced the risk of AF development.	Significant inverse association between blood serum levels of total fish-derived ω-3 PUFAs with incident AF.	Rix et al, 2014; Virtanen et al, 2009
Fish oil capsules (supplemented with ω-3 PUFAs)		Atrial tissue redox status and inflammation was attenuated while antioxidant potential was	Reduction in incidence of post-operative atrial fibrillation (POAF) and a significant shorter length of hospital stay.	Rodrigo et al, 2013 Rodrigo et al, 2013; Calò et al, 2005

		increased.		

Abbreviations

CAD Coronary artery disease;

CVD Cardiovascular disease;

DHA Docosahexaenoic acid

EPA Eicosapentaenoic acid

IL-1 Interleukin-1;

IL-6 Interleukin-6;

MI Myocardial infarction;

NF-κB nuclear factor-κB;

PUFA Polyunsaturated fatty acid;

TNF-α Tumor necrosis factor-α.

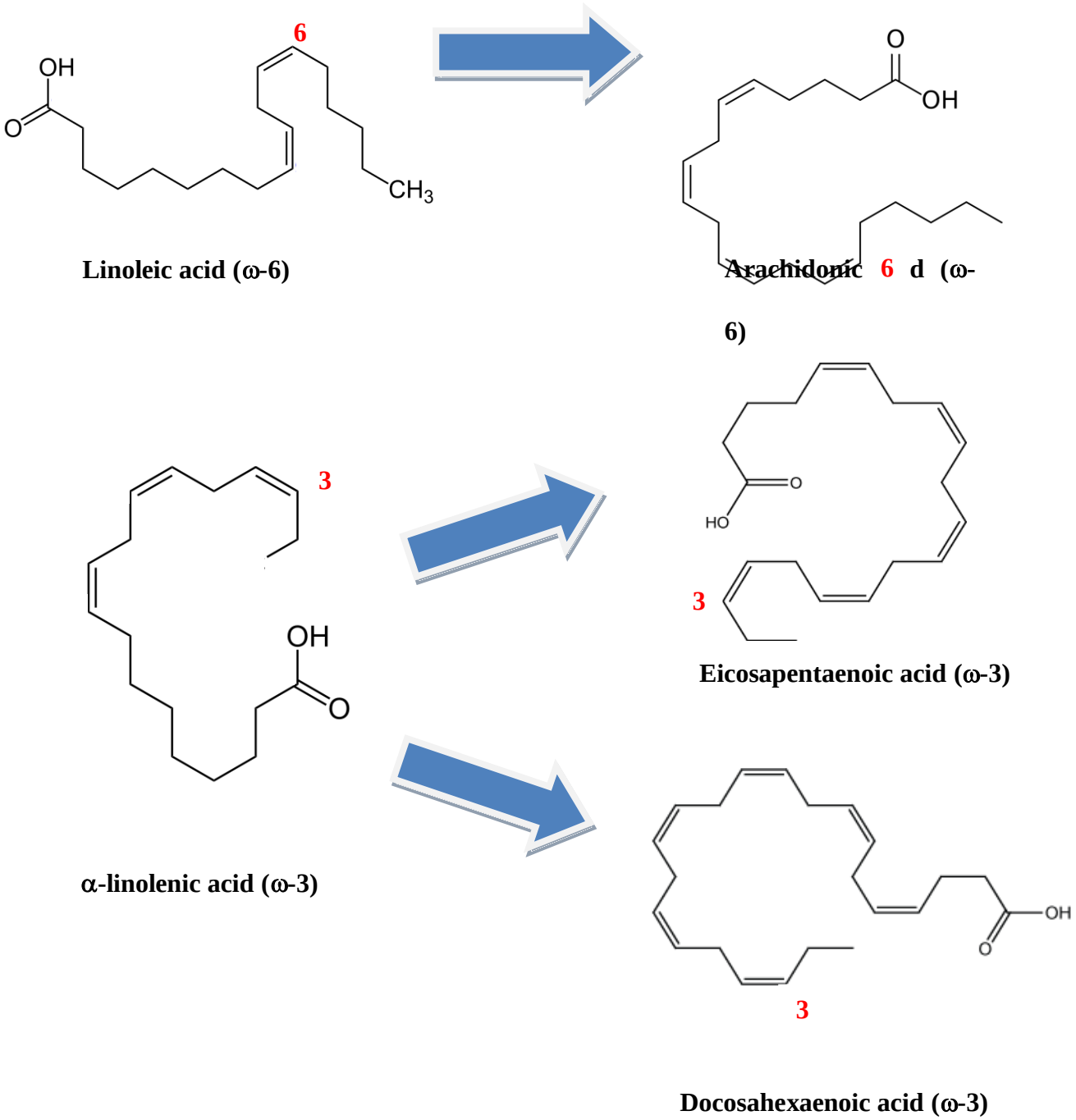

Figure 1. Synthesis routes of the most important ω-3 and ω-6 PUFAs.

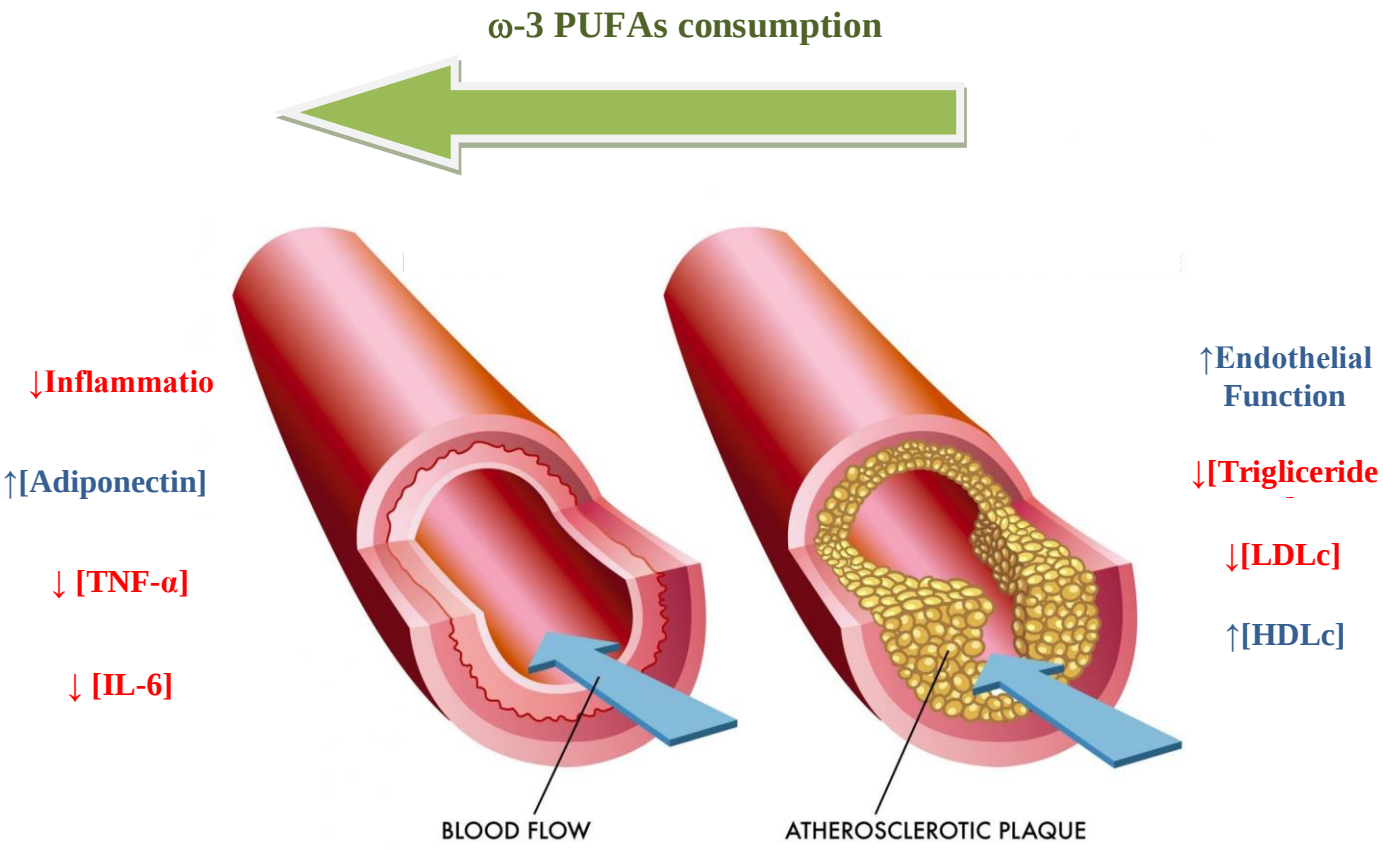

Figure 2. Omega-3 PUFAs effects on atherosclerosis improvement. The consumption of ω-3 PUFAs promotes several beneficial effects for atherosclerosclerotic plaque reduction (decreasing of inflammation biomarkers such as IL-6 or THF-α, lower serum concentration of triglycerides and LDL cholesterol, endothelial function improving and higher serum concentration of adiponectin and HDL cholesterol).