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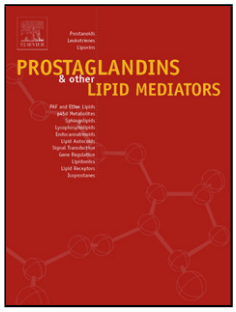

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Omega-3 fatty acids and adipose tissue function in obesity and metabolic syndrome

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Abstract

The n-3 long-chain polyunsaturated fatty acids (n-3 PUFAs) such as eicosapentaenoic (EPA) and docosahexaenoic (DHA) have been reported to improve obesity-associated metabolic disorders includingchronic inflammation, insulin resistance and dyslipidaemia. Growing evidence exits about adipose tissue as a target in mediating the beneficial effects of these marine n-3 PUFAs in adverse metabolic syndrome manifestations. Therefore, in this manuscript we focus in reviewing the current knowledge about effects of marine n-3 PUFAs on adipose tissue metabolism and secretory functions. This scope includes n-3 PUFAs actions on adipogenesis, lipogenesis and lipolysis as well as on fatty acid oxidation and mitochondrial biogenesis. The effects of n-3 PUFAs on adipose tissue glucose uptake and insulin signaling are also summarized. Moreover, the roles of peroxisome proliferator-activated receptor γ (PPARγ) and AMPK activation in mediating n-3 PUFAs actions on adipose tissue functionsare discussed. Finally, the mechanisms underlying the ability of n-3 PUFAs to prevent and/or ameliorate adipose tissue inflammation are also revised,focusing on the role of n-3 PUFAs-derived specialized proresolving lipid mediators such as resolvins, protectins and maresins.

Keywords: Marine origin omega-3 fatty acids, obesity, metabolic syndrome, adipose tissue, glucose metabolism, lipid metabolism, adipogenesis, adipokines, omega-3-derived proresolving lipid mediators.

Contents

1. Adipose tissue dysfunctionin obesity and metabolic complications

1.1. Obesity and adipose tissue

Obesity constitutes a global health problem responsible of 2.8 million deaths each year and whose prevalence has almost doubled in the last thirty years [1]. This condition, characterized by an excessive fat accumulation and accompanied by chronic low-grade inflammation,is related to metabolic diseases including type 2 diabetes, dyslipidemia, atherosclerosis or hypertension being those main components of Metabolic Syndrome (MetS)[2].

Adipose tissue plays a key role in the pathogenesis of obesity and associated complications. Three types of adipose tissue with different precursor cells, phenotype, function and regulation have been, so far,identified: 1) the energy storing white adipose tissue (WAT), 2) the energy consuming brown adipose tissue (BAT), and3) the recently describedbeige/"brite" adipose tissue[3].

WAT is the main storage organ, accumulating the excess of energy in the form of triglycerides, which can be mobilized under energy deprivation conditions. In addition, WAT acts as an important endocrine organ releasing a broad range of molecules called adipokines involved in the regulation of many physiological functions including body weight (leptin), vascular metabolism (PAI-1), glucose metabolism and insulin sensitivity (adiponectin) and a number of inflammatory cytokines and chemokines(TNF-α, IL-1, IL-6, RBP-4 or MCP-1)among others [4,5].Therefore, WAT is integrated in an overall cross-talk between different organs and tissues involved in energy homeostasis, including central nervous system (CNS), liver, skeletal muscle and pancreas due to the release of adipocytokines and the expression of receptors that facilitates two-waycommunications[6].

WAT is distributed around the body in different depots such as abdominal, subcutaneous or gonadal regions with different adipokine secretion profiles. It has been reported that accumulation of visceral adipose tissue (VAT) has a prominent role as a risk factor for

MetSdue to its location surrounding important organs such as liver, which directly receives venous blood from VAT through the portal vein. Moreover it is known to be more metabolically active than other depots with increased protein secretion[7]. In addition, in obesity VAT expandability is more limited than subcutaneous adipose tissue leading more easily to hypertrophied adipocytes [2,7].

On the other hand, BAT is known to be specialized in adaptativethermogenesis being uncoupling protein 1 (UCP1) the main responsible[8]. This thermogenic mechanism plays a key role defending against hypothermia and obesity. However, the endocrine function of suchadipocytes is poorly characterized yet. Increasing evidence indicates that BAT produces factors with autocrine and paracrine actions on metabolism such as fibroblast growth factor 21 (FGF-21) or retinol binding protein 4 (RBP4)[9–11].

During the last years a new type of adipose tissue has been described and named as beige or “brite” adipose tissue. These recently discovered adipocytes have been found within some white adipose depots, but exerting similar functional and molecular characteristics as brown adipocytes. As a matter of fact, beige adipocytes have morphological characteristics of classical brown adipocytes. Thus, they are multilocularand have increased mitochondrial respiratory machinery and express inducible UCP1 having thereforethermogenic characteristics. However, it has been recently described that beige adipocytes express several beige adipocyte-specific genes that are not expressed in classical brown adipocytes such as *Tbx1*, *Tmem26* and *CD137*, among others[12,13].

1.2 Obesity and inflammation

Increased adiposity is accompanied by a low-grade chronic inflammation.In order to accumulate the excess of energy intake, a hypertrophy and hyperplasia of adipocytes take place. These hypertrophied adipocytes present an altered secretory pattern resulting in increased secretion of proinflammatoryadipokines, cytokines and chemokines such

asmonocyte chemoattractant protein-1 (MCP-1), leptin, interleukin (IL)-6 or tumor necrosis factor (TNF)-α, and reduced production of anti-inflammatory adipokines, including adiponectin[14,15].

In addition, abundant researchhas demonstrated that a progressive infiltration and activation of macrophages and T cells to adipose tissue occurs in hypertrophied adipose tissue [16–19].During obesity, the pro-inflammatory MCP-1 is secreted at high levels promoting the recruitment of macrophages to WAT[20]. Furthermore, it is recognized that a polarization of macrophages with an anti-inflammatory phenotype M2 to a M1 pro-inflammatory phenotype occurs in WAT during obesity, which also contributes to the generation of an inflammatory state[21,22]. These M1 macrophages usually are accumulated surrounding the hypertrophic necrotic adipocytes forming a crown like structure[23].

Although,initially all these inflammatory processes belong to the adipose tissue, they can finally derive in a chronic systemic inflammation[24,25], affecting different tissues such as liver and skeletal muscle, and causing metabolic disturbances including insulin resistance (IR) or non-alcoholic fatty liver disease[26–30].

Therefore, modulatingthe production/release of pro-inflammatory/anti-inflammatory moleculesfrom adipose tissue becomes an important target to avoid or alleviate the systemic inflammation andto reduce the development of comorbidities associated with obesity such as type 2 diabetes or dyslipidemia.

2. N-3 PUFAs in obesity and related-metabolic disorders

N-3 long-chain polyunsaturated fatty acids (n-3 PUFAs) are essential nutrients derived from marine or vegetal sources, being the most relevant those from marine origin as eicosapentaenoic acid (EPA, 20:5) and docosahexaenoic acid (DHA, 22:6), which can be found in oily fish including salmon, tuna, mackerel, anchovy and sardines[31]. Moreover,

although the vegetable derivative, α-linolenic acid (ALA, C18:3) is able to be converted to EPA and DHA into the organism, the conversion rate is apparently modest, making necessary a direct intake of these marine n-3 PUFAs to achieve an optimal consumption [32–34]. Varying depending of gender, conversion rate in men ranges between 0-4% and between 4-8% for DHA and EPA, respectively [32,34] while in women is approximately 9.2% and 21% for DHA and EPA, respectively[33].

Several trials in humans and rodents have suggested potential beneficial effects of these marine n-3 PUFAs in different chronic inflammatory diseases such as cardiovascular disease, atherosclerosis, Alzheimer, asthma, arthritis, colitis or obesity and MetS[35].

In this review we summarize the current knowledge about the beneficial properties of n-3 PUFAs of marine origin on obesity and associated disorders, particularly focusing on their actions on adipose tissue size and adipocyte metabolism and function.

2.1. Evidence from animal models

There is evidence of n-3 PUFAs beneficial effects on obesity associated diseases as MetS or type 2diabetes. Table 1 summarizes trials analyzing the effects of marine origin n-3 PUFAs supplementation on adiposity and metabolic syndrome features in animal models of obesity.

The body lowering actions of marine origin n-3 PUFAs supplementation are controversial. Thus, some studies support that n-3 PUFAs can significantly decrease body weight and fat mass[36–47]. Other trials did not find any significant action on body weight loss but a significant reduction in some fat depots was observed in n-3 PUFAs supplemented groups [45,48–50]. In contrast, other studies did not report any change in body weight or fat mass after dietary supplementation with n-3 PUFAs[51–56].

Regarding lipid metabolism, a wide range of studies support thetriglyceride (TG)-lowering properties of marine origin n-3 PUFAs supplementation[42,47,51,53,39,36,44,57,46,43,45,56,49,50] (see Table 1).

Additionally, most of studies in rodents also described favorable effects of dietary supplementation with marine origin n-3 PUFAs on glucose metabolism and insulin sensitivity (see Table 1). Thus, although there are some investigations that did not reach conclusive results[50–52], most of the reviewed publications reported improvements in fasting glycemia[47,53,39,41,42,46,36,44,49]and insulinemia[47,41,54,48,43,44,46,45,56].Furthermore, some studies have found an improvement inglucose or insulin tolerance[36,41,45,46,49]in murine models treated with EPA, DHA, a mixture of both or in combination with Rosiglitazone. However, other trials did not find any significant change in glucose tolerance in n-3 PUFAs supplemented groups[52,54](see Table 1).

The apparent controversial outcomes between trials regarding the effects on n-3 PUFAs on body weight, glucose and lipid metabolism could be due to the different animal model of obesity (genetic vs diet-induced obesity) used, as well as to the type and formulation of n-3 PUFAs (EPA or DHA or a combination in TG form or as Ethyl ester), the dosage and the duration of treatment.

Moreover, Table 2 summarizes studies evaluating the effects of endogenous production of n-3 PUFAs, using the fat-1 transgenic mice, which contain the fat-1 gene from *Caenorhabditiselegans*and are able to convert n-6 to n-3 PUFAs *in vivo*[58]. Although the evidence suggest that the general increment of n-3 PUFAs into the organism of fat-1 mice has no effect in the reduction of weight in the context of either a isocaloric diet or versus a calorie restriction regime [59–61], several studies have observed that these mice are protected against the weight gain subsequent to a high fat diet (HFD) [61,62]. Moreover, even though the study of White et al. [60] did not observe differences in both body weight and adiposity between the fat-1 mice and their matched wild-type fed with a HFD, other study of the same group [63], found changes in the adipocyte size into the epididymal adipose tissue of transgenic mice,

predominating the mid-sized adipocytes upon the large and very large adipocytes. The effects of endogenous production of n-3 PUFAs on lipid metabolism in the fat-1 mice have been evaluated only in few studies.Although Belchior et al. [61] observed no effect in any of the blood lipid parameters measured, Romanatto et al. [64] found in the 8-month-old fat-1 mice lower levels of TG and cholesterol than the littermate controls (see Table 2). Concerningglucose homeostasismarkers in fat-1 transgenic mice, slightly different outcomes have been found.While some studies observed low fasting glucose and improvements in insulin sensitivity in fat-1 male mice fed with HFD [60,61], other trial did not detect significant changes [65]. Despite these findings, the increment in the endogenous production of n-3 PUFAs has been shown to have beneficial impact in glucose tolerance [60,61,63,65] and in metabolic age-related glucose alterations [64]. In this sense, Bellenger et al. [66] observed that in the fat-1 mice, the β-cell damage and the impairments in glucose metabolism caused by the toxic effects of streptozotocin were prevented (see Table 2).

2.2. Evidences from clinical trials in humans

During the last years a number of clinical trials have been carried out to find outthe potential benefits of n-3 PUFAs supplementation in subjects with obesity and metabolic syndrome features (see reviews[31,67,68]).

In accordance with the outcomes in animal models, most of clinical trials in humans strongly support the hypotriglyceridemic benefits of marine origin n-3 PUFAs supplementation. Based on this available evidence, several agencies and associations have recommended intakes of 2 to 4 g per day as an effective therapy for hypertriglyceridemia[69,70].However, the effects of marine origin n-3 PUFAs on body weight and body composition and on cholesterol metabolism in patients with MetS remain unclear. Furthermore, in contrast to the observations in murine models suggesting that the supplementation with marine origin n-3 PUFAs could promote an improvement in insulin sensitivity, most of trials in subjects with MetS suggest

that n-3 PUFAs are not effective in decreasing glucose metabolism parameters or improving the insulin sensitivity[68].Further larger clinical trials are needed to better elucidate the efficacy of n-3 PUFAs on these MetSfeatures.

3. n-3 PUFAs actions in adipose tissue

A significant number of studies consider that n-3PUFAs are able to improve impaired metabolism in obesity by modulating main metabolic pathways in key metabolic organs such as adipose tissue, liver and skeletal muscle[71,38,72,73,46,15,31].Here, we will focus in reviewing theactions and mechanisms of marine origin n-3 PUFAs in adipose tissue metabolism and functions.

3.1. Effects on adipocyte proliferation and differentiation

Adipogenesis is the process of differentiation of preadipocytes to mature adipocytes. Adipocyte differentiation is a complex process mainly regulated by two families of transcription factors, CCAAT/enhancer-binding proteins (C/EBPs) and peroxisome proliferator-activated receptor γ (PPARγ). Thus,C/EBPβ and C/EBPδ are involved in the early stages of adipogenesis. In fact, once activated, C/EBPβ trans-activates the expression of C/EBPα and PPARγ, two master transcription factors for maintain terminal adipocytedifferentiation, which coordinately activate genes whose expression produces the adipocyte phenotype [74,75].

In this context, marine origin n-3 PUFAs have been shown to regulate adipocyte differentiation, but their actions are still controversial. Thus, some studies referred that an increase in adipogenesis occurred when n-3 PUFAs are added to the culture medium [76,77]. Moreover, it has been reported that DHA (50µM)more than EPA induced differentiation of adipocytes by upregulating mRNA levels of *C/ebpα*, *Pparγ* and adipocyte protein 2 (*aP2*) in

3T3-L1 cells [76]. Besides, it has been described increased protein levels of PPARγ, followed by an accumulation of lipid droplets when EPA(250µM) was added [77].

In contrast, other trials support the ability of marine origin n-3 PUFAs to inhibit adipocyte proliferation and differentiation by downregulating the main transcription factors involved in adipogenesis[78–81]. In such a way, Kim et al. [81] reported that DHA (25-200µM)treatment resulted in a dose-dependent inhibition of adipose differentiation, reducing lipid area and number of lipid droplets. Further investigations have revealed that DHA (100 µM) and EPAas well, reduced lipid accumulation and led to lower *Pparγ* gene expression during differentiation. Moreover, EPA is also able to suppress *C/ebpβ* expression levels in 3T3-L1 cells [78,79].

In addition to the effects on adipocyte differentiation, some studies have suggested that n-3 PUFAs can also regulate adipocyte apoptosis. In this way, Kim et al. [81] reported that DHA (100-200 µM) induced apoptosis in 3T3-L1 adipocytes. Other study found that EPA (250 µM) reduced pAKT, BCL-2 and NF-κB, while increase AKT, BAD and PPARγ levels, suggesting that n-3 PUFAs promote differentiation, inhibit proliferation and induce apoptosis in this preadipocyte cell line [77].

Furthermore, marine origin n-3 PUFAs have been related with a modulation in cellularity in adipose tissue in rodents. In this sense, Tekeleselassie et al. [82] found increased number of adipocytes in inguinal fat depots rats when n-3 PUFAs (3.33%-6.67% wt/wt)were added to diet for 22 weeks. Accordingly, White at al. [63] observed an increment of the pro-adipogenic transcription factor *Pparγ*gene expression and an inhibition of *Gata3* gene, an inhibitor of adipocyte transition to fully differentiated adipocytein epididymal adipose tissue of fat-1 mice, suggesting that transgenic restoration of n-3 PUFAs promotes adipogenesis. In contrast, other study in mice demonstrated that a low dose of n-3 PUFAsadded to diet led to a

reduction in number of cells, which was responsible of a decrease in adipose tissue weight [83].

Taking all these data together, it can be concluded that marine origin n-3 PUFAs may potentially modulate adipocyte size and number by regulating adipocyte differentiation and apoptosis. However, more studies are necessary to better clarify the mechanisms involved in these actions of n-3 PUFAs on adipocytes.

3.2. Effects on lipid storage and mobilization

Accumulation of triglycerides in adipocytes is settled by a balance between lipolysis and fatty acid oxidation (fat breakdown) and lipogenesis (fat synthesis). Triglycerides storage in adipocytes can be the result of dietary fatty acid (FA) uptake or *de novo* FA biosynthesis. This last process takes place mainly in liver and in a lower extent in adipose tissue, but recently it has been pointed out the importance of lipogenesis in adipose tissue as a possible strategy to combat obesity and diabetes conditions [84].

N-3 PUFAs have been identified as modulators of lipogenic enzymes and thus, being able to regulate lipogenesis in WAT. Thus, both DHA and EPA (100µM)decreased stearoyl-CoA desaturase (*Scd*)-1 gene expression and protein levels in 3T3-L1 cells [79,80]. In the same cell line, it has been found that EPA(150 µM, 48 h) decreased glycerol-3phosphate dehydrogenase another enzyme involved in lipogenesis[42]. In contrast, Guo et al. [74] did not find any significant change in lipogenesis in EPA-treated (100µM, 24 h)3T3-L1 adipocytes. However, a previous study of our group in primary cultured rat adipocytes evidenced a decrease in the percentage of glucose incorporated into triglycerides in EPA-treated (200µM, 96 h) cells, suggesting a decrease in lipogenesis[85]. The apparent differential outcomes among studies may be due to differences in culture characteristics (cell lines *vs.* primary adipocytes) as well as the doses tested and the duration of the treatments.

In addition to cultured adipocytes studies, some groups also found important features of marine origin n-3 PUFAs in animal models. For instance, a trial with rats fed with high sucrose diet revealed that fish oil supplementation for 2 weekssuppressed fatty acid synthase (*Fas)* mRNA levels in brown adipose tissue [86]. Furthermore, a study with Wistar rats demonstrated that *Fas* mRNA levels were lower in retroperitoneal adipose tissue of animals fed with a with a mixture of EPA and DHA (20% of fat) or DHA-rich diet for 4 weeks [50]. Moreover, adipose tissue specific PPARγ knockout mice showed a downregulation in *Scd-1* expression when a n-3 PUFAs concentrate containing 45%DHA, 14%EPA (replacing 15% of dietary lipids)was added to their diet for 42 days[37]. Interestingly, Hiller et al. [87] found a downregulation of *Fas*, but not of *Scd-1* mRNA levels in subcutaneous adipose tissue when German Holstein bulls were fed with increased levels of n-3 PUFAsup to 58.8% in their diet. In summary, the studies in animal models pointed out the importance of n-3 PUFAs in downregulatinglipogenic genes expression and therefore decreasing lipogenesis and fat accumulation.

Lipoprotein lipase (LPL) is the primary enzyme responsible for chylomicron- and VLDL-TG lipolysis in endothelial cells of capillaries in adipose tissue, and therefore is considered as a master regulator for adipocyte fatty acid uptake from triglyceride-rich lipoprotein. It is thought, that n-3 PUFAs could modulate this enzyme. In this regard, Baltzell et al. [88] found decreased fat weight and adipose LPL in parallel to increased soleus muscle LPL and decreased plasma triacylglycerol in fish oil fed rats, suggesting a shift from fat deposition to oxidation. Nozaki et al. [89]also found that post-heparin LPL activity was lower at 60 min when fish oil (20 capsules day, containing 280mg of EPA and 120mg of DHA)was administered to hypertriacylglycerolemic patientsfor 24 days. However, Harris et al. [90] showed an increase of LPL activity in healthy and hypertriacylglycerolemic patients after supplementation with a fish oil concentrate (5 g/day, containing 41% EPA and 23% DHA

during 4 weeks). Besides, other study demonstrated increased levels LPL activity in post-heparin plasma of healthy males after 6 weeks of intervention with supplemented diet either with 6g of fish oil or six 1g capsules of EPA/DHA concentrate (EPAX 5500TG) [91], suggesting that the effect of n3- PUFAs to LPL activity may differ during time.

Lipolysis is the main pathway involved in the breakdown of lipids in WAT. Lipolysis is a highly regulated process in which TG are hydrolyzed through the consecutive action of three major lipases: adipose triglyceride lipase (ATGL/desnutrin), hormone sensitive lipase (HSL) and monoacylglycerol lipase (MGL). Some lipid droplet proteins such as perilipin also play a key role in the lipolytic process. Thus, under basal conditions, perilipin A maintains a low rate of basal lipolysis by restricting the access of cytosolic lipases to the lipid droplet [92].

Several studies have reported the ability n-3 PUFAs to modulate lipolysis by acting on the main lipases and lipid droplets proteins. Some trials have suggested that DHA seems to promote lipid mobilization. Thus, DHA (50-200 µM) addition to fully differentiated 3T3-L1 adipocytes increased basal lipolysis by inducing glycerol release [81]. Other authors also observed that DHA (100 µM)treatment increased lipolysis in 3T3-L1 cells by an up-regulation of *Atgl* and a down-regulation of perilipin gene expression [80]. In the same adipocyte line, it has been found that treatment with EPA (100 µM) during the 7-days of adipocyte differentiation reduced lipid droplet size and increase *Hsl* gene expression [79]. However, other assay found that the treatment of mature primary rat adipocytes with EPA (100-200µM) for 96 h decreased basal lipolysis [93]. In obesity, the increased levels of pro-inflammatory cytokines secreted by adipose tissue are responsible of the upregulation of lipolysis observed in obese subjects, leading to increased circulating levels of free fatty acids (FFA), which interfere with insulin signaling in other tissues such as liver and skeletal muscle favoring the development of insulin resistance [94]. Interestingly, a previous study of our group found that EPA treatment is able to prevent the lipolytic effects of TNF-α in cultured

adipocytes in parallel with the reduction of both TNF-α induced NF-kB-DNA binding and phosphorylation of ERK1/2. EPA also reduced ATGL levels and induced phosphorylation of HSL in the serine^{565} residue, which prevent PKA-mediated activation of HSL [93]

Regarding the effects of *in vivo* treatment with n-3 PUFAs on lipolytic enzymes, Sun et al. [71] found that DHA (6.25-12.5 g/kg, intragastric daily administration) for 3 weeks increased in a dose-dependent manner the gene expression of *Hsl*and triglyceride hydrolase (*Tgh*) in adipose tissue of mice. Moreover, dietary supplementation with EPA to high-fat diet (HFD)-fed rats is also able to regulate the expression levels of lipases in WAT. Hence, oral supplementation with EPA ethyl ester (1 g/kg) daily for 35 dayspartially reversed the down-regulation of *Hsl* and *Atgl* mRNA observed in retroperitoneal fat of HFD-fed rats [93].

Moreover, several investigations have suggested that n-3 PUFAs may increase fatty acid oxidation in mitochondria and peroxisome. In this sense, EPA-treated (100µM, 24h) 3T3-L1 adipocytes exhibited increased fatty acid β-oxidation [74] in parallel with a rise in carnitine palmitoyltransferase-1 (CPT-1A) activity[74]. Similar results have been reported in animal models. Flachs et al. [38] demonstrated that the addition of n-3 PUFAs to diet **(**6% EPA/51%DHA, replacing 44% of dietary fat for 4 weeks) in male C57BL/6J mice increased mRNA levels of *Cpt1a* in epididymal adipose tissue and acyl-CoA oxidase 1 (*Acox1*) in epididymal and dorsolumbar fat suggesting stimulation of fatty acid oxidation in these fat depots.

In summary, current evidences about marine origin n-3 PUFAs actions on adipocyte lipid metabolism suggest that these fatty acids orchestrate a modulation of different enzymes involves in metabolic pathways responsible for lipid storage and lipid breakdown and oxidation, facilitating the reduction of triglyceride accumulation in adipose tissue.

3.3. Effects on mitochondrial biogenesis and adipose tissue browning

Several studies have pointed out to an association between adipose tissue mitochondrial dysfunction with the progress of obesity and type 2 diabetes [95]. In fact, a reduction in the abundance of adipocyte mitochondrial number and impaired mitochondrial function leads to reduced fatty acid β-oxidation facilitating fat accumulation and the development of obesity-associated comorbidities such as insulin resistance and dyslipidemia [96]. Therefore, nutritional or pharmacological strategies to increase mitochondrial function and biogenesis could contribute to prevent or treat these metabolic disorders.

Interestingly, some studies have suggested the ability of marine origin n-3 PUFAs to upregulate mitochondrial biogenesis in WAT. In this context, it has been described that n-3 PUFAs(DHA and ALA, 200 µM for 24 h) increased mRNA levels of peroxisome proliferator-activated receptor gamma coactivator 1-alpha (*Pgc-1α)*and*nuclear respiratory factor 1 (Nrf1),*which aretwo transcription factors that are particularly important for mitochondrial biogenesis in cultured 3T3-L1 adipocytes [38]. In addition, a recent study have revealed the capacity of EPA (200 µM) to not only induce mitochondrial DNA content and the expression of genes involved in mitochondrial biogenesis (*PGC1α*, *Nrf1* and *COXiv*), but also to increase *Ucp1, Ucp2, Ucp3 and Cidea* mRNA during differentiation of adipocytes from stroma vascular cells of inguinal fat, suggesting that EPA promotes browning of inguinal fat adipocytes. Importantly, this effect was not found when EPA (200 µMfor 24 h)was added to mature inguinal adipocytes, suggesting that EPA exerts the browning effects via recruiting brite adipocytes [97].

Importantly, Flachs et al. [38] evidenced that supplementation of HFD with an EPA/DHA concentrate (6% EPA/51%DHA, replacing 44% of dietary fat) for 4 weeksupregulated*PGC1α*and *Nrf1*and also genes encoding for mitochondrial proteins involved in oxidative phosphorylation, in addition to an increase of mitochondrial SDHA, MT-CO1, COX6 and ATP5A1 protein levels in epididymal fat. Further studies of the same

group have demonstrated that a combination treatment of marine origin n-3 PUFAs (46% DHA, 14% EPA, replacing 15% of dietary lipids)and mild caloric restriction for 5 weeks had synergistic actions in the prevention of obesity and related metabolic disturbances such as inflammation and insulin resistance in parallel with a synergistic induction of mitochondrial oxidative phosphorylation (OXPHOS) and FFA oxidation, specifically in epididymal WAT. Interestingly, these changes occurred without induction of UCP1 [56]. In support of this finding, the study of Janovska et al. [49] showed that the anti-obesity effects of marine origin n-3 PUFAs (46%DHA, 14%EPA, replacing 15% of dietary lipids) in mice fed HFD for 7 months were independent of cold-induced thermogenesis. Taking together these observations, it was suggested that n-3 PUFAsare able to promote mitochondrial biogenesis and oxidative capacity in WAT independently of UCP1 [56].

Also, n-3 PUFAs have been shown to increase brown adipose tissue mitochondrial mass and induce a marked stimulation of BAT thermogenic activity without changes in the UCP content. Interestingly, a synergistic effect of EPA and DHA (27.5 g/100 gdiet for 4 weeks) was found [98]. However, other study found that fish-oil enriched diet (200 g/kg diet for 21 days) increased *Ucp1* mRNA levels in brown adipose tissue in rats [99].

Further studies are needed to better characterize the potential brightening properties of marine origin n-3 PUFAs *in vivo* and especially in human adipose tissue.

3.4. Effects on Glucose metabolism and insulin signaling

Dysfunctional WAT expansion in obesity with concomitant immune cells mobilization leads to the activation of inflammatory cascades that have an adverse impact on insulin signaling and glucose uptake, favoring the development of insulin resistance [100]. Insulin binds its cell surface receptor (IR) leading to the phosphorylation of IRS proteins (IRS-1 and IRS-2) on tyrosine residues and starts a downstream cascade. Proteins such as phosphatidylinositol3-kinase (PI3K) and AKT play essential roles along this signaling pathway promoting a wide

range of biological responses including glucose transporter (GLUT) 4 translocation to the plasma membrane or glycogen synthesis [101].

While several studies in animal models have largely suggested that n-3 PUFAs may have insulin sensitizing properties, the underlying mechanisms are not completely understood yet. Accumulating evidence shows that marine origin n-3 PUFAs may improve insulin signal transduction in adipocytes, affecting in turn, the insulin-stimulated glucose uptake through to regulation of the expression or the translocation of the insulin-dependent glucose transporter GLUT4 [55,102,103].

Interestingly, it has been reported that adipocytes from n-3 PUFAs-depleted rats had lower basal and insulin-stimulated glucose incorporation [104] suggesting a role of n-3 PUFAs in the regulation of glucose uptake by adipocytes. *In vitro* investigations carried out in cultured adipocytes demonstrated that treatment with EPA (200 μM, 96 h) increased glucose uptake in primary rat adipocytes [85]. Moreover, cultured adipocytes from rats supplemented with fish oil for a week reported increased levels of GLUT4and GLUT1 with concomitant promotion of insulin-stimulated glucose uptake [105].

An upregulation of *Glut4*in adipose tissue has been also reported in high sucrose diet (HSD)-insulin resistant ratsfed with fish oil (14% of lipids replacement) for 3 weeks [106]. Similarly, an increase in adipose *Glut4*was observed in HFD-induced obese rats fed with n-3 PUFAs (19% of fat from fish oil) for 4 weeks, accompanied with lower glycaemia and insulinemia levels despite the expression of the regulatory subunit (p85) of PI3K remained unchanged[102]. Furthermore, a longer administration (4 months) of marine origin n-3 PUFAs (EPA and DHA, 45–64% respectively, replacing 15 or 44% of lipids) was also found to enhance glucose transport via *Glut4* expression in both epididymal and dorsolumbar depots of HFD-fed mice[83]. González-Periz et al. [55]alsoreportedthatfeedingwith a marine origin n-3 PUFAs-enricheddiet(6% of total lipidcontent) during 5 weeksimprovedinsulinresistance

in associationwithanincreasedexpression of *Irs-1* and *Glut4*mRNA in adiposetissue of geneticallyobese*ob/ob*mice. Nevertheless, other authors reported only slight effects on *Glut4* expression in adipose tissue (while a significant upregulation was found in skeletal muscle) after 9 weeks of treatment with EPA (0.5 g/kg body weight), in association with a higher glucose tolerance and lower insulinemia in spontaneous diabetic rats[54]. In contrast, Gillam et al.[52] found no effects on *Glut4* and *IR* mRNA levels in adipose tissue of *fa/fa*Zucker rats given 10% of fat in the form of fish (menhaden) oil for 8.5 weeks. LeFoll et al. [107] observed no beneficial effects of fish oil(4.9% of metabolizable energy from fat) for 4 weeks on dexamethasone-induced insulin resistant rats. In fact, WAT PI3K activity was decreased in the supplemented group of both, dexamethasone treated and control rats, and GLUT4proteinlevels remained unchanged. However, Akt phosphorylation was increased in n-3 PUFAs supplemented control rats suggesting adissociation between the effects of n-3 PUFAs on PI3K activity and Akt phosphorylation. As the authors pointed out, the lack of larger results could be due to an excessive dose of dexamethasone.

In conclusion, these data support that marine origin n-3 PUFAs can modulate glucose uptake and insulin response in adipose tissue, through different mechanisms. In this context, it is important to mention that n-3 PUFAs can change fatty acid content of the membrane phospholipids, increasing its insaturation[108–110], which could also mediate its effects on insulin signaling [110]. In addition, n-3 PUFAs can also influence the so-called adipokines released by adipose tissue which has an impact on inflammatory status and insulin sensitivity in obesity-related comorbidities (reviewed in the next section). However, further research is needed to deepen in the understanding of n-3 PUFAs actions on glucose homeostasis.

3.5. Effects on adipokines production

Accumulating evidence suggests that marine origin n-3 PUFAs can counteract the adipokine dysregulation that occurs in obesity [15,111]. Along this review, we will provide an overview

of the current knowledge in the regulation by n-3 PUFAs of some adipokines with key roles in energy homeostasis as well as in glucose and lipid metabolism such as adiponectin, leptin and apelin.

Adiponectin

Adiponectin is an important insulin-sensitizing adipokine that regulates glucose and lipid metabolism reducing fat storage (lipogenesis) and promoting fat utilization (fatty acid oxidation). Moreover, adiponectin stimulates mitochondrial biogenesis and has important anti-inflammatory properties. These actions of adiponectin are in part mediated through the activation of PPARγ and AMPK[112]. It is well documented that adiponectin levels are reduced in subjects with obesity, which may contribute to the development of insulin resistance and cardiovascular disorders [113].

Several studies have suggested that n-3 PUFAs are regulators of adiponectin production by adipocytes. Thus, the study of Oster et al. [114] in 3T3-L1 adipocytes revealed that only DHA (125 μM, 24 h), but not EPA was able to induce adiponectin gene expression and protein secretion. More recently, it has been found that treatment with EPA (100 μM) and DHA (50 μM) for 48 hincreased adiponectin only in 3T3-L1 adipocytes at early stage of maturation (8 days after induction of differentiation), while no significant effects were observed when adipocytes were treated with these n-3 PUFAs in later stages (12 and 16 days) post-induction of differentiation[115]. On the other hand, Lorente-Cebrián et al. [116] showed that a long-term treatment with EPA (200 μM, 96 h) of primary cultured rat adipocytes decreased adiponectin expression and secretion as well as PPAR-γ mRNA levels. However, studies in human adipocytes found that EPA (100 μM) and DHA (100 μM) treatment for 48 h increases adiponectin secretion, although only EPA led to higher cellular adiponectin levels into the adipocytes [117]. Altogether, these findings suggest that the regulation of adiponectin by n-3

PUFAs is dose and time-dependent and that can be affected by the maturation stage of the adipocytes.

Moreover,the differential effects of EPA and DHA observed in some studies highlights the need of studying their actions separately and in different models.

A growing body of evidence indicates that *in vivo*marine origin n-3 PUFAs treatment leads to an upregulation of adiponectin (circulating levels and/or adipose mRNA) in both rodents [55,72,118] and humans [119,120]. In this sense, replacement of dietary lipids (6-15%) in the form of n-3 PUFAs concentrate for 5 weeks increased adiponectin circulating levels in HFD-fed mice [118] and adiponectin expression in both, HFD-fed mice [118] and *ob/ob* mice [55]. These results are in agreement with Tishinsky et al. [121], who reported that the HFD-induced adiponectin decrease in visceral adipose tissue of rats was prevented by replacing 15% of total kcal with marine origin n-3 PUFAs for 4 weeks. There are also results from rat studies that found how intragastric administration of n-3 PUFAs (1 g/day) for a period of 20 weeks increased adiponectin levels and mRNA in WAT and serum levels of HFD-fed Sprague-Dawley rats [122].A previous study of our group also indicated that treatment of Wistar rats with a similar dose of EPA (1 g/day) for 5 weeks caused an upregulation of adiponectin in adipose tissue [48].

Given all these data, the ability of marine origin n-3 PUFAs to stimulate adiponectin has been proposed to be involved in the beneficial actions of n-3 PUFAs on insulin sensitivity, fatty acid oxidation and inflammation, among others [123].

Leptin

Other widely studied adipokine with important metabolic functions is leptin. It is well recognized that leptin plays a key role in the regulation of food intake and appetite[124], energy expenditure, insulin signaling [125], as well as on the reproductive [126] and immune system[127]. Moreover, leptin is known to have proinflammatory effects given its ability to

up-regulate the immune response and the secretion of proinflammatory cytokines, such as TNF-α and IL-6 [128,129].

Regarding leptin's roles in body weight regulation, it is well demonstrated that leptin deficiency causes severe hyperphagia and early-onset obesity[130]. In spite of its critical role on food intake and body weight, hyperleptinemia is a common consequence of obesity in humans and rodents suggesting the presence of a resistance process that may be involved in the disturbance of body weight regulation[131].

There is evidence of the ability of dietary n-3 PUFAs to regulate leptin production *in vitro* and *in vivo*. Some assays in cultured adipocytes have observed that EPA (10, 100 and 1000 μM, 24 h) induces leptin expression in 3T3-L1 [132] and primary rat adipocytes (10, 100, and 200 μM, 96 h), which may be triggered by increasing the oxidative metabolism of glucose [85]. In addition, it has been reported differential effects of EPA and DHA (100 μM and 50 μM respectively, 48 h) on leptin expression of 3T3-L1 adipocytes, being EPA a stimulant of leptin while DHA did not have any significant effect [115].

Regarding studies in animal models of obesity treated with n-3 PUFAs, the outcomes about leptin are apparently controversial. In a recent publication, HFD-stimulated leptin expression in adipose tissue was reversed by intragastric administration of marine origin n-3 PUFAs (1 g/day, 20 weeks) although differences in serum levels did not reach statistical significance, suggesting that variations of adipokine expression possibly precede modifications in serum levels [122]. A decrease in both leptin expression and circulating levels has been also observed after fish oil (8.6% of fat composition in form of EPA and 43.8% DHA) supplementation in combination with 4% of taurine as an adjuvant for 4 weeks in obese/diabetic KK-A^y mice[133]. Similar outcomes have been observed in other trials [15], suggesting that the decrease in adipose tissue leptin could be secondary to the reduction of fat pad size observed in n-3 PUFAs-supplemented groups.

In contrast, there are some studies that found a positive regulation of leptin expression by n-3 PUFAs. In this sense, Pérez-Matute et al. [48]reported that a 35 days-treatment with highly purified EPA (1 g/kg) significantly increased leptin circulating levels in overweight rats while significantly decreased in lean rats. These results correlate with Peyron-Caso et al. [40] and Rossi et al. [53], which also observed positive regulation of leptin after dietary supplementation with marine origin n-3 PUFAs (replacing 14% of lipids with fish oil for 3 weeks or replacing the source of fat with 7 g of cod liver oil/100 g for 2 months, respectively). The differential outcomes between studies may rely on differences in the physiological state of the animals and the type, dose and duration of treatments [15].

Concerning human studies, a recent meta-analysis showed that supplementation with n-3 PUFAs from marine sources could moderately reduce leptin plasma levels in non-obese, but not in obese subjects[134]. Indeed, n-3 PUFAs associated increases in leptin levels have been observed in obese subjects[135]. In this context, a recent study of our group has found that EPA supplementation (1300 mg/day, 10 weeks) prevents the fall of leptin during weight loss in overweight/obese women, suggesting that EPA could contribute to prevent weight regain in healthy weight-reduced subjects[136]. Taken together, these data highlight the relevance of the dose and duration of the treatment as well as the composition of the dietary fish oil and the metabolic state of the subjects on leptin production.

Apelin

Apelin is an adipokine with potential anti-diabetic, anti-obesity and cardioprotective properties [137]. Apelin circulating levels have been observed to be upregulated in hyperinsulinemic obese subjects [138]. However, it has been proposed that apelin could be a protective mechanism against type 2 diabetes development [139]. In fact, apelin treatment decreased body adiposity and increased energy expenditure through the upregulation of UCP1 in brown adipose tissue in mice [140]. Moreover, apelin administration to obese and insulin-

resistant mice also restored glucose tolerance and insulin sensitivity by modifying serum levels of adiponectin, insulin and TG in DIO mice [140,141]. Furthermore, apelin activates AMPK leading to enhanced skeletal muscle mitochondrial biogenesis, complete fatty acid oxidation and insulin-stimulated glucose uptake[142].

Treatment with EPA has been seen to exert modulatory effects of apelin both, *in vitro* and *in vivo*. For instance, EPA treatment (100μM, 24 h) stimulatesapelin production in cultured adipocytes [143] and myocytes [41]. A previous study of our group found that EPA supplementation (1 g/kg for 35 days) in HFD-fed rats increasesapelin mRNA in adipose tissue and suggested that the insulin-sensitizing effects of EPA in rodents could be associated to its stimulatory effect on apelin[144]. EPA supplementation (36 g/kg EPA, 10 weeks) also up-regulatesapelin in soleous muscle of HFD-fed mice [41].

In summary, all these data sheds light into the modulatory role of marine origin n-3 PUFAs on the production of key adipokinesby adipose tissue, which may mediate in part the beneficial effects of these fatty acids on glucose and lipid metabolism and contribute to manage inflammatory status of adipose tissue.

3.6. Role of PPARs and AMPK in the actions of n-3 PUFAs in adipose tissue

N-3 PUFAs are naturally occurring ligands of a family of transcription factors called peroxisome proliferator-activated receptor (PPARs), which have been largely proposed as mediators of the actions of these fatty acids.

In this context, n-3 PUFAs are known to activate PPARα, which is abundantly present in mammalian liver[145]. The activation of this nuclear receptor triggers the expression of key genes involved in lipid metabolism that promote fat catabolism[145]. Fish oil has been also shown to modulate the expression of sterol regulatory element binding protein-1 (SREBP1)[146,147] with concomitant decreases of cholesterologenic and lipogenic enzymes

expression. On the other hand, PPARγis mainly expressed in adipose tissue, where it is known to induce differentiation of preadipocytes and triglyceride storage by activating a great number of genes involved in adipogenesis and fatty acid transport, storage and oxidation [145]. This nuclear receptor has been proved to bind fatty acids and lipid-derived substrates as well as Thiazolidinediones (TZDs)[145], which have been utilized as hypoglycemic and muscle insulin-sensitizing drugs in type 2 diabetes. In mature adipocytes, ligand activation of PPARγinduces the expression of a number of genes involved in glucose and lipid metabolism, improving insulin sensitivity and promoting fatty acid oxidation. Moreover, this transcription factor participates in the modulation of adipocytokines production.

Oster et al. [114] found that DHA, but not EPA (125 µM, 24 h) led to increased expression of *Pparγ,* while both stimulate adiponectinin 3T3-L1 adipocytes. Moreover, treatment with BADGE, a PPARγ antagonist, inhibited the stimulatory effect of DHA on adiponectin, but did not affect EPA action on this adipokine, suggesting that EPA stimulatory effects on adiponectin production may be given through a *Pparγ*-independent mechanism. Studies from our group have reported decreased *Pparγ*expression after chronic treatment with EPA (100-200 µM, 96h) of cultured rat adipocytes [116].

Regarding the effects of n-3 PUFAs supplementation on PPARγ in rodents, González-Périz et al. [55] observed an upregulation of *Pparγ*mRNA levels in WAT of mice fed with a diet enriched in marine origin n-3 PUFAs (replacement of 6% total lipids, 5 weeks) accompanying the improvement in insulin sensitivity, adiponectin and decrease of inflammation. Neschen et al. [148]found a PPARγ dependent upregulation of adiponectin by n-3 PUFAs-rich fish oil (59% of fat-derived calories, 15 days) in mice epididymal adipose tissue, independently of PPARα. However, studies from our group have reported decreased *Pparγ*expression after supplementation with EPA ethyl ester (1 g/kg, 35 days)[48].Taken together, the *in vitro* and *in*

vivo data suggest potential differential effects of EPA and DHA on PPARγ, which deserves further investigation.

Moreover, supplementation with n-3 PUFAs (3 g/day, 944 mg EPA and 2.088 DHA for 12 weeks) has been associated with a downregulated expression of *PPARγ*in adipose tissue of obese adolescents[149].

Activation of AMPK phosphorylation has also been implicated in the effects of n-3 PUFAs. This heterotrimeric protein acts as an energy sensing enzyme stimulating those signaling pathways that increase energy production (i.e. glucose transport or fatty acid oxidation) and switching off energy-consuming pathways (lipogenesis, protein synthesis, gluconeogenesis). Therefore, AMPK activation has important regulatory effects of glucose and lipid metabolism in key organs including liver, skeletal muscle, adipose tissue and pancreas[150]. For example, AMPK seems to be necessary for the preservation of hepatic insulin sensitivity by n-3 PUFAs[151].

A study from our group showed that EPA (100-200 µM, 24 h) stimulated AMPK activation in 3T3-L1 adipocytes, and interestingly it was demonstrated that AMPK activation is involved in the stimulatory action of EPA on visfatin production by adipocytes [143]. It was also suggested that AMPK activation is involved in the ability of EPA to prevent the lipolytic effects of the pro-inflammatory cytokine TNF-α in adipocytes [81]. Furthermore, several studies have reported AMPK activation in WAT after supplementation with marine origin n-3 PUFAs. For instance, Kopecky et al. [73] found an elevation of phosphorylated AMPK levels in DIO mice fed with n-3 PUFAs (44% of lipids replacement, 5 weeks). Moreover, González-Périz et al.[55]foundthat DHA treatmentstimulated AMPK phosphorylationin WAT of *ob/ob*mice in paralleltoanimprovement in insulinsensitivity and theupregulation of insulin receptor signaling (IRS-1 and IRS-2).

3.7. Effectson adipose tissue inflammation

A growing body of evidence supports that marine origin n-3 PUFAs may ameliorate adipose tissue inflammation both in obese rodents and humans [42,152,153]. Several mechanisms have been proposed for the anti-inflammatory actions of n-3 PUFAs on WAT: (a) Reducing the production of pro-inflammatory adipocytokines and increasing the release of anti-inflammatory adipocytokines from adipose tissue; (b) Decreasing macrophage infiltration; (c) Reducing the formation of n-6 derived pro-inflammatory lipid mediators; (d) Being substrates for the formation of pro-resolutive lipid mediators.

(a) Modulation of cytokines, chemokines and adipokines production patterns

Strong scientific support exists about that marine origin n-3 PUFAs may alleviate adipocyte dysregulation and the subsequent inflammation by promoting the production of anti-inflammatory adipose-released substances, including adiponectin or IL-10, and down-regulating the secretion of the pro-inflammatory adipocytokines and chemokines including MCP-1, IL-6 or resistin[42,54,111].

Studies in cultured adipocytes indicate the ability of n-3 PUFAs to downregulate the production of pro-inflammatory molecules. For instance, the administration of EPA (150 μM) to 3T3-L1 adipocytes significantly decreases the secretion of IL-6 and increases adiponectin levels after 48 h of treatment [42].

Animal studies also reveal this modulatory capacity of the production of pro and anti-inflammatoryadipokines. In this sense, Rossmeisl et al. [47] reported a decrease in *Mcp-1* and an increase in adiponectin expression in WAT after 4 months HFD-feeding period followed by 9 weeks of supplementation with DHA and EPA (30 g/kg of diet) in mice. Interestingly, Ding et al. [122] has recently shown that marine origin n-3 PUFAs intragastric administration (1 g/day for 20 weeks) decreased resistin and leptin and increased adiponectin protein levels in adipose tissue. However, Gonzalez-Périz et al. [55] did not observe any effect on *Mcp-1*, *Il-*

6 or *Tnf-α* mRNA in adipose tissue of *ob/ob* mice supplemented 6% of total lipids of diet with n-3 PUFAs for 5 weeks, although adiponectin expression was also significantly increased.

In DIO mice a 20-weeks replacement of 5% of fat in the form of EPA decreased MCP-1 expression in adipose tissue and leptin serum levels while plasma adiponectin was increased[44]. In fact, diet supplementation with EPA (0.5 g/kg) for 4 weeks resulted in a decreased expression of *Il-6* in adipose tissue of spontaneous diabetic rats[54]. Thisis in concordance with the study of Kalupahana et al.[42]showing that the replacement of dietary fat with EPA (36g/kg of diet for 11 weeks) reduced MCP-1 and PAI-1 in gonadal fat despite there was no change in serum levels of these proteins. In the same way, previous studies of our group reported that administration of EPA-ethyl ester to DIO rats (1g/kg, 35 days) decreased *Tnf-α* and *Il-6* mRNA expression in WAT in parallel with an increase in adiponectin gene expression [48,154].

Furthermore, in the epididymal adipose tissue of fat-1 transgenic male mice, it has been observed a reduction in the levels of some pro-inflammatory cytokines (MCP-1, RANTES, IL-1β, IL-2 and IL-6), in parallel with a decrease in either the percent of F4/80^{+} cells or the crown-like structures cells [60]. In concordance with these observations, other study using the same animal model and in the same fat depot reported positive changes in the expression of some genes associated with inflammation processes, decreasing *Mcp-1* and increasing genes linked with anti-inflammatory actions [62] (see Table 2).

All this data reveal that the anti-inflammatory actions of n-3 PUFAsare in part mediated by the modulation of the production of adipocytokines, and that more research is needed to further understand the effects of n-3 PUFAs on adipose tissue secretion.

(b) Reduction of M1 macrophages infiltration and promotion of switch to M2

As explained before, obesity courses with increased levels of macrophages infiltration to WAT. Several studies have demonstrated the capacity of n-3 PUFAs to decrease macrophages

infiltration and to promote the switch from M1 phenotype to M2. In this way, DHA (200 µM, 9 h) also raised mRNA levels of the main M2 phenotype indicators as *Cd36, Il-10,* and*Tgfβ*in RAW264.7 cells [155]. Additionally, the study of Todoric et al. [51] found downregulated expression of MCP-1 and markers related with macrophage infiltration as *Msr1, Il1rn* and *CD14* in WAT ofHFD-fed *db/db* mice fed with a diet enriched inmarine origin n-3 PUFAs (40% of oil volume being replaced by a concentrate of highly purified n-3 PUFA EPA and DHA re-esterified to triglyceride). Titos et al. [156] reported that DHA (4 µg/g i.p. for 10 days) did not change the number of adipose tissue macrophages, but promoted a phenotyping switch in macrophage polarization toward an M2-like phenotype in HFD-fed obese mice.

It is important to mention that the study of Oh et al. [157] identified that GPR120 is an n-3 PUFAs receptor mediating their potent anti-inflammatory and insulin-sensitizing effects in mice. In fact, n-3 PUFAs were not able to reduce inflammation and macrophages infiltration when administered to GPR120 knockout mice. Therefore, these findings suggest the key role of GPR120 as mediator of n-3 PUFAs anti-inflammatory actions.

Studies in fat-1 transgenic mice have strengthened the previous information, observinga drop in the macrophage migration markers into the adipose tissue of these mice as compared with the matched wild type group fed with a HFD [158], together with an induction of a phenotypic shift from the pro-inflammatory M1 macrophages to the anti-inflammatory M2 macrophages [61,62](see Table 2).

In parallel with cultured adipocytes models, the study of Itariu et al. [159] performed in severely obese non-diabetic patients also found that supplementation with 3.36 g/day of highly purified EPA and DHA for 8 weeks decreased the expression of inflammatory markers related with macrophage signaling into adipose tissue and down-regulated the expression of the CD140 M1 macrophage marker but only in subcutaneous adipose tissue without effect in visceral fat.

(c) Reduction of n-6 PUFAs- derived proinflammatory lipid mediators

In adipose tissue, another switch occurs when n-3 PUFAs are increased. In fact, treatment with n-3 PUFAs may reduce the formation of pro-inflammatory lipid mediators derived from n-6 PUFAs such as leukotrienes and prostaglandins derived from Arachidonic acid. It has been proved that EPA and DHA modulate the utilization of Arachidonic acid [160], and a competitive inhibition of the production of n-6 PUFAs lipid mediators by n-3 PUFAs seems to take place [153,160,161]. DHA is able to inhibit the production of prostaglandins (PG) also by a strong competition for PG synthetase, an enzyme responsible to produce prostaglandins [162]. Interestingly, the study of González-Périz et al. [55] found that marine origin n-3 PUFAs dietary enrichment reduced the formation of n-6 PUFAs-derived proinflammatory mediators such as PGE_2, $PGF_{2\alpha}$, TXB_2, 5-HETE, 12-HETE and 15-HETE in adipose tissue of *ob/ob* mice. This mechanism could reduce the inflammation in adipose tissue, and help to the resolution of the low-grade inflammation that is established in obesity and metabolic complications.

(d) Constitute substrates for the formation of pro-resolutive lipid mediators

Serhanand collaborators discovered that n-3PUFAs serve as substrates for the formation of specialized proresolving lipid mediators (SPMs)[163–165]. EPA-derived SPMs are known as E-series Resolvins (RvE1-3) and DHA-derived lipid mediators are named as D-series Resolvins (RvD1-6), (Neuro)Protectins (NPD1) and Maresins (MaR1-2)[166](see Figure 1). These novel bioactive compounds exert potent anti-inflammatory and pro-resolutive actions in acute and chronic inflammation helping to restore tissue homeostasis[166,167]. It is important to highlight that unlike their precursors (DHA and EPA), these SPMs exert potent actions at picomolar to nanomolar range.

Interestingly, Claria et al.[168] using a metabolo-lipidomics approach detected a range of these SPMs in human subcutaneous adipose tissue, such as RvD1, RvD2, PD1, lipoxin (LX) A4, and the monohydroxy biosynthetic pathway markers of RvD1 and PD1 (17-HDHA), RvE1 (18-HEPE), and maresin 1 (14-HDHA). Importantly, it has been identified that obesity is accompanied by an impaired adipose tissue local production of some proresolving lipid mediators[169,170]. Neuhofer et al.[170]also found that adipose tissue reduction of 17-HDHA and PD1 represents one of the earliest alterations in diet-induced inflammation.

Several studies have revealed that dietary marine origin n-3 PUFAssupplementationpromoted an increment of the synthesis of n-3 PUFA–derived SPMs and their precursors in adipose tissue of obese mice[55,170]. Interestingly, treatment withhighly purifiedn-3 PUFAs (3.36 g/day for 8 weeks) to severely obese-nondiabetic patients significantly increased the production of some n-3 PUFAs-derived SPMs, including RvE1, 17-HDHA, PD1, and RvD1 in visceral adipose tissue in parallel with the reduction of adipose tissue and systemic inflammation[159].

4. Effects of n-3 PUFAs-derived SPMs administration in obesity and MetS

Recently, some research groups have focused on analyzing the capacity of some SPMs to improve adipose tissue inflammation in obesity and their associated metabolic complications[152,171].Table 3 summarizes the studies in animal modelsof obesity and related disorders treated with different n-3 PUFAs-derived SPMs.

González-Périz et al.[55]showed that treatment with RvE1 and PD1 to*ob/ob* mice mimicked the beneficial actions of n-3 PUFAs supplementation. Thus, RvE1 was able to attenuate hepatic steatosis and upregulated mRNAlevels of adiponectin, *Glut4, Irs1, Pparγ* as well as AMPK phosphorylation in adipose tissue. Interestingly, PD1 increased adiponectin

expression in adipose tissue explants of *ob/ob* mice.Furthermore, RvD1 has revealed to have beneficial effects on inflammatory processes, adipokine secretion, and insulin sensitivity in both, diet-induced and genetically obese mice[156,169,172,173].Thus, Hellman et al.[173]found that RvD1 improved glucose tolerance, decreased fasting blood glucose, increased adiponectin, and in WAT promoted Akt and AMPK activation,while decreased the expression of pro-inflammatory adipokines such as IL-6. In addition, a decrease in crown-like structures rich in inflammatory F4/80+CD11c+ macrophages and an increase in F4/80+ cells expressing MGL-1 was found, supporting arise in the ratio M2:M1 adipose tissue macrophages in RvD1-treated *db/db* mice.

In agreement with these results, Titos et al.[156]showed that treatment of macrophages with RvD1 downregulated pro-inflammatory cytokines complementary to an increase of M2 markers such as Ym1 and arginase-1. In this sense, a promotion of the switch in macrophage polarization toward an M2-like phenotype and nonphlogistic phagocytosis in adipose tissue was described. This group also reported that *ex vivo* treatment of inflamed obese adipose tissue explants with RvD1 and RvD2 attenuated in a dose-dependent manner the impaired expression and secretion of adiponectin and also decreased the levels of proinflammatoryadipokinessuch asleptin, TNF-α, IL-6, and IL-1β. Moreover, RvD1 and RvD2 reduced MCP-1 and leukotriene B_4-stimulated monocyte adhesion to adipocytes and their transadipose migration[169]. Recently, it has been reported that RvD1 promoted the resolution process initiated by calorie restriction in obesity-induced steatohepatitis[172].

Neuhofer et al.[170]found that treatment of *db/db* mice with the n-3 docosanoid lipid mediator 17-HDHA reducedadipose tissue expression of inflammatory cytokines (such as MCP-1, TNF-α, IL-6 and osteopontin) and increased adiponectin levels, in parallel with an improvement of insulin sensitivity and glucose tolerance.

The recent study of White et al.[174]demonstrated that Protectin DX (PDX) has importantinsulin-sensitizing and glucoregulatoryactions by selectively stimulating the release of the myokine IL-6 from skeletal muscle and initiating a myokine-liver signaling axis. PDX treatment also increased AMPK phosphorylation in muscle, but did not have any impact on adipose tissue inflammation in obese diabetic *db/db* mice.

Conclusions

Obesity leads to several chronic morbidities including type 2 diabetes, dyslipidaemia, atherosclerosis and hypertension, which are major components of MetS. Low-grade inflammation has been identified as a key factor in the development of MetS features affecting obese subjects. WAT metabolism and WAT-derived factors (fatty acids and adipokines) play an important role in the development of these metabolic disturbances. In obesity, the expanding WAT makes a substantial contribution to the development of inflammation via increased secretion of pro-inflammatory cytokines, chemokines and adipokines and the reduction of anti-inflammatory adipokines. The state of chronic low-grade inflammation is powerfully amplified through the infiltration of macrophages into WAT. This dysregulated situation primarily initiated within WAT can affect the function of other metabolic organs, including liver, muscle and pancreas. These adverse facts highlight the importanceof finding effective nutritional or pharmacological strategies for preventing or attenuating the adipose tissue inflammation and associated dysfunctions that accompany obesity. Growing evidence exits about the role of WAT in mediating the beneficial effects ofmarine n-3 PUFAsin obesity-associated metabolic disorders. Figure 2 summarizes the mechanisms by which marine origin n-3 PUFAs control adipose tissue metabolism and function. N-3 PUFAs have been shown to modulate adipocyte number by regulating adipocyte proliferation and differentiation as well as apoptosis. Moreover, n-3 PUFAs also

regulates pathways controlling fat storage and fat mobilization, decreasing lipid accumulation processes and favoring adipocyte oxidative metabolism by promoting mitochondrial biogenesis and fatty acid oxidation.In addition, EPA and DHA are also capable of modulate adipocyte insulin sensitivity and glucose utilization. These n-3 PUFAs actions have been related in part to their ability to stimulate PPARγ and AMPK activation. Further studies are needed to better characterize the potential britening actions of n-3 PUFAs on WAT. Importantly, marine origin n-3 PUFAs can mitigate adipose tissue inflammation by restoring the dysfunctional proinflammatory secretory pattern of hypertrophied adipocytes, and specially by promoting the formation of important proresolutive lipid mediators such as resolvins, protectins and maresins.Most of these findings have been observed in animal and cell culture models and, there is still few clinical trials addressing if these actions occur also in human adipose tissue after n-3 PUFAs supplementation. Therefore, there is a need of performing clinical trials in humans aiming to establish the more effective n-3 PUFAs doses and formulations to counteract adipose tissue dysfunction and reverse clinical metabolic disturbances in subjects with obesity and metabolic syndrome.

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Table 1. Effects of marine n-3 PUFAs on obesity and MetS features in animal models

Animal model	Treatment	Duration	Metabolic outcomes	Study
Male mice (aP2-Cre-ER^{T2} PPARγ$^{L2/L2}$) fed HFD	Corn oil-based HFD with LC n-3 PUFAs concentrate replacing 15% (wt/wt) of dietary lipids.	42 days	↓Body weight ↓Epididymal fat ↓Subcutaneous fat	[37]
Male Wistar rats fed a sucrose-rich diet	Fish oil (7 g/100 g of fish oil plus 1 g/100 g of corn oil) replacing the source of fat diet	60 days	↔Body weight ↓Epididymal Fat ↓Retroperitoneal fat ↓FFA ↓TG ↓Glucose ↔Insulin	[39]
Male Wistar rats fed with HFD	Native fish oil (200 g/kg diet), ethyl ester of EPA or DHA or as a mixture of ethylesters of these two fatty acids	4 weeks	↔Body weight ↔NEFA ↓TG ↔Insulin	[50]
Male C57BL/6N mice fed HFD	6% of EPA and 51% of DHA (EPAX 1050) replacing 44% of dietary fat	4 weeks	↓Body weight ↓Epididymal Fat	[38]
	n-3 PUFAs deprivation for 2 weeks followed by 5 weeks EPAX 1050 replacing 15% of dietary lipids	5 weeks	↓Epididymal Fat	

Male C57BL/6N mice fed HFD	n-3 PUFAs concentrate (46% wt/wt DHA, 14% wt/wt EPA) replacing 15% of dietary lipids	5 weeks	↓ TG ↓β-hydroxybutyrate ↔Glucose ↓ Insulin ↔Body weight	[56]
Male *ob/ob* mice	n-3 PUFA-enriched diet (6% of total lipid content)	5 weeks	↔Epididymal fat ↓Cholesterol ↔TG ↔FFA	[55]
Male Sprague-Dawley rats	Fish oil (MAXEPA; 14 g/100 g diet wt/wt) replacing the source of fat diet	3 and 6 weeks	↔Body weight ↓Epididymal Fat ↓Retroperitoneal fat	[106]
Male *db/db* mice fed with HFD	Purified marine n-3 PUFAs (Re-esterified to triglycerides) replacing 40% of oil volume	6 weeks	↔Body weight ↔NEFA ↓TG ↔Glucose	[51]
Male C57BL/6N mice fed HFD	Herring derived n-3 PUFAs concentrate rich in phosphatidylcholine (EPAX AS; 5 g DHA/EPA per kg diet) replacing 10% of dietary lipids	7 weeks	↓Body weight ↓Cholesterol ↓NEFA ↓TG ↓Glucose ↓Insulin	[47]

*fa/fa*Zucker rats	Menhaden oil replacing 10% (wt/wt) of dietary fat	8.5 weeks	↔Body weight ↔Fat depots ↓FFA ↔TG ↔Glucose tolerance	[52]
Male Golden Syrian hamsters fed HFD	n-3 PUFAs oil mixture replacing 10% of lard oil	20 weeks	↓Body weight ↓Cholesterol ↓TG ↓HDL-c ↓Glucose ↑Glucose tolerance	[36]
Male Wistar rats fed with sucrose-rich diet 7 months prior treatment	Fish oil (7 g cod liver oil/ 100 g diet) replacing the source of fat diet	2 months	↔Body weight ↓FFA ↓TG ↓Glucose ↔Insulin	[53]
Male C57BK/6J (B/6J) mice fed HFD	n-3 PUFAs concentrate (46% wt/wt DHA, 14% wt/wt EPA) replacing 15% of dietary lipids	7 months	↔Body weight ↓Epididymal fat ↓NEFA ↓TG ↓Glucose ↑Glucose tolerance	[49]

Male C57BL/6N mice fed HFD 4 months prior treatment	DHA (α-ethyl DHA ester) replaced 1.5% of dietary lipids	2 months	↓Body weight ↓Epididymal fat ↓Subcutaneous fat ↓NEFA ↓TG ↓Glucose ↓Insulin	[46]
Male C57BL/6N and C57BL/6J mice fed HFD	DHA (α-ethyl DHA ester) replaced 1.5% of dietary lipids	4 months	↓Body weight ↓Cholesterol ↓NEFA ↓TG ↓Glucose ↑Glucose tolerance ↓Insulin	
Male Wistar rats fed with control or cafeteria diet	EPA ethyl ester (1 g/kg body weight daily; oral gavage)	35 days	↔Body weight ↓ Retroperitoneal fat ↑Glucose tolerance ↓Insulin	[48]
			↓Cholesterol ↓ TG ↔FFA	[144]
Male Goto-Kakizaki rats	EPA (0.5 g/kg body weight; oral gavage)	Daily for 4 weeks	↔Body weight ↔Glucose ↔Glucose tolerance ↓Insulin	[54]

Male C57BL6/J fed HFD	EPA ethyl ester (36 g/kg diet wt/wt)	10 weeks	↓Body weight ↓Glucose ↑Glucose tolerance ↓Insulin	[41]
Male C57BL/6J mice fed HFD	EPA ethyl ester (36 g/kg diet (wt/wt))	11 weeks	↓ Body weight ↓ TG ↓Glucose ↑Glucose tolerance ↓Insulin	[42]
Male C57BL/6J mice fed HFD 6 weeks prior treatment		5 weeks	↔Body weight ↓TG ↓Glucose ↑Glucose tolerance ↓Insulin	
Male C57BL/6J mice fed a high fat/high sucrose diet (HF/HS) or a HFD	EPA ethyl ester (5 wt% of diet)	20 weeks	↓Body weight ↓Cholesterol ↓NEFA ↓TG ↓Glucose ↓Insulin	[44]

Male C57BL/6N mice fed HFD	n-3 PUFAs concentrate (46% wt/wt DHA, 14% wt/wt EPA) replacing 15% of dietary lipids + **Rosiglitazone**	6 weeks	↓Body weight ↔NEFA ↓TG ↔Glucose ↓Insulin	[43]
Male C57BL/6N mice fed HFD	n-3 PUFAs concentrate (46% wt/wt DHA, 14% wt/wt EPA) replacing 15% of dietary lipids + **Rosiglitazone**	8 weeks	↓Cholesterol ↔NEFA ↔TG ↔Insulin	[45]
		20 weeks	↓Cholesterol ↓NEFA ↔Glucose ↑Insulin sensitivity ↓Insulin	
Male C57BL/6N mice fed HFD 5 months prior to treatment	n-3 PUFAs concentrate (46% wt/wt DHA, 14% wt/wt EPA) replacing 15% of dietary lipids + **Rosiglitazone**	8 weeks	↓Body weight ↓NEFA ↓TG ↓Glucose ↑Glucose tolerance	

↓, decrease; ↑, increase; ↔, no change; DHA, docosahexaenoic acid; EPA, eicosapentaenoic acid; HFD, high fat diet; HS, high sucrose; NEFA, non-esterified fatty acids;TG: triglycerides.

Table 2. Effects of endogenously produced n-3 PUFAs in the transgenic mice fat-1 on body composition and metabolic disorders

Animal model	Treatment	Duration	Outcomes	Study
Males and females *fat-1* and wild type mice fed with high n-6 unsaturated fat (HUSF)	HUSF (15% CHO, 62% fat of which 77% from linoleic acid and 13% oleic acid, 23% protein). After HUSF diet, mice were either sacrificed or switched to high carbohydrate diet period (58% CHO, 13% fat and 29% protein).	≈8 weeks (HUSF diet) ≈3 weeks (HC diet)	↓Body weight in males ↔Body weight (females) ↔Fat pads (both males and females), ↔Fasting blood glucose ↓Glucose AUC (males) ↑Glucose AUC (females) ↔Insulin sensitivity	[65]
Males *fat-1* and wild type mice fed chow diet or HFD	Chow diet (13% kcal from fat) and HFD (55% kcal from fat)	8 weeks	↔In any variable in LFD groups **Versus HFD group** ↔Body weight, food intake, ↔Adiposity, ↔NEFA ↓Insulin resistance ↓Glucose intolerance **Epididymal adipose tissue** ↓F4/80^{+} cells and formation of crown-like structures ↓MCP-1 (CCL2), RANTES (CCL5), IL-1β, IL-2, IL-6 ↑17-HDoHE, PD1, 18-HEPE	[60]

Male f*at-1* and wild type mice fed HFD	55 % kcal from fat	8 weeks	**Epididymal adipose tissue** ↑Mid-sized adipocytes ↓Large and very large adipocytes ↓Gata3 ↑PPARγ gene expression ↓Inhibitors of insulin signal transduction (Enpp1, Ptprf)	[63]
Male and female *fat-1* mice breeders on C57BL/6 background	Modified AIN-76A rodent diet (10% corn oil) Femoral artery thrombosis and chronic artery damage were induced by $FeCl_3$	8 weeks	↓Macrophage migration in perivascular adipose tissue N-3 PUFAs exerts its effects via activation of FFAR4 (GRP120) ↓Thrombus formation ↓Artery hyperplasia	[158]
Male *fat-1* mice and C57BL/6 mice as control, either fed with LFD or with HFD	LFD (70% CHO, 20% protein, 10% fat) and HFD (20% CHO, 20% protein, 60% fat)	8 weeks	↔In any variable in LFD groups **Versus HFD group** ↓Body weight gain, adiposity and food efficiency ↑Energy expenditure ↓Plasma leptin ↔Food intake, ↔TG, NEFA, cholesterol, insulin, adiponectin or resistin ↓Fasting glycaemia and glucose AUC (mediated by PPARγ) ↓ M1 ($F4/80^+$, $CD11c^+$ cells) ↑ M2 ($F4/80^+$, $CD206^+$ cells)	[61]

Males *fat-1* mice and C57BL/6 mice as control, either fed with chow diet or with HFD. C57BL/6 with HFD+n-3 PUFAs	Chow diet (13% kcal from fat) and HFD (60% kcal from fat). Control mice fed with n-3 PUFAs-enriched diet.	16 weeks	↔In any variable in LFD groups **Versus HFD group** ↓HFD-induced weight gain ↓White adipose tissue (epididymal), ↓Adipocyte size **Epididymal adipose tissue** ↓Macrophage infiltration and fibrosis ↓MCP-1 gene expression ↑CD206, IL-10, MGL1 gene expression ↔IL-6, IL-1β, Arg1, RELMα and Ym1 gene expression	[62]
2-months and 8-months aged males *fat-1* mice and wild type mice fed with AIN-76A test diet	AIN-76 test diet (10 % corn oil diet).	2 months or 8 months	↔In any variable in the 2-month-old mice (fat-1 *vs* wild type) **8-month-old-mice** ↓Body weight and epididymal fat ↓Blood glucose and insulin ↓Glucose AUC ↑Insulin sensitivity ↓TG and cholesterol	[64]

↓, decrease; ↑; increase; ↔, no change; 18-HEPE, 18-hydroxyeicosapentaenoic acid; Arg1, arginase-1; AUC, area under curve; CCL, chemokine (C-C motif) ligand; Enpp1, ectonucleotidepyrophosphatase/phosphodiesterase 1; FFAR4, free fatty acid receptor 4; GPR120, G protein-coupled receptor 120; HFD, high fat diet; IL, interleukin; LFD, low fat diet; M, macrophage, MCP-1, monocyte chemoattractant protein 1; MGL1, macrophage galactose-type C-type lectin 1; NEFA, non-esterified fatty acids; PD1, protectin D 1; PPARγ, peroxisome proliferator-activated receptor gamma; Ptprf, protein tyrosine phosphatase receptor type, F; RELMα, resistin-like molecule-α; RANTES, regulated on activation, normal T cell expressed and secreted; TG, triglycerides.

Table 3.Effects of treatment with n-3 PUFAs-derived SPMs in animal models of obesity and related metabolic disorders.

SPM	Animal	Treatment (dose & duration)	Observations	References
RvD1	*ob/ob* mice	1.2 ng/g b.w. every 24h during 4 days	↑PPARγ, GLUT4 and IRS-1 gene expression ↑ Adiponectin ↓ Formation of n-6 PUFAs derived eicosanoids ↑ Formation of n-3 PUFAs derived resolvins and protectins	[55]
RvD1	*db/db* mice	2µg/kg b.w.for 8 to 16 days	↑ Glucose tolerance ↓ Fasting blood glucose ↑ Adiponectin ↑ Insulin-stimulated Akt phosphorylation in WAT ↑ AMPK phosphorylation in WAT ↓IL-6 expression in WAT ↓ Crown-like structures rich in inflammatory F4/80+ CD11c+ macrophages ↑ F4/80+ cells expressing MGL-1.	[170]
RvD1	C57BL/6J mice HFD	300ng every 24h during 3 weeks + Calorie restriction	↑ Adiponectin ↑ IL-4 and IL-10 ↓Macrophage innate immune response in liver	[169]

17- HDHA	*db/db* mice	50 ng/g b.w. every 12 h during 8 days, or continuous application for 15 days	↓ Expression of MCP-1, TNF-α, IL-6 and osteopontin in WAT ↑ Adiponectin ↑ Glucose tolerance and insulin sensitivity	[166]
Protectin DX	*db/db* mice	1 µg intravenously immediately before and 2.5 h into the 6-h lipid infusion	↑ IL-6 expression in skeletal muscle ↑ AMPK phosphorylation in skeletal muscle ↑ Insulin sensitivity in skeletal muscle	[171]

↓, decrease; ↑, increase; ↔, no change; GLUT4, glucose transporter 4; IL, interleukin; IRS-1, insulin receptor substrate-1; MCP-1, macrophage chemoattractant protein; MGL-1, macrophage galactose-type C-type lectin-1; PPARγ, proliferator-activated receptor γ; PUFAs, polyunsaturated fatty acids; TNF-α, tumor necrosis factor-α; WAT, white adipose tissue.

FIGURE LEGENDS

Fig. 1. Overview of the pathways involved in the formation of n-3 PUFAs-derived bioactive lipid mediators. COX: cyclooxygenase, DHA: docosahexaenoic acid, EPA: eicosapentaenoic acid, HEPE: hydroxyeicosapentaenoic acid, HpDHA: hydroperoxydocosahexaenoic acid, HpEPE: hydroperoxyeicosapentaenoicacid, LOX lipoxygenase, 17-HDHA: 17-hydroxydocosahexaenoic acid.

Fig. 2.Summary of mechanisms by which n-3 PUFAs (EPA and DHA) regulate adipose tissue metabolism and functions. Marinen-3 PUFAs modulate adipocyte fat storage and mobilization, favoring adipocyte oxidative metabolism through the stimulation of mitochondrial biogenesis and fatty acid oxidation. EPA and DHA also regulate adipocyte glucose utilization and insulin sensitivity (Akt phosphorylation). These n-3 PUFAs actions are in part mediated by PPARγ and AMPK activation. Potential britening actions of n-3 PUFAs on WAT have been also suggested. Marine origin n-3 PUFAs also regulate the secretion of adipokines involved in energy homeostasis and intermediate metabolism, which could also contribute to the beneficial effects of these fatty acids on glucose and lipid metabolism. EPA and DHA can mitigate adipose tissue inflammation by regulating the production of pro-inflammatory chemokines and cytokines, by decreasing M1 macrophage infiltration, by reducing the formation of n-6 derived pro-inflammatory lipid mediators and being substrates for the formation of pro-resolutive lipid mediators, such as resolvins, protectins and maresins.

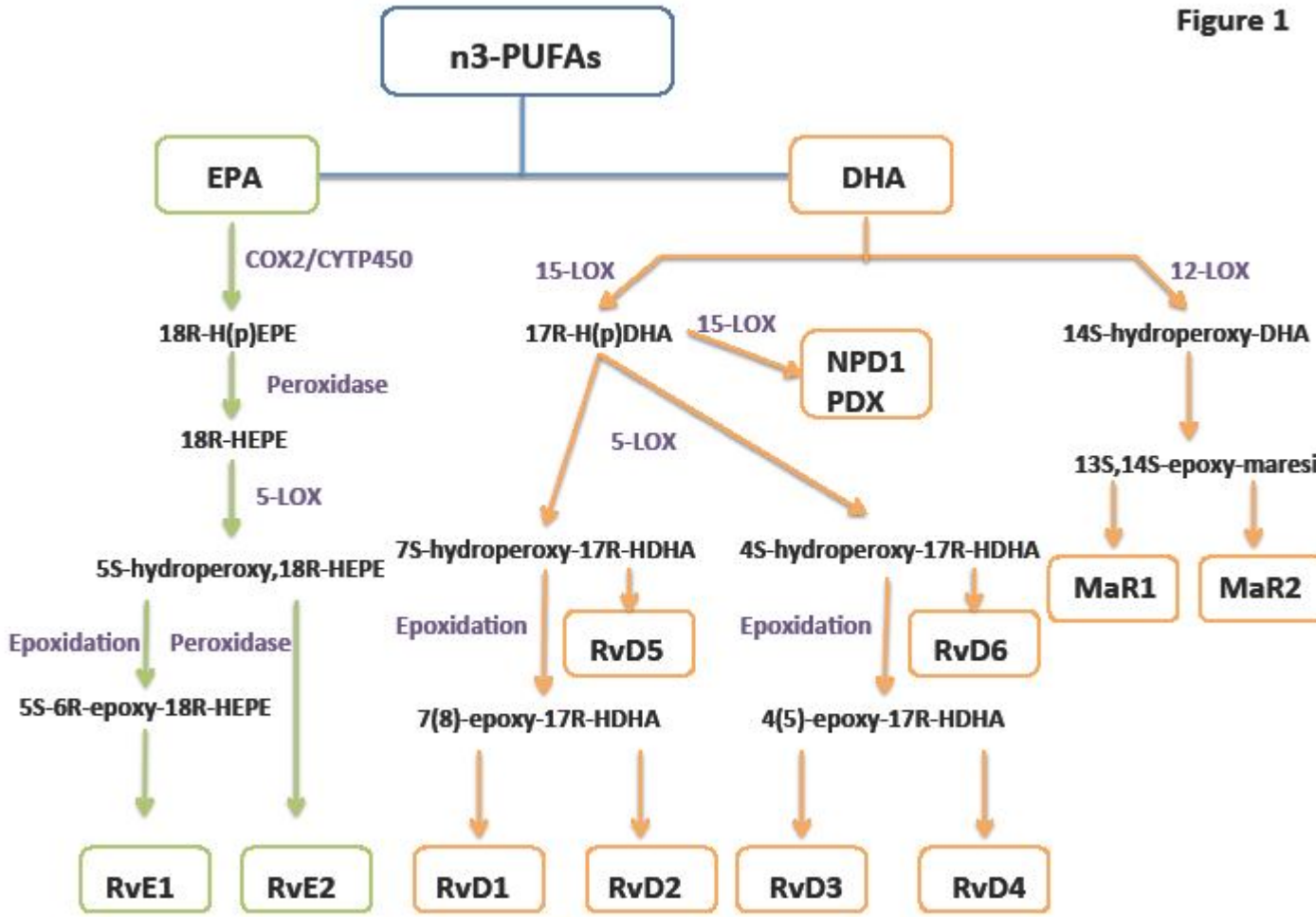

Figure 2