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n-3 PUFA and obesity: from peripheral tissues to the central nervous system

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Abstract

The current paradigms of prevention and treatment are unable to curb obesity rates, which indicates the need to explore alternative therapeutic approaches. Obesity leads to several damages to the body and is an important risk factor for a number of other chronic diseases. Furthermore, despite the first alterations in obesity being observed and reported in peripheral tissues, studies indicate that obesity can also cause brain damage. Obesity leads to a chronic low-grade inflammatory state, and the therapeutic manipulation of inflammation can be explored. In this context, the use of *n*-3 PUFA (especially in the form of fish oil, rich in EPA and DHA) may be an interesting strategy, as this substance is known by its anti-inflammatory effect and numerous benefits to the body, such as reduction of TAG, cardiac arrhythmias, blood pressure and platelet aggregation, and has shown potential to help treat obesity. Thereby, the aim of this narrative review was to summarise the literature related to *n*-3 PUFA use in obesity treatment. First, the review provides a brief description of the obesity pathophysiology, including alterations that occur in peripheral tissues and at the central nervous system. In the sequence, we describe what are *n*-3 PUFA, their sources and their general effects. Finally, we explore the main topic linking obesity and *n*-3 PUFA. Animal and human studies were included and alterations on the whole organism were described (peripheral tissues and brain).

Key words: Obesity: Inflammation: Brain: *n*-3 PUFA

Introduction

The obesity epidemic is recognised as one of the major public health problems facing the world[1]. The number of obese people in the world has more than doubled since 1980. By 2014, more than 1·9 billion adults were overweight, and among these more than 600 million were obese. In percentages, 39 % of adults were overweight in 2014 and 13 % were obese[2].

The majority of body alterations related to obesity occur initially in peripheral tissues[3–5], such as adipose tissue, liver and muscles. Nevertheless, some studies have already revealed that obesity can also cause central nervous system (CNS) impairments[6,7].

The alterations related to obesity include low-grade chronic inflammation. As obesity has been considered as an inflammatory disease, it has aroused interest in the therapeutic manipulation of inflammation[8–10]. In this context, certain substances may play an important role in mediating inflammation and related alterations[11]. Some studies have shown that *n*-3 PUFA, which are essential fatty acids with several important biological effects[12–14], could contribute to treating obesity and related metabolic alterations[15–17].

Thereby, considering that *n*-3 PUFA could improve metabolic alterations related to obesity, the aim of this narrative review was to summarise the literature concerning the application of *n*-3 PUFA as an obesity treatment. First, we provide a brief description of the obesity pathophysiology, including alterations that occur in peripheral tissues and in the CNS. Next, we define *n*-3 PUFA, describe its sources and the general effects. In the sequence, we explore the main topic linking obesity and *n*-3 PUFA.

Methods

The literature research was conducted in PubMed and SciELO electronic databases, by the selection of articles related to the topic published between 2007 and 2017. A combination of the following keywords was used: obesity, inflammation, brain, CNS, *n*-3 and fish oil. The following combination of terms was searched: obesity AND inflammation, obesity AND inflammation AND brain, obesity AND brain, obesity AND central nervous system, omega-3, obesity AND omega-3, obesity AND fish oil, obesity AND eicosapentaenoic acid, obesity AND docosahexaenoic acid.

Studies using animal models, clinical trials and review articles were included. Clinical trials that tested the use of *n*-3 PUFA with lifestyle modification were included. Review articles were included both to identify other papers and to provide a view of what has already been revised about the topic. Regarding animal studies, the focus was on the effects of *n*-3 PUFA on diet-induced obesity, more similar to obesity in humans. Therefore, studies using obesity animal models by genetic modification or applying other interventions to lead to obesity (e.g. castration in rabbits) were excluded. Studies involving any surgical intervention (e.g. bariatric surgery) were also excluded.

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The search was carried out by two individual researchers. After screening by keywords, the titles and abstracts of articles were examined to determine whether they contained relevant data for this review. The two researchers carried out the reading of the titles and abstracts and selected the articles following the inclusion and exclusion criteria established. After that, both researchers had a consensus meeting to align any disparity in the inclusion or exclusion of articles. Subsequently, the complete reading of the articles was carried out. The original articles that addressed the use of *n*-3 PUFA to treat obesity and related alterations are included in Tables 1 and 2.

Obesity

The World Health Organization[2] defines obesity as an abnormal or excessive fat accumulation that can harm an individual's health. One of the major problems of obesity is being both a disease and a risk factor for several other disorders, such as cardiovascular diseases, type 2 diabetes mellitus, respiratory diseases, musculoskeletal disorders and some cancers, which have a great impact on quality of life and longevity of people[2,5,54].

Changes in dietary patterns and physical activity in recent decades, such as excessive consumption of food or high-energy foods, and sedentary lifestyle are major factors that contribute to the genesis of obesity[2]. If the total daily energy intake surpasses the amount of energy spent, the excess is stored as TAG in cells called adipocytes, which form the white adipose tissue[8]. Adipose tissue responds rapidly to excess nutrient consumption by adipocyte hypertrophy and hyperplasia[55]. Therefore, obesity is characterised by increased storage of fatty acids in an expanded mass of adipose tissue[3].

White adipose tissue, along with its important role in energy storage, is an important endocrine organ[3,8]. This tissue produces many bioactive molecules, such as cytokines (when secreted by adipose tissue, the cytokines can be called adipokines or adipocytokines), which not only serve as regulators of systemic metabolism but also have immunoregulatory properties[3,56,57].

Obesity leads to changes in adipokine secretion. Progressive increase of the adipocytes and consequent expansion of the adipose tissue leads to reduced blood supply, with consequent hypoxia, which is related to necrosis and infiltration of macrophages into adipose tissue. Infiltrated macrophages form crown-like structures surrounding adipocytes, leading to adipokine overproduction, which includes pro-inflammatory mediators such as TNF-α, IL-6 and IL-1β[3,10,58,59].

Obesity is characterised by a low-grade chronic inflammation, once the elevation of inflammatory markers and cytokines, as well as the presence of macrophages infiltrated into the white adipose tissue, can be detected[10]. This low-grade chronic inflammation in adipose tissue spreads to systemic inflammation and contributes to the onset and progression of associated metabolic disorders, such as insulin resistance, type 2 diabetes mellitus, hyperlipidaemia, atherosclerosis and metabolic syndrome[56,60,61]. Although most of the changes were initially identified and reported in peripheral tissues, studies conducted in the past decade have shown that obesity is also related to brain changes[6,7,62].

Obesity and the brain

Studies have shown that both excessive consumption of saturated fats and obesity can lead to brain damage[6,7,63]. More specifically, although little is known about the effects of obesity on the brain[64], studies have found associations between obesity and abnormalities in the hypothalamus[63,65,66], hippocampus, prefrontal cortex and striatum[67,68].

The hypothalamus is a brain structure that plays a central role in the regulation of energy homoeostasis, integrating multiple metabolic signals from peripheral organs and modulating eating behaviour and energy metabolism[69–72]. Therefore, changes at this site may cause neural control loss and make room for obesity onset and worsening[70].

The hypothalamus rapidly responds to metabolic challenges (e.g. hyperenergetic diet)[73]. Overnutrition causes hypothalamic inflammation, which disrupts the normal homoeostasis of energy intake and expenditure, as well as alters insulin secretion and sensitivity[7,63]. Unlike inflammation in peripheral tissues – a process that develops over weeks of high-fat-diet feeding in rodent models – markers of hypothalamic inflammation are elevated within 1 to 3 d of high-fat-diet exposure, before weight gain[63,73]. Therefore, the excess nutrients, as well as circulating inflammatory cytokines seen in obesity, such as TNF-α, IL-1β and IL-6, activate intracellular inflammatory pathways in a variety of target cells[74–76].

By using MRI in humans, Thaler *et al.*[63] have found evidence of increased gliosis in the mediobasal hypothalamus of obese individuals, suggesting that, similarly to what occurs in rodents with obesity induced by a high-fat diet, obesity in humans is associated with the neuronal injury in the hypothalamus, which is a crucial brain area for body weight control. Thereby, the hypothalamus functions may be altered when inflamed, leading to an imbalance between food intake and energy expenditure[62,65].

The hippocampus, the brain structure involved in cognition, memory, learning and emotions, is also vulnerable to the inflammatory process present in obesity[7,67,77–79]. Excessive consumption of food rich in saturated fat and sugar, besides being related to obesity, is associated with hippocampal impairment[78]. Therefore, cognitive function may also be impaired by high-fat intake and by obesity[79,80].

In rodent studies, Moroz *et al.*[81] showed that high-fat-diet feeding increased lipid peroxidation in the hippocampus, as indicated by high 4-hydroxynonenal levels. Park *et al.*[80] also showed that consumption of a high-fat diet leads to increased lipid peroxidation and impairs neurogenesis in the hippocampus. Jeon *et al.*[82] showed that a high-fat diet promotes an increase in hippocampal TNF-α expression and activates microglia. Boitard *et al.*[67] reported that the intake of a high-fat diet increases the expression of pro-inflammatory cytokines in the hippocampus.

Studies have shown that obesity may also be related to changes in the reward system, highlighting abnormalities in the prefrontal cortex and striatum[68,83,84]. It has been shown that dopamine levels in the medial prefrontal cortex and in the striatum of rats prone to obesity have been reduced[85]. In addition, a study on rodents has shown hypofunction of the

Table 1. Review of animal studies on *n*-3 PUFA for obesity (and related alterations)

References	Animal	Groups/Intervention	Duration*	Tissues evaluated	Main outcomes (main effects of the *n*-3 PUFA)
Mori *et al.*[18]	C57BL/6J mice	Expt 1 (5 groups): 5 % TAG, 30 % TAG, 28 % TAG + 2 % FO, 26 % TAG + 4 % FO, or 22 % TAG + 8 % FO Expt 2 (3 groups): 5 %TAG, 30 % TAG or 22 % TAG + 8 % FO	Expt 1: 5 months Expt 2: 2 weeks	Blood, adipose tissue, liver and intestinal mucosa	↓ Hepatic fat in diet-induced obesity-prone C57BL/6J mice ↑ Fatty acid catabolism in the small intestine
Moritz *et al.*[19]	Wistar rats	Control group, control group + swimming, *n*-3 group and *n*-3 group + swimming. The groups received 0·5 or 1·0 g/kg/d *n*-3 (EPA and DHA, or water) via gavage (8 groups)	4 weeks	Plasma	↓ Plasma concentrations of total cholesterol and TAG (especially when associated with swimming exercise)
Rokling-Andersen *et al.*[20]	Wistar rats	Group 1: lard (19·5 % lard) Group 2: *n*-3 (9·1 % lard and 10·4 % TriomarTM – EPA and DHA) for 7 weeks	7 weeks	Plasma, adipose tissue, muscle, and liver	↓ Visceral adipose depots (without affecting body weight and body composition) ↓ Plasma lipid concentrations
Samane *et al.*[21]	Wistar rats	Group 1: standard chow diet (controls) Group 2: HFHS diet Group 3: HFHS diet with 6 % of fat replaced by FO Group 4: HFHS diet with 6 % of fat replaced by AO	4 weeks	Plasma, adipose tissue, muscle and liver	FO prevented fat accretion, reduced fasting glycaemia and normalised glycaemic or insulin responses to intraperitoneal glucose tolerance test. FO intake also prevented insulin resistance
Kalupahana *et al.*[22]	C57BL/6J mice	Low-fat (10 % fat), HFD (45 % fat), or HF-EPA (45 % fat; prevention) for 11 weeks. A 4th group was fed HFD for 6 weeks followed by HF-EPA for 5 weeks (reversal)	11 and 5 weeks	Plasma, adipose tissue and liver	EPA both prevented and reversed the HF diet-induced insulin resistance in mice
Cintra *et al.*[23]	Swiss mice and Wistar rats	Mice: 8 weeks of standard chow or HFD, and more 8 of HFD + flax seed oil or olive oil fat substitution diet (both 10, 20 or 30 %). Rats: HFD for 8 weeks and icv injection of albumin, *n*-3, *n*-9 or stearic acid for 1 week	Mice: 8 weeks Rats: 1 week	Blood, adipose tissue, and hypothalamus	↓ Hypothalamic inflammation ↓ Hypothalamic and whole-body insulin resistance ↓ Body adiposity ↓ Expression of hypothalamic apoptotic proteins
Liu *et al.*[24]	C57BL/6J mice	Group 1: 5 % maize oil (control diet) Group 2: HFHF diet Group 3: HFHF diet with 1 % SOY-PL Group 4: HFHF diet with 1 % EPA-PL	4 weeks	Serum and liver	↓ Body fat accumulation ↓ Insulin resistance and serum fasting glucose ↓ Serum TNF-*α* and IL-6 levels ↓ Hepatic steatosis
Ávila *et al.*[25]	Wistar rats	Standard rodent chow (lean group) or HFD (obese group) for 2 months. More 2 months, obese rats grouped: non-supplemented; resveratrol; FO; or resveratrol plus FO	8 weeks	Myocardial and aortic tissues	↑ Survival rate of obese rats catecholaminergic stress ↑ Activity of some antioxidant enzymes ↓ Superoxide production, oxidative damage to lipids and proteins
Pimentel *et al.*[26]	Wistar rats	Group 1: balanced chow Group 2: high-fat diet enriched with soya oil (*n*-6) Group 3: high-fat diet enriched with FO (*n*-3)	8 weeks	Blood, liver, gastrocnemius muscle and hypothalamus	↓ Hypothalamic levels of TNF-*α*, IL-6 and TRAF6 ↑ Levels of IL-10 receptor ↓ TNF-*α* and IL-6 levels in muscle and liver
Rossmeisl *et al.*[27]	C57BL/6 N mice	Group 1: cHF Group 2: cHF with 10 % lipids replaced by *n*-3 (DHA/EPA) Group 3: cHF with rosiglitazone Group 4: cHF with *n*-3 and rosiglitazone Group 5: Chow-fed mice (lean controls)	7 weeks	Plasma, adipose tissue and liver	Weight gain prevention Insulin resistance prevention ↓ Hepatic and plasma cholesterol ↓ Abdominal fat ↓ Plasma TAG ↓ Hepatic steatosis
Bargut *et al.*[28]	C57BL/6 mice	Group 1: SC diet (SC; 10 % energy from fat) Group 2: SC + FO diet (10 % energy from fat), Group 3: HF lard diet (50 % energy from lard) Group 4: HF + FO oil diet (50 % energy from FO)	8 weeks	Blood and epididymal fat pad	↓ Body mass gain and adiposity Improved glucose tolerance and insulin signalling ↓ WAT insulin resistance ↓ WAT inflammation
Philp *et al.*[29]	C57BL/6 mice	Group 1: standard chow Group 2: high saturated fat Group 3: high saturated fat with 7·5 % replaced with FO	14 weeks	Skeletal muscle and plasma	FO may prevent high-saturated-fat-induced dysfunction in fatty acid metabolism pathways in skeletal muscle
Yook *et al.*[30]	C57BL/6J mice	Normal diet or HFD for 8 weeks to induce obesity, plus 8 weeks of oral supplementation: Group 1: normal diet with distilled water Group 2: HFD with distilled water Group 3: HFD with beef tallow Group 4: HFD with maize oil Group 5: HFD with FO Group 6: HFD with MO (also rich in *n*-3)	8 weeks	Blood, liver, and epididymal fat pad	↓ Body weight gain, epididymal fat pad weights, serum TAG and total cholesterol levels. Serum insulin and leptin concentrations were lower in the MO group

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Table 1. *Continued*

References	Animal	Groups/Intervention	Duration*	Tissues evaluated	Main outcomes (main effects of the *n*-3 PUFA)
Abdel-Maksoud *et al.*[31]	Sprague–Dawley rats	Group 1: controls fed normal chow diet Group 2: obese controls fed 60 % saturated fat diet Group 3: *n*-3 fed 60 % saturated fat diet with oral administration of *n*-3 (DHA and EPA), from weeks 12 to 14	2 weeks	Blood and hypothalamus	↓ Serum total cholesterol, TAG, serum glucose level and HOMA index *n*-3 Also reversed negative effect on BDNF gene expression in hypothalamus caused by obesity
Cavaliere *et al.*[32]	Wistar rats	Group 1: control diet Group 2: HFD rich in lard Group 3: HFD rich in FO	6 weeks	Blood and skeletal muscle	↓ Fat mass ↓ Insulin resistance ↑ Lipid oxidation ↓ ROS generation in mitochondria
Viggiano *et al.*[33]	Wistar rats	Group 1: control diet Group 2: HFD rich in lard Group 3: HFD rich in FO	6 weeks	Blood and hypothalamus	↓ Body weight gain ↓ Serum lipid profile ↓ Pro-inflammatory parameters ↓ Insulin resistance
de Sá *et al.*[34]	C57BL/6 mice	4 weeks with the control diet, and 8 more weeks: Control diet, control diet + FO, HF or HF + FO (FO by gavage; three times per week)	12 weeks	Blood and adipose fat depots (inguinal and retroperitoneal)	FO exerted beneficial effects on dyslipidaemia and insulin resistance. FO also could prevent changes in metabolism and secretion of hormones and cytokines in adipocytes induced by HFD
Go *et al.*[35]	C57BL/6 mice	HFD for 4 weeks to induce obesity and additional 9 weeks with oral administration of PBS (control group), MO, FO or maize oil, while taking in a normal diet	9 weeks	Blood and liver	↓ Weight (MO-induced loss was the most significant). MO showed an apparent inhibitory effect on lipid accumulation in the liver
Bargut *et al.*[36]	C57BL/6 mice	Control diet or a HFru for three weeks. After that, the HFru group was subdivided into four new groups for another five weeks: HFru, HFru + EPA, HFru + DHA and HFru-EPA + DHA	5 weeks	Epididymal fat	Treated animals showed reversion of adipocyte hypertrophy, inhibition of inflammation with activation of anti-inflammatory mediators and regularisation of lipolysis. Overall, the beneficial effects were more marked with DHA than with EPA

↓, Decrease. ↑, increase; AO, argan oil; cHF, maize-oil-based high-fat diet; FO, fish oil; HF, high fat; HFD, high-fat diet; HFHF, high-fat/high-fructose; HFHS, high-fat/high-sucrose; Icv, intracerebroventricular; MO, microalgal oil; SC, standard chow; WAT, white adipose tissue; HFru, high-fructose diet.
* The column 'Duration' refers to the time that the *n*-3 PUFA was tested, not the complete experiment.

Table 2. Review of human studies on *n*-3 PUFA for obesity (and related alterations)
(Mean values and standard deviations and 95 % confidence intervals)

References	Sample	Groups/intervention	Duration	Main outcomes (main effects of the *n*-3 PUFA)
DeFina *et al.*[37]	128 sedentary men and women	(1) 5 *n*-3 capsules daily (3 g) EPA + DHA at a 5:1 ratio, 1000 mg EPA and 200 mg DHA per dose) (*n* 64) (2) placebo capsules daily (*n* 64) Both groups received dietary and exercise counselling	6 months	*n*-3 PUFA were not effective as an adjunct for weight loss in this population. No significant differences in weight loss were observed between the *n*-3 PUFA (−5·2 kg; 95 % CI −6·0, −4·4) and placebo (−5·8 kg; 95 % CI −6·7, −5·1) ($P=0·29$)
Itariu *et al.*[38]	55 severely obese non-diabetic patients	(1) 3·36 g *n*-3/d (460 mg EPA and 380 mg DHA; *n* 27) (2) butterfat (control; *n* 28)	2 months	↓ Gene expression of inflammatory genes in adipose tissue ($P<0·05$) ↑ Production of anti-inflammatory eicosanoids in adipose tissue ($P<0·05$) ↓ IL-6 ($P=0·04$) ↓ TAG ($P=0·03$)
Crochemore *et al.*[39]	41 menopausal women with high blood pressure and type 2 diabetes mellitus	A) (2·5 g/d fish oil; 547·5 mg EPA and 352·5 mg DHA; *n* 14) B) (1·5 g/d fish oil; 328·5 mg EPA and 211·5 mg DHA; *n* 14) C) (placebo; control group; *n* 13)	1 month	Group B presented ↓body mass and WC ($P<0·05$) (*v.* Group A)
Kiecolt-Glaser *et al.*[40]	138 healthy middle-aged and older adults, sedentary and overweight	(1) Placebo capsules (*n* 46) (2) 1·25 g/d *n*-3; 1042·5 mg/d of EPA and 174 mg/d of DHA (*n* 46) (3) 2·5 g/d *n*-3; 2085 mg/d of EPA and 348 mg/d of DHA (*n* 46)	4 months	↓ Serum TNF-*α* (group 2 *v.* placebo: −0·11; 95 % CI −0·028, −0·19; $P=0·03$) (group 3 *v.* placebo: −0·13; 95 % CI −0·052, −0·22; $P=0·004$) ↓ Serum IL-6 (group 2 *v.* placebo: −0·41; 95 % CI −0·21, −0·62; $P=0·0003$) (group 3 *v.* placebo: −0·43; 95 % CI −0·22, −0·64; $P=0·0002$)
Kiecolt-Glaser *et al.*[41]	106 healthy sedentary overweight middle-aged and older adults	(1) Placebo capsules (*n* 31) (2) 1·25 g/d *n*-3; 1042·5 mg/d of EPA and 174 mg/d of DHA (*n* 40) (3) 2·5 g/d *n*-3; 2085 mg/d of EPA and 348 mg/d of DHA (*n* 35)	4 months	↓ Oxidative stress (measured by F2-isoprostanes) Low dose *v.* placebo: −0·094; 95 % CI −0·17, −0·014; $P=0·02$. High dose *v.* placebo: −0·086; 95 % CI −0·17, 0·0009; $P=0·04$
Munro & Garg[42]	32 participants with a BMI between 30 and 40 kg/m^2 (male and female)	(1) placebo group (PB): 6 × 1 g capsules/d of monounsaturated oil (2) fish oil group (FO): 6 × 1 g capsules/d of *n*-3 (70 mg EPA and 270 mg DHA) First 4 weeks: both groups were on very-low-energy diet (*n* 14 PB, *n* 18 FO) Last 10 weeks: weight maintenance (*n* 12 PB, *n* 17 FO)	14 weeks	At week 4, the mean weight loss was −6·54 (SD 2·08) kg (−6·9 %) for placebo and −6·87 (SD 1·83) kg (−7·7 %) for fish oil. At week 14, after the maintenance phase, there was a further mean decrease in weight, −1·57 (SD 3·7) kg (1·85 %) for placebo and −1·69 (SD 2·32) kg (−1·9 %) for fish oil. In conclusion, supplementation with *n*-3 PUFA had no significant effect on weight loss or weight maintenance over the 14 weeks
Munro & Garg[43]	35 male and female participants with a BMI between 30 and 40 kg/m^2	(1) Placebo (6 × 1 g capsules/d monounsaturated oil (*n* 18) (2) Fish oil (6 × 1 g capsules/d fish oil; 70 mg EPA and 270 mg DHA) (*n* 17) Both groups followed a low-energy diet for 12 weeks	12 weeks	There was no significant difference between the placebo and the fish oil groups for weight reduction (3·37 and 4·35 %, respectively), fat mass reduction (8·95 and 9·76 % respectively) or changes in inflammatory biomarkers and blood lipids apart from TAG, reduced by 27 % in fish oil group ($P<0·05$)
Munro & Garg[44]	39 obese men and women (BMI 30–40 kg/m^2)	(1) placebo group (PB): 6 × 1 g capsules/d of monounsaturated oil (*n* 19) (2) fish oil group (FO): 6 × 1 g capsules/d of *n*-3 (70 mg EPA and 270 mg DHA) (*n* 20) First 4 weeks: followed their usual diet Last 4 weeks: very-low-energy diet regimen	8 weeks	No significant changes at week 4. At week 8 a significant 3-way interaction between time, group and sex was observed for percentage reduction in weight, $F_{1,35}=5·55$, $P=0·024$, and BMI, $F_{1,35}=5·3$, $P=0·027$ with a greater percentage decrease for females in FO compared with PB for weight (−7·21 *v.* −5·82 %) and BMI (−7·43 % *v.* −5·91 %), respectively ($P<0·05$ for both)
Juárez-López *et al.*[45]	201 obese and insulin-resistant children and adolescents	(1) 500 mg of metformin (*n* 98) (2) 1·8 g/d of *n*-3 (3 capsules/d, each containing 360 mg EPA and 240 mg DHA; *n* 103)	12 weeks	↓ Concentrations of glucose: −3·66 *v.* metformin (95 % CI −6·03, −1·28) $P=0·003$ ↓ TAG: −37·69 *v.* metformin (95 % CI −58·91, −16·46) $P=0·001$
Ellulu *et al.*[46]	64 hypertensive and/or diabetic obese patients	(1) 1 g/d fish oil (300 mg EPA and 200 mg DHA; *n* 31) (2) control group (*n* 33)	8 weeks	*n*-3 PUFA reduced the level of hs-CRP (14·78 (SD 10·7) to 8·49 (SD 6·69) mg/l, $P<0·001$), fasting blood glucose (178·13 (SD 58·54) to 157·32 (SD 59·77) mg/dl (9·89 (SD 3·25) to 8·73 (SD 3·32) mmol/l), $P=0·024$) and TAG (209·23 (SD 108·3) to 167·0 (SD 79·9) mg/dl (2·36 (SD 1·22) to 1·89 (SD 0·90) mmol/l), $P<0·05$). However, *n*-3 PUFA treatment did not reach clinical significance for any of the clinical variables
Wang *et al.*[47]	99 type 2 diabetic patients with abdominal obesity	(1) 4 g/d fish oil (1·34 g EPA and 1·07 g DHA; *n* 49) (2) placebo (maize oil; *n* 50)	6 months	Serum TAG decreased ($P=0·007$), whereas HDL increased ($P=0·006$) in the fish oil group *v.* placebo group

Table 2. *Continued*

References	Sample	Groups/intervention	Duration	Main outcomes (main effects of the *n*-3 PUFA)
Huerta *et al.*[48–50] (OBEPALIP study)	73 Caucasian women with a BMI between 27·5 and 40 kg/m^2	(1) Control (*n* 21) (2) EPA (1·3 g/d) (*n* 16) (3) *α*-lipoic acid (0·3 g/d) (*n* 19) 4) EPA + *α*-lipoic acid (1·3 g/d + 0·3 g/d) (*n* 17) All groups followed an energy-restricted diet	10 weeks	EPA supplementation significantly attenuated ($P<0·001$) the decrease in leptin levels during weight loss[48]. In adipose tissue, EPA-supplemented groups exhibited a down-regulation of ADGRE1 (0·7 ± 0·1-fold compared with 1·0 (SD 0·1)-fold) ($P<0·05$) and an up-regulation of IL-10 (1·8 (SD 0·2)-fold compared with 1·0 (SD 0·2)-fold) ($P<0·05$) gene expression[49]. EPA promoted changes in extracellular matrix remodelling gene expression in adipose tissue[50]
Allaire *et al.*[51,52] and Vors *et al.*[53] (ComparED study)	Healthy men (*n* 48) and women (*n* 106) with abdominal obesity and low-grade systemic inflammation	(1) EPA (2·7 g/d) (2) DHA (2·7 g/d) (3) maize oil as a control (3 g/d)	10 weeks	DHA *v.* EPA led to a greater reduction in IL-18 (−7·0 (SD 2·8) % *v.* −0·5 (SD 3·0) %, respectively; $P=0·01$) and a greater increase in adiponectin (3·1 (SD 1·6) % *v.* −1·2 (SD 1·7) %, respectively; $P<0·001$). DHA *v.* EPA led to more pronounced reductions in TAG (−13·3 (SD 2·3) % *v.* −11·9 (SD 2·2) %, respectively; $P=0·005$) and the cholesterol: HDL-cholesterol ratio (−2·5 (SD 1·3) % *v.* 0·3 (SD 1·1) %, respectively; $P=0·006$) and greater increases in HDL-cholesterol (7·6 (SD 1·4) % *v.* −0·7 (SD 1·1) %, respectively; $P<0·0001$)[51]. The increase in the O3I after supplementation with DHA (+5·6 % *v.* control, $P<0·0001$) was significantly greater than after EPA (+3·3 % *v.* control, $P<0·0001$; DHA *v.* EPA, $P<0·0001$)[52]. EPA and DHA have similar effects on the expression of many inflammation-related genes in immune cells[53]

↓, Decrease. ↑, Increase; ADGRE1, adhesion G protein-coupled receptor E1; CRP, C-reactive protein; hs-CRP, high-sensitivity C-reactive protein; O3I, Omega-3 Index; WC, waist circumference.

dopaminergic system in obese rats[86]. Dysregulation of the dopaminergic system is associated with changes that include addiction and hyperphagia[86]. Regarding humans, a link has been found between the elevation of BMI and low dopaminergic activation in the striatum in obese women[87]. Furthermore, MRI of the brain of young women showed striated hypofunction in those who were prone to weight gain[88].

Obesity treatment

Obesity treatment is extremely important. One should not only seek weight loss but the individual's metabolic health as well. Lifestyle modification (intervention focusing on diet and exercise) constitutes the conventional and first-choice treatment for obesity. The failure of these measures, mainly with regard to the maintenance of the results, has emphasised the need for adjuvant therapeutic resources[89].

Obesity treatment remains a major challenge. Food re-education therapy and exercise often do not achieve satisfactory results. Pharmacological therapy has been shown to be fraught with serious adverse effects, and many drugs have been withdrawn from the market because of unfavourable risk–benefit relationships[89].

In view of increasing obesity rates in the world, as well as the recurrent treatment difficulties currently observed, several studies are required to broaden treatment options. In this context, studies have shown that *n*-3 PUFA have the potential to help treat obesity[16,17,38,90,91].

n-3 PUFA

n-3 Fatty acids (*ω*-3, *n*-3 or *w*-3) are a family of PUFA, which are vital for the functioning of the body, termed essential fatty acids[92,93]. The term '*n*' refers to the position of the first double bond, and *n*-3 PUFA have the first double bond between the third and fourth carbon atoms[94]. The major *n*-3 PUFA are *α*-linolenic acid (ALA) (eighteen carbons, three double bonds), EPA (twenty carbons, five double bonds) and DHA (twenty-two carbons, six double bonds)[93–95].

Lipid components, especially fatty acids, play an important role in the structure of cell membranes and in metabolic processes[94]. Because *n*-3 PUFA cannot be synthesised by the body, they need to be obtained from dietary sources[92,94]. These sources may be foods of plant origin, in the form of ALA, or from some species of fish, in the form of EPA and DHA[13,92,95].

ALA is found in flaxseed, soyabean, chia, rapeseed and walnuts, and it can be metabolised in EPA and DHA via elongase and desaturase enzymes[94,96]. However, humans are inefficient in performing this synthesis from ALA[95,97,98], as these enzymes are influenced by innumerable aspects, such as smoking, alcohol consumption, diabetes, stress and ageing[95,96,98,99]. Sea fish, such as sardines, salmon, tuna, mackerel and herring, are the main sources of EPA and DHA[94,99].

n-3 PUFA are present in cell membranes, particularly in the lipid bilayer of the plasma membrane, and depending on their proportion in the membranes they may undergo changes in fluidity and, therefore, in their functions[93]. DHA, in particular, is one of the most abundant components in the brain's

structural lipids[96,100] and is a key component of neuronal membranes at signal transduction sites, which indicates that its action is vital for brain function[14,100]. The incorporation of EPA and DHA into the diet can influence not only lipid composition and structure of cell membranes but also the physiological responses that depend on these membranes, as is the case with cell signalling mechanisms[101]. There is evidence that inadequate intake of maternal *n*-3 PUFA may lead to abnormal development and function of the CNS[102]. DHA-derived lipid mediators are neuroprotective and ameliorate neurological disorders[102]. There is also evidence that DHA may ameliorate cognitive decline and affect behavioural symptoms in major neuropsychiatric disorders such as dementia, schizophrenia and depression[103].

n-3 PUFA derived from fish oil (EPA and DHA) exerts important effects on the inflammatory pathways, acting as anti-inflammatory agents[12,13,104,105], because of its ability to interact with the major inflammatory signalling pathways, as well as its suppressive effect on the production of cytokines[105,106]. The anti-inflammatory mechanisms of action exerted by EPA and DHA include suppression of NF-κB, reduction of eicosanoid production, as well as alteration of membrane organisation, particularly those related to the functions of Toll-like receptors and T-lymphocyte signalling[104,107]. In addition, the anti-inflammatory properties of EPA and DHA are mediated also through the inhibition of TLR signalling pathways[107].

EPA and DHA exert their anti-inflammatory effects by decreasing the production of pro-inflammatory eicosanoids derived from arachidonic acid, as well as by serving as substrates for production of lipid mediators with pro-resolution properties, such as resolvins, protectins and maresins[107,108]. These specialised pro-resolving lipid mediators have potent immunoregulatory actions as they activate specific mechanisms to promote resolution of inflammation[107,108]. Mediators derived from EPA are known as E series resolvins, and those derived from DHA are named as D series resolvins, whereas protectins and maresins are derived only from DHA[107,108].

Furthermore, other documented *n*-3 PUFA effects include cardiovascular benefits such as reduction of TAG, cardiac arrhythmias, blood pressure and platelet aggregation[107,109,110]. Studies have also shown that an *n*-3 PUFA-enriched diet may be able to inhibit neuroinflammation and delay oxidative stress and cell apoptosis[101,111]. Therefore, considering that inflammation and related changes are strongly linked to many chronic diseases (among them obesity), the ingestion of *n*-3 PUFA (mainly in the form of EPA and DHA) can play a fundamental role in preventing and treating these diseases[17,96,107].

n-3 PUFA and obesity

n-3 PUFA has the potential to induce a number of effects that may be useful for the treatment of obesity as this substance can attenuate weight gain and reduce body fat[15]. Most studies on *n*-3 PUFA and obesity have focused on peripheral tissues, as well as on plasma and serum. *n*-3 PUFA have shown several beneficial effects on obesity-related changes in animals, such as reduced body-fat gain, reduced fat accumulation in visceral region, improved lipid profile, insulin resistance, glucose intolerance and hepatic steatosis, as well as inflammation reduction in peripheral tissues[20,22,24,27,28]. The effect of *n*-3 PUFA in the brain alterations related to obesity was less studied, with hypothalamus being the major focus of the investigation. *n*-3 PUFA showed beneficial effects on modulating inflammation and hypothalamic function in rodents[23,26,33] and was able to reverse the negative effect on the brain-derived neurotrophic factor (BDNF) gene expression caused by obesity in the hypothalamus of rats[31]. A review of animal studies on *n*-3 PUFA for obesity (and related alterations) is summarised in Table 1.

In humans with overweight or obesity, studies have shown that *n*-3 PUFA treatment can modulate adipose tissue, reduce adiposity, improve inflammation (adipose tissue and serum), reduce TAG and reduce oxidative stress in plasma, indicating that *n*-3 PUFA may be beneficial to help treat obesity[38,40,41]. A review of human studies on *n*-3 PUFA for obesity (and related alterations) is summarised in Table 2.

n-3 PUFA, especially EPA and DHA, have been shown to play an important role in the treatment of obesity[107,112,113]. A systematic review with meta-analysis conducted by Bender *et al.*[114] showed evidence that the consumption of fish or encapsulated fish oil (rich in *n*-3 PUFA) is related to slight reductions in body weight and waist circumference. However, the authors of that study concluded that further research is needed to clarify the possible mechanisms by which *n*-3 PUFA can lead to weight reductions[114].

A meta-analysis conducted by Du *et al.*[115] revealed that fish oil had no effect on the reduction of body weight and BMI in overweight or obese individuals. However, waist circumference and hip:waist ratio were significantly reduced in individuals taking fish oil supplementation, especially when combined with life modification intervention. The authors conclude that current evidence does not prove that fish oil intake may decrease body weight in overweight or obese adults, but that these individuals may benefit from reduced abdominal fat. They have also emphasised that the results should be treated with caution and suggested a large-scale investigation over a long period to draw definitive conclusions[115].

A more recent meta-analysis conducted by Zhang *et al.*[116] also showed that a statistically non-significant difference was revealed in weight loss between *n*-3 PUFA and placebo, whereas *n*-3 PUFA might effectively reduce waist circumference and TAG levels in overweight and obese adults. The authors also suggested more studies to explore and clarify this issue[116].

n-3 PUFA, especially EPA and DHA, can modulate adipocyte number by regulating adipocyte proliferation, differentiation and apoptosis. *n*-3 PUFA also regulates pathways related to fat storage and fat mobilisation, decreasing lipid accumulation processes and favouring adipocyte oxidative metabolism by promoting mitochondrial biogenesis and fatty acid oxidation. In addition, *n*-3 PUFA can modulate adipocyte insulin sensitivity and glucose utilisation[108].

Other mechanisms by which EPA and DHA can help to treat obesity are related to the capacity of this substance to inhibit NF-κB activity and TLR-mediated inflammatory signalling[107]. *n*-3 PUFA can also reduce adipose tissue inflammation by regulating the production of pro-inflammatory cytokines, by

decreasing M1 macrophage infiltration and by reducing the formation of *n*-6-derived pro-inflammatory lipid mediators[108]. Fish oil supplementation can inclusively polarise macrophages and microglia towards the anti-inflammatory phenotype[117,118]. Moreover, the treatment with *n*-3 PUFA can increase the production of lipid mediators with pro-resolution properties (resolvins, protectins and maresins) in adipose tissue[119,120] and promote the reduction of adipose tissue and systemic inflammation[38].

Inflammation also links obesity with the development of insulin resistance and hepatic steatosis[107,119]. The adverse metabolic changes associated with insulin resistance occur as a result of inflamed adipose tissue. Thus, EPA and DHA also may improve insulin sensitivity by generating pro-resolving lipid mediators and promoting alternatively activated macrophages[107]. González-Périz *et al.*[119] showed that dietary intake of *n*-3 PUFA, by triggering the formation of *n*-3 PUFA-derived resolvins and protectins, had insulin-sensitising actions in adipose tissue and liver and improved insulin tolerance in obese mice, as well as alleviated hepatic steatosis[119].

Most studies utilise a combination of DHA and EPA as *n*-3 PUFA supplement, which may mask the effects of each individual fatty acid. The individual effect of EPA and DHA must be considered[121]. In a rodent study that compared EPA and DHA supplementation, Bargut *et al.*[36] showed that DHA had the most prominent action in white adipose tissue metabolism, modulating pro- and anti-inflammatory pathways and alleviating adipocyte abnormalities (caused by a high-fructose diet). In human studies comparing supplementation of EPA *v.* DHA, Allaire *et al.*[51] showed that, related to modulation of specific markers of inflammation and blood lipids, DHA is more effective than EPA. However, Vors *et al.*[53] showed that EPA or DHA has similar effects on the expression of many inflammation-related genes in immune cells of men and women at risk for cardiometabolic diseases.

As EPA and DHA can exert different effects, the ratio of EPA:DHA could affect the outcomes. It is observed that there is considerable variability in the ratio of EPA:DHA in the studies, and this should be taken into account. Shang *et al.*[122] investigated diets with different ratios of DHA:EPA (2:1, 1:1 and 1:2) and showed that a lower DHA:EPA ratio seems to be more beneficial for alleviation of high-fat-diet-induced liver damage in mice, and a DHA:EPA ratio of 1:2 mitigated the inflammatory risk factors.

The form of *n*-3 PUFA formulations (as TAG, ethyl ester, free fatty acid or phospholipid) could also affect the bioavailability and actions of *n*-3 PUFA. Tang *et al.*[123] compared the effects ofTAG, ethyl ester, free fatty acid and phospholipid forms of *n*-3 PUFA (DHA) on lipid metabolism in mice (fed high-fat or low-fat diet) and showed that DHA-bound phospholipid showed effective bioactivity in decreasing hepatic and serum total cholesterol, TAG levels and increasing *n*-3 PUFA concentration in liver and brain. Rossmeisl *et al.*[124] showed that, compared with TAG, *n*-3 PUFA (DHA and EPA) administered as phospholipids are superior in preserving a healthy metabolic profile under obesogenic conditions, possibly reflecting better bioavailability and improved modulation of the endocannabinoid system activity in white adipose tissue.

Another important topic that should be mentioned is the ratio *n*-6/*n*-3 PUFA. As vegetable oils (soyabean, corn, sunflower, safflower and cottonseed oils), which are rich in *n*-6 PUFA, became popularised, there was a significant increase in *n*-6 PUFA intake[121]. Western diets contain excessive levels of *n*-6 PUFA and very low levels of *n*-3 PUFA, leading to an unhealthy *n*-6/*n*-3 ratio of 20:1, instead of 1:1 during evolution[125]. A high *n*-6 intake and a high *n*-6:*n*-3 ratio is pro-thrombotic, pro-inflammatory and are associated with weight gain in both animal and human studies, whereas a high *n*-3 PUFA intake decreases the risk for weight gain[125]. Therefore, a balanced *n*-6:*n*-3 ratio is also important for the prevention and management of obesity (it is essential to decrease the *n*-6 PUFA in the diet while increasing the *n*-3 PUFA)[125].

Conclusion

In conclusion, *n*-3 PUFA has shown a large number of effects that could be beneficial to treat obesity and related alterations. Animal and human studies have shown that in peripheral tissues (and in the blood) *n*-3 PUFA can reduce body and visceral fat, inflammation, hepatic steatosis and oxidative stress, as well as improve insulin sensitivity and lipid profile. In the brain, animal studies have shown that *n*-3 PUFA can reduce hypothalamic inflammation and apoptosis, improving hypothalamic function, and that it was able to reverse the negative effect on the BDNF caused by obesity in the hypothalamus. The effect of *n*-3 PUFA on body weight has shown contradictory results.

Therefore, the use of *n*-3 PUFA to help obesity treatment still needs further investigation, given that there are still many gaps on its effects, especially to clarify the mechanisms by which *n*-3 PUFA could help treat the disease. Most studies have focused on peripheral tissues, but brain aspects have been poorly explored. The focus has been only on the hypothalamus, and thus the effect of the *n*-3 PUFA on other brain structures has not been explored in animal models of obesity.

In addition, there were many differences in the methods of the studies, both with animals and with humans, which limit the comparison of the data and generalisation of the results. In general, it seems to us that the beneficial effect of *n*-3 PUFA would not be directly on weight, but on metabolic changes related to obesity.

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