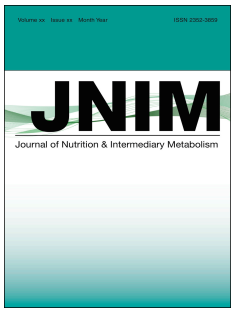
Accepted Manuscript



The role of omega-3 polyunsaturated fatty acid supplementation in the management of type 2 diabetes mellitus: A narrative review

C. Itsiopoulos, W. Marx, H.L. Mayr, O.A. Tatucu-Babet, S.R. Dash, E.S. George, G.L. Trakman, J.T. Kelly, C.J. Thomas, L. Brazionis

PII: S2352-3859(17)30274-8

DOI: 10.1016/j.jnim.2018.02.002

Reference: JNIM 60

To appear in: *Journal of Nutrition & Intermediary Metabolism*

Received Date: 13 November 2017

Revised Date: 23 February 2018

Accepted Date: 27 February 2018

Please cite this article as: Itsiopoulos C, Marx W, Mayr HL, Tatucu-Babet OA, Dash SR, George ES, Trakman GL, Kelly JT, Thomas CJ, Brazionis L, The role of omega-3 polyunsaturated fatty acid supplementation in the management of type 2 diabetes mellitus: A narrative review, *Journal of Nutrition & Intermediary Metabolism* (2018), doi: 10.1016/j.jnim.2018.02.002.

The Role of Omega-3 Polyunsaturated Fatty Acid Supplementation in the Management of Type 2 Diabetes Mellitus: a narrative review

Itsiopoulos C[1α]*, Marx W[1]*, Mayr HL[1], Tatucu-Babet OA[1], Dash SR[2], George ES[1,3], Trakman GL[1], Kelly JT[4], Thomas CJ[5], Brazionis L[6,7].

1. Department of Rehabilitation, Nutrition and, Sport, School of Allied Health, College of Science, Health and Engineering, La Trobe University, Bundoora, Victoria, Australia
2. Food and Mood Centre, IMPACT SRC Deakin University, Geelong, Victoria, Australia
3. School of Exercise and Nutrition Sciences, Deakin University, Geelong, Victoria, Australia
4. Faculty of Health Sciences and Medicine, Bond University, Gold Coast, Queensland, Australia
5. Department of Physiology, Anatomy and Microbiology, School of Life Sciences, College of Science, Health and Engineering, La Trobe University, Bundoora, Victoria Australia.
6. Department of Medicine, The University of Melbourne, Melbourne, Victoria, Australia
7. CRE in Diabetic Retinopathy, NHMRC Clinical Trials Centre, University of Sydney, Camperdown, Sydney, Australia

*Joint first author

[α]corresponding author:

Email: C.Itsiopoulos@latrobe.edu.au

Mailing address: Health Sciences Building 1, La Trobe University, Bundoora, Victoria, 3086

Abstract

Background: Type 2 Diabetes Mellitus (T2DM) poses a significant health and financial burden to individuals and healthcare systems. Omega-3 polyunsaturated fatty acids (PUFA) possess numerous properties (e.g. anti-inflammatory, anti-thrombotic, anti-lipidemic) that may be beneficial in the management of T2DM and its complications.

Methods: In this narrative review, we discuss the potential mechanisms, clinical evidence-base, and practical considerations regarding the use of omega-3 PUFA supplementation for the management of glycaemic control and common comorbid conditions, including diabetic nephropathy and retinopathy, liver disease, cognition and mental health, and cardiometabolic disease.

Results/Conclusion: Omega-3 PUFA supplementation is generally well-tolerated and does not appear to be contraindicated for patients on anticoagulant therapy; however, uncertainty persists regarding the purity and stability of commercial omega-3 PUFA products. Despite promising animal studies, the current clinical evidence for the use of omega-3 supplementation for the management of T2DM and associated conditions is both limited and conflicting. Results from existing clinical trials do not support the use of omega-3 PUFA for glycaemic control and there are limited studies in T2DM populations to support the use of omega-3 PUFAs for associated complications of diabetes. Possible contributors to the conflicting evidence base are study design issues, such as inadequate intervention period, sample size, omega 3 supplement dose, variations in the EPA to DHA ratio and clinical heterogeneity among diabetic populations.

Keywords: omega-3; diabetes; diabetes complications; nutrient supplementation; review;

Abbreviations:

PUFA: Polyunsaturated Fatty Acid

HDL: High Density Lipoprotein

LDL: Low Density Lipoprotein

ALA: Alpha-linolenic Acid

EPA: Eicosapentaenoic Acid

DHA: Docosahexaenoic acid

DPA: Docosapentaenoic acid T2DM: Type 2 Diabetes Mellitus

RCT: Randomized Controlled Trial

HbA1c: Glycated haemoglobin VLDL: Very Low-Density Lipoprotein

CVD: Cardiovascular Disease

TG: Triglycerides

ALT: Alanine transaminase

AST: Aspartate transaminase

GGT: Gamma-glutamyltransferase

CKD: Chronic Kidney Disease

UPE: Urine Protein Excretion

Introduction

Type 2 diabetes mellitus (T2DM) is a highly inflammatory and pro-oxidant condition often resulting in comorbidities that affect multiple body systems including large vessel diseases such as cardiovascular disease, small vessel diseases such as retinopathy, nephropathy, non-alcoholic fatty liver disease, and conditions that affect cognitive performance and mental health [1-3].

Despite public health efforts to curb this pervasive chronic disease, it is currently estimated that over 414 million people worldwide have T2DM and, by 2040, this number is projected to rise to over 640 million [4]. T2DM has a high burden of disease; the direct healthcare costs relating to T2DM in Australia are estimated at $1.7 billion per annum and indirect costs, including reduced productivity, absence from work and early retirement, are estimated at $14 billion per annum [5].

Consistent evidence from prospective cohort studies and large primary prevention trials have demonstrated the protective benefits of dietary patterns such as the Mediterranean diet, rich in anti-inflammatory and antioxidant nutrients such as omega-3 fatty acids, in prevention of T2DM and its complications [6-9].

Omega-3 polyunsaturated fatty acids (PUFA) include eicosapentanoic acid (EPA, 20:5n-3) and docosahexanoic acid (DHA, 22:6n-3), derived primarily from fish and seafood, and alpha-linoleic acid (ALA, 18:3n-3), from plant sources, such as leafy greens, seeds, particularly flaxseed/linseed, and nuts, primarily walnuts [10]. Long chain omega-3-PUFA modulate inflammatory pathways by competing with the enzymatic metabolism of omega-6 PUFA (arachidonic acid), which is converted to pro-inflammatory eicosanoids such as prostaglandins, thromboxane, and leukotrienes [11]. EPA is metabolised to the prostaglandins (PGE3), thromboxanes (TXA3), and leukotrienes (LTB5), which exert anti-inflammatory and anti-coagulant effects [11]. In addition to anti-inflammatory properties, omega-3 PUFAs possess several other potentially beneficial properties, including anti-lipidemic, anti-hypertensive, and anti-coagulant actions, and they have recently been demonstrated to modulate gastrointestinal microbiota [12]. Furthermore, in animal studies, supplementation with omega-3 PUFA improved insulin sensitisation, potentially via increased levels of adiponectin, an emerging protective risk factor, and reduced inflammation [13, 14].

The aim of this narrative review is to evaluate the efficacy of omega-3 PUFA supplementation in the control of T2DM as well as the amelioration of diabetic comorbidities

such as diabetic retinopathy and nephropathy, cardiovascular disease, cognitive and mental health issues, and liver disease. Furthermore, practical considerations regarding omega-3 PUFA supplementation including adherence, symptoms, and potential adverse effects will be discussed.

Relevant studies were primarily retrieved from PubMed and Google Scholar search engines using search terms related to each section of the review (e.g. diabetes, nephropathy) and omega-3 PUFA (e.g. omega 3, EPA, DHA). A snowball strategy was also used to retrieve relevant studies from the reference lists of included studies. Due to the varied evidence-base for each condition discussed in this review, all study designs were eligible for inclusion (e.g. clinical trials, observational, animal studies); however, when extensive evidence was available, RCTs were prioritised. Finally, due to EPA and DHA, derived from fish oil, being the predominant long chain omega-3 PUFAs within the literature, all reference to omega-3 PUFA within this manuscript refers to fish oil-sourced EPA and DHA unless otherwise stated.

Omega-3 PUFA Supplementation and Glycaemic Control

Optimal glycaemic control is the cornerstone of diabetes management. Based on the findings of early epidemiological work suggesting an inverse relationship between fish intake and glucose intolerance [15], omega-3 PUFA supplementation was postulated to improve glycaemic control. Although the mechanisms involved are still unclear [16], animal models have revealed the following potential mechanisms: improved hepatic insulin sensitivity [17] via hepatic fatty acid oxidation and reducing lipogenesis [18, 19], increased production of adipocytokines such as adiponectin and leptin [20], direct[13] and indirect[21] anti-inflammatory effects and associated improvements in insulin sensitivity in the liver, muscle and adipose tissue, and modulation of incretin hormones, which are involved in glucose-stimulated insulin secretion [22].

Despite the promising findings from animal studies, early human trials reported that omega-3 PUFA supplementation was associated with deteriorated glycaemic control in T2DM patients [23, 24]. A recent meta-analysis of twenty RCTs with a total of 1209 T2DM patients reported that there were no significant differences in markers of glycaemic control, including fasting blood glucose (19 of 20 studies included), postprandial plasma glucose (3 of 20 studies included), fasting insulin (17 of 20 studies included) and HbA1c (10 of 20 studies included) with omega-3 PUFA supplementation (0.52 to 3.89 g/day EPA and up to 3.69 g/day of DHA, duration ranged 2-48 weeks) in comparison to control groups [25]. Subgroup analysis

identified that duration of intervention (>8 weeks, ≤8 weeks), dose of EPA (<1.8 g/day, ≥1.8 g/day), dose of DHA (≤1.0 g/day, >1.0 g/day) and the ratio of EPA/DHA (EPA/DHA<1.4, 1.4≤EPA/DHA≤1.5, EPA/DHA>1.5) were not associated with statistically significant differences in glycaemic control [25]. Conversely, fasting blood glucose was mildly increased in Asian (weighted mean difference: 0.419 mmol/L, 95% CI: 0.058 to 0.781 mmol/L, *p*=0.023) versus US/European populations [25]. However, a recent review exploring the impact of PUFA intake (interventions included fish oil, nut oil, *Portulaca oleracea* L. seed and a fish-based diet) on glycaemic control in T2DM populations , concluded that PUFA supplementation of 0.42-5.2 g/day for at least 8 weeks may benefit glycaemic control, particularly in Asian populations [26]. Geographical disparities in the effects of omega-3 PUFA supplementation have been previously reported, which may be explained in part by genetic and/or lifestyle differences [27].

The findings of Chen and colleagues[25] are comparable to an earlier Cochrane review of 23 randomised controlled trials with a total of 1075 T2DM patients [28]. The dose of omega-3 PUFAs in the included studies ranged from 1.08 to 5.2 g/day EPA and 0.3 to 4.8 g/day DHA, with a mean total omega-3 PUFA dose of 3.5 g/d over a 2 week to 8-month duration. Omega-3 PUFA supplementation did not significantly alter HbA1c (15 of 23 studies included), fasting glucose (16 of 23 studies included) and fasting insulin levels (6 of 23 studies included). Dietary intake of omega-3 PUFAs was not controlled for in the meta-analyses and measures of insulin resistance were not included. The heterogeneous nature of diabetic populations and variation in trial durations further hinders the interpretation of findings. In addition, the discussed meta-analyses reported on fasting insulin but the included studies did not use gold standard measures of insulin sensitivity such as the hyperinsulinemic-euglycemic clamp technique.

The effects of omega-3 PUFA supplementation on insulin sensitivity in people with T2DM have also been summarised in a recent review (EPA/DHA dose not specified in the review, duration ranged 2 weeks – 6 months) [27]. The majority of RCTs discussed in the paper reported no change in insulin sensitivity with omega-3 PUFA supplementation [27]. The remaining studies reported inconsistent results, with omega-3 PUFA supplementation found to both decrease [29] and improve [30] insulin sensitivity. The method used to measure insulin sensitivity varied amongst studies and further clarification regarding the effects of omega-3 PUFA supplementation on measures of insulin sensitivity are required [27].

The effects of only docosapentaenoic acid (DPA, 22:5n-3), an omega-3 PUFA found in red meat and some seafood, has not been studied as extensively as combined DHA and EPA due to lower levels of DPA in fish oil and a previous lack of concentrated DPA products [31]. Recently, DPA supplementation was shown to be effective in reducing blood glucose levels and improving homeostasis model assessment of insulin resistance (HOMA-IR) in a rodent model [32]. No human trials to our knowledge have investigated the effects of pure DPA supplementation on the management of T2DM and associated comorbidities, representing a gap in current knowledge.

Based on the available evidence in human trials, omega-3 PUFA supplementation to date appears to have a negligible effect on insulin sensitivity and markers of glycaemic control including fasting glucose, HbA1c, fasting insulin[28, 33] and postprandial plasma glucose . Further research is required to ascertain the effects of omega-3 PUFA supplementation on glycaemic control in select ethnic groups and using newer formulations.

Cardiovascular Disease

Cardiovascular disease (CVD) is the most common cause of morbidity and mortality in people with T2DM [35]. In Australia, 65% of all CVD deaths occur in people with T2DM or pre-diabetes [36]. Cardiovascular risk factors such as obesity, hypertension, dyslipidaemia, chronic low grade inflammation and oxidative stress are common in patients with T2DM [35, 37]. Insulin resistance also has a direct biological effect on the vascular system, including micro- or macro-angiopathy, reduced blood flow, peripheral arterial dysfunction, as well as cardiomyocyte and endothelial cell dysfunction [38]. Together, the high prevalence of cardiovascular risk factors and the direct vascular complications in diabetes increase the risk of coronary artery blockage, chronic heart failure and stroke [37, 38]. It is therefore important to consider whether evidence supports a beneficial effect of omega-3 PUFA supplementation on CVD risk factors and clinical end-points in the context of T2DM.

The most commonly analysed CVD risk factors regarding the effect of omega-3 PUFA are plasma lipid levels. Three meta-analyses have investigated lipid outcomes in studies of T2DM. The most recent of these studies included 20 RCTs which tested EPA (0.52-3.89g) and DHA (0.48-3.69g) over 2-48 weeks duration [25]. The second meta-analysis included 23 trials which tested EPA (1.08-5.2g) and DHA (0.3-4.8g) over 2-8 months duration [28]. The final meta-analysis included 18 RCTs which tested EPA (1.08-5.2g) and DHA (0.3-4.8g) over 3-24 weeks duration [33]. Each meta-analysis reported a significant mean reduction in

triglycerides levels ranging from -0.24 mmol/L to -0.56 mmol/L compared to control groups [39-41]. The pooled effect of omega-3 PUFAs on low-density lipoprotein (LDL) and high-density lipoprotein (HDL) cholesterol levels was reported in two of these meta-analyses [40, 41]. Both demonstrated a significant mean increase in LDL cholesterol, of 0.21 mmol/L and 0.11 mmol/L, respectively, but had no effect on HDL levels. One meta-analysis did, however, demonstrate a small but significant mean reduction in very low-density lipoprotein (VLDL) levels of 0.07 mmol/L compared to control [41]. Interestingly, subgroup analyses in these latter two meta-analyses highlighted different effects of omega-3 PUFA supplementation when isolated to T2DM patients with hypertriglyceridemia. In one study, the triglyceride-lowering effect and the elevation in LDL cholesterol were most marked in trials that recruited hyper-triglyceridemic subjects [40]. In the other study, in hyper-triglyceridemic patients alone, the increase in LDL was no longer significant but the significant reduction in VLDL was seen in these patients [41].

Whether omega-3 PUFAs can improve haemodynamic factors in diabetes is important to consider as 60% of patients with T2DM have high blood pressure [42]. A meta-analysis of five trials in T2DM found that omega-3 supplementation (1.8-4g EPA,1.2-4g DHA, duration ranged 4-6 weeks) compared to placebo significantly reduced diastolic blood pressure by a mean of 1.8 mmHg [43]; however, there was a non-significant reduction in systolic blood pressure and heart rate (assessed in two trials). A more recent trial in women with T2DM demonstrated a significant mean reduction in both systolic (-5.4 mmHg) and diastolic (-1.2mmHg) blood pressure with omega-3 PUFA supplementation (360mg EPA, 240mg DHA) when compared to placebo after 8 weeks [44]. It has been proposed that the antagonist effects of omega-3 PUFA on angiotensin II receptors are responsible for its beneficial effect on elevated blood pressure [45].

Due to their effect on satiety, fat oxidation, and adipogenesis, omega-3 PUFAs have also been investigated for their effect on weight management [46]. However, a meta-analysis (previously described with regards to lipids) reported omega-3 PUFA interventions had no significant effect on body weight (9 trials pooled) or BMI (4 trials pooled) when compared with control groups in patients with T2DM [39]. These results did not differ when subgroups for EPA/DHA dosage or study duration were analysed. One included study, conducted in women only, reported that omega-3 PUFA (1.08 g EPA, 0.72g DHA) supplementation had no effect on body weight but significantly reduced total fat mass and subcutaneous adipocyte diameter compared to placebo after 2-months [47].

One of the clear pathophysiological links between T2DM and the development of CVD is the defective production of nitric oxide and concomitant rise in oxidative stress [48]. However, studies investigating omega-3 PUFA interventions and markers of oxidative stress in humans are sparse [49]. One study has specifically investigated the effect of omega-3 PUFAs (1.8 g EPA, 1.5 g DHA) on redox balance in T2DM *in vivo* [50]. After 8-weeks, omega-3 PUFA supplementation reduced 8-isoprostane and superoxide levels in platelets from patients with T2DM and hypertension, but not in patients with hypertension alone, without effect on nitrite production.

Other risk factors which have been investigated in omega-3 PUFA interventions of T2DM are markers of vascular function. A meta-analysis of 10 trials, conducted in both humans and animals, concluded that omega-3 PUFA supplementation significantly improved arterial stiffness, and this effect was despite no significant changes in blood pressure [51]. The authors proposed that reduced arterial stiffness related to changes in functional mechanisms such as changes in aortic blood pressure and wave reflections, which are distinct from brachial blood pressure. Two of the reviewed trials were specifically conducted in patients with T2DM. One study found that purified EPA (1.8 g) improved pulse wave velocity in large elastic (carotid) arteries after 2-years[52] and the other demonstrated improved arterial compliance, but no effect on stroke volume or systemic vascular resistance with 6-weeks fish oil supplementation (1.8 g EPA, 1.2 g DHA) [53]. Endothelial dysfunction is recognised as a major mediator of vascular disease associated with diabetes [54]. A recent paper reviewed the ability of omega-3 PUFAs to improve endothelial dysfunction in individuals with classic risk factors for atherosclerosis [55]. They concluded that omega-3 PUFAs improved endothelial dysfunction (as measured using flow mediated dilation, forearm blood flow, or peripheral arterial tonometry) in 16 of 17 trials in individuals with hyperlipidaemia, metabolic syndrome, elevated BMI, or that smoked, but only in 2 of 5 studies of patients with T2DM. The 5 studies in T2DM patients each tested effects of EPA and DHA (total 1-4g), except one which tested EPA (3.8g) versus DHA (3.7g), and their duration ranged between 4 to 12 weeks.

The evidence for prevention of clinical CVD with omega-3 supplementation has recently been summarised in a review from the American Heart Association (AHA) [56]. The review was limited to RCTs of supplementation with major clinical CVD end-points. Their review located only one RCT that was designed to test the effects of omega-3 PUFA supplements on CVD end-points in patients with T2DM: the ORIGIN (Outcome Reduction With Initial Glargine Intervention) trial[57] which randomly assigned patients who were at high risk for

cardiovascular events and had pre-diabetes or T2DM to receive 1 g of ethyl esters of omega-3 (465mg EPA, 375mg DHA) PUFAs (n=6281) or placebo (n=6255) daily and to receive either insulin glargine or standard care. After 6-years follow up they found no difference in incidence of CVD deaths or major vascular events between the omega-3 PUFA supplementation and placebo groups. There is currently an ongoing RCT in the United Kingdom, ASCEND (A Study of Cardiovascular Events in Diabetes), that seeks to examine the effects of omega-3 PUFA supplements (1g ethyl esters, 0.41g EPA, 0.34g DHA daily) on cardiovascular events among patients with T2DM that are free of prior clinical CVD [58].

Other RCTs investigating the effect of omega-3 PUFA supplementation on CVD end-points have performed sub-group analyses in patients with T2DM. One study found that in recent myocardial infarction (MI) patients with T2DM there was no difference in sudden cardiac death within 3-weeks of hospital stay between groups randomised to omega-3 PUFA (460mg EPA, 380mg DHA) or placebo [59]. Conversely, in Japanese subjects with hypercholesterolemia and impaired glucose metabolism supplementation with highly purified EPA (300 mg) significantly reduced coronary artery disease incidence by 22% at 4.6 years follow-up [60]. Another study, in a sub-group of patients post- MI with T2DM, found that combined EPA (223mg), DHA (149mg) and ALA (1.9g) supplementation resulted in lower incidence of combined ventricular arrhythmia-related events and fatal MI compared to placebo after 4-years [61].

Despite the substantial body of evidence that has investigated omega-3 PUFA supplementation on CVD risk factors within T2DM populations, the effect of omega-3 PUFAs on clinical CVD endpoints (e.g. mortality, CVD events) is currently unclear. Omega 3 PUFA supplementation is therefore not recommended by the AHA for the prevention of CVD in patients with T2DM [56]. However, for the secondary prevention of CVD in the general population, the AHA considers omega-3 PUFA supplementation reasonable [56]. In Australia, The National Heart Foundation recommend combined EPA and DHA 1g/day through 2-3 serves of oily fish per week, supplements or enriched food/drinks, and ALA >2g per day through foods for secondary prevention of CVD [62].

Non-alcoholic Fatty Liver Disease

Non-alcoholic fatty liver disease (NAFLD) is the most common liver disease globally, affecting approximately 30% of the population [63]. NAFLD is a progressive disease that encompasses a spectrum of conditions ranging from simple steatosis, non-alcoholic

steatohepatitis (NASH) and finally cirrhosis [64]. As the condition progresses, there is an increase in hepatic steatosis, fibrosis, and inflammation. NAFLD is frequently referred to as the hepatic manifestation of the metabolic syndrome and pre-diabetes, as they often coexist with several other cardio-metabolic risk factors [65]. The pathophysiological mechanism which underpins NAFLD is insulin resistance and it is therefore, strongly associated with the onset and presence of T2DM [65]. Increased concentrations of blood glucose specifically stimulate hepatic lipogenesis, promoting liver lipid accumulation leading to higher incidence of NAFLD [66]. Thus, NAFLD is present in 70-90% of patients with T2DM and has been recognised as an independent risk factor for cardiovascular disease in this patient group [64, 67, 68]. In addition, NAFLD is an independent risk factor for the development of T2DM[69] and T2DM increases the risk of NAFLD patients further developing cirrhosis or hepatocellular carcinoma [70].

Omega-3 PUFAs lower hepatic lipids and attenuate inflammation [71, 72]. These beneficial effects are mediated through the regulation of hepatic lipid metabolism, adipose tissue function and through interfering with the arachidonic acid pathway of inflammation, reducing hepatic triglyceride (TG) accumulation [73]. Within hepatocytes, omega-3 PUFAs downregulate gene expression of several genes involved in lipogenesis by inhibiting SREBP-1c and upregulate lipid oxidation by activating PPARα which facilitates fatty acid transfer into the mitochondria [74, 75]. EPA and DHA have been shown to regulate a number of transcription factors that control critical components of hepatic fatty acid metabolism [76, 77]. This includes attenuating the expression of transcripts linked to fibrosis such as collagen subtypes, extracellular matrix remodelling, tissue inhibitors of metalloproteases, matrix metalloproteases, and lysyl oxidases [72].

The effect of omega-3 PUFA treatment in NAFLD has recently been summarised in four meta-analyses of RCT's [78-81]. These meta-analyses assessed between three and nine clinical trials each with up to 591 patients. The median dose of omega-3 PUFA ranged from 0.83 to 9.0 g/day and the treatment duration ranged from 2 to 18 months. The distribution of EPA and DHA was variable, with EPA ranging from 35-60%, DHA from 23.9-250% and three studies did not specify composition of EPA and DHA. The results indicated that omega-3 PUFA treatment may improve markers of hepatic damage, most of these parameters measured were plasma markers of liver function (e.g. ALT, AST and/or GGT). For ultrasound-proven assessment of liver fat, a meta-analysis that included five studies was conducted. There was significant heterogeneity observed between studies. Results indicated a

significant pooled omega-3 PUFA therapy was effective for liver fat (OR = 3.60, 95% CI: 1.31 to 9.89, ?? = 0.01) [79]. It is of note, however, that limited NASH specific markers were assessed and thus, improvement in liver integrity can only be inferred.

Only one small (N=37), albeit double-blind randomized placebo-controlled clinical trial was identified by these reviews that was conducted in NAFLD participants specifically with T2DM. This study reported no improvement in measures of NASH histology with the treatment of omega-3 PUFA supplementation (2.16g EPA, 1.44g DHA) compared to placebo [82].

The existing clinical research that has investigated the effect of omega-3 PUFAs in patients with NAFLD and T2DM is limited by variability in omega-3 PUFA dosage and differing EPA to DHA ratios. Due to the range of dosages used in the current body of literature, the relative superiority of either EPA and/or DHA to improve health outcomes in patients with NAFLD is unclear. Furthermore, in participants with NAFLD, it is also important to quantify the effect of omega-3 PUFA supplementation on hepatic steatosis and/or fibrosis to determine the direct impact on liver specific outcomes.

Diabetic Nephropathy and Kidney-related Complications

Diabetic nephropathy is a common consequence of both diabetes and chronic kidney disease (CKD). Diet is an important modifiable risk factor in CKD[83] and diabetic nephropathy [84]. While renal guidelines have many isolated nutrient targets, dietary fat targets are not common features in renal best practice guidelines [85, 86]. This comes despite the fact that dietary fat intake is approximately 40% of total energy intake in renal populations, with the majority of that being from saturated fat [87-90]. The issue with this being that a diet high in saturated fat was shown to be associated with higher incidence of albuminuria,[91] which is a common complication of diabetic nephropathy and important risk factor for kidney disease progression.

Dietary omega-3 PUFAs have gained an interest in CKD for their anti-inflammatory properties, and potentially beneficial effects on blood pressure, endothelial function, and proteinurea [92, 93]. In the general population (free from CKD), omega-3 PUFA intake (0·31–4·18g daily) has been shown to correlate with lower incidence of CKD [94]. For people with T2DM, the European Prospective Investigation of Cancer (EPIC) study showed that consuming at least two servings of fish per week lowered their risk of macroalbuminuria [95]. Interestingly, this association was independent of omega-3 PUFA content of the fish

consumed, where higher intake of fish both high and low in omega-3 PUFAs was inversely associated with macroalbuminuria [95]. However, this study did not quantify omega-3 PUFAs in their analysis, making conclusions on omega-3 PUFAs less reliable. In the CKD population specifically, a 12-week intervention study showed omega-3 PUFA supplementation (3.6 g daily) to reduce triglyceride levels, retard CKD progression, and having the capacity to reduce inflammation and oxidative stress [96].

Studies in diabetic nephropathy specifically are limited. Early rodent models suggest a higher omega-3 PUFAs intake, particularly omega-3 PUFAs (from fish oil), to reduce albuminuria in diabetic nephropathy[93] In human trials, however, the effects are far from conclusive, likely owing to the short durations and small sample sizes of current studies [97]. An early study in patients with T2DM did not find any benefit for 12 month omega-3 PUFA (4.6g/day) supplementation and albuminuria, kidney function, blood pressure, and dyslipidaemia [98]. Another similar trial supports this finding, however, when the analysis was restricted to people with diabetes who were taking renin–angiotensin system blocking medication, albuminuria was significantly lower in the omega-3 PUFA intervention arm (4g/day; duration 6 weeks) compared to the placebo [99].

Notwithstanding the inconsistencies in the evidence to date, a multitude of studies have shown reductions in proteinuria/albuminuria following omega-3 PUFA (0.85g EPA,0.58g DHA per day; duration 4 years) supplementations in CKD complications [100, 101]. For example, meta-analysis of trials in patients with diabetic nephropathy, lupus, or IgA nephropathy have suggested a greater reduction in urine protein excretion (UPE) after omega-3 PUFA supplementation (dose range for EPA and/or DHA: 0.7 to 5.1g/day; median follow-up 9 months) [102]. These conclusions became less reliable, however, when the analysis was restricted to studies involving only participants with diabetes, who showed no significant reduction in UPE [103].

Currently, omega-3 PUFA supplementation should not be advocated for preventing kidney complications in diabetic nephropathy [93]. The existing literature is limited by insufficient study power, clinical heterogeneity among diabetic and CKD populations, and comparing microalbuminuria with macroalbuminuria. Well designed and adequately powered effectiveness trials are needed to confirm the hypothesis that omega-3 PUFA supplementations is an effective strategy to combat kidney complications in diabetic nephropathy.

Diabetic Retinopathy

Diabetic retinopathy is the most common microvascular and ocular complication of diabetes and is a leading and increasing cause of preventable vision loss and blindness in the working-age population [(104)]. A growing body of evidence suggests omega-3 long-chain polyunsaturated fatty acids may have a role not only in retinal health, but also in some retinal diseases [(105)], including diabetic retinopathy.

In the earliest animal study, the adverse effects of omega-3 PUFAs in rats with diabetes induced by streptozotocin, a compound toxic to pancreatic beta cells, were observed, including increased formation of occluded retinal capillaries and no reduction in pericyte loss [(106)]. By contrast, another study reported that increasing levels of omega-3 PUFAs or their bioactive metabolites reduced pathological angiogenesis (i.e. proliferative diabetic retinopathy) in mice with diabetes [(107)]. Since Western diets often contain sub-optimal levels of omega-3 PUFAs, supplementation was flagged as potentially beneficial in preventing diabetic retinopathy [(107)]. A subsequent study found a diet balanced in long-chain PUFAs modified retinal lipid membranes in diabetic rats and prevented rod photoreceptor dysfunction [(108)]. Soon after, 5-Lipoxygenase metabolite 4-HDHA was identified as the mediator of the anti-angiogenic effect of omega-3 PUFA in a mouse model of proliferative diabetic retinopathy [(109)]. The same research group expanded their animal proliferative diabetic retinopathy research to include retinal function in a mouse model of T2DM and reported beneficial effects of dietary omega-3 PUFAs and adverse effects of omega-6 PUFAs on visual function in T2DM. These results suggest dyslipidaemia in diabetes may negatively impact vision [(110)]. Diabetic rats supplemented with a range of nutrients, including omega-3 PUFAs, for 4 months prevented increased cell apoptosis in capillaries and other vascular pathology, and attenuated diabetes-induced features of diabetic retinopathy [(111)].

Although omega-3 PUFAs have a beneficial effect in animal models of diabetic retinopathy, the clinical relevance of omega-3 PUFAs in human retinopathies is unclear, possibly due to the paucity of human studies in this area. Another reason for uncertainty may be that circulating lipid levels need to be interpreted carefully since they may be dependent on fasting status and medication use, particularly statins, independent of retinal disease or diabetes status [(112)]. The first review of effects of omega-3 fatty acids on eye health in humans noted that, in a poorly-reported small study of 48 individuals with diabetes supplemented with 4g omega-3 fatty acids for 3 months, small improvements in some ill-defined proxy

outcomes for diabetic retinopathy, such as functioning retinal capillaries within 1 mm of the 'field of vision', were observed [113].

In contrast, in a well-conducted prospective observational study in Spain [114], older patients with T2DM who consumed a background Mediterranean diet and had a dietary omega-3 PUFA intake equivalent to at least two weekly servings of oily fish had a significantly lower risk of sight-threatening diabetic retinopathy than those who ate less than the recommended amount. To determine the effect of baseline intake of different fats on the risk of 3,614 people, ages 55–80, with T2DM were enrolled in the Prevencion con Dieta Mediterranea (PREDIMED) study, which compared Mediterranean diets supplemented with either extra-virgin olive oil or nuts with a low-fat control diet. According to completed food questionnaires, 75% of participants adhered to the recommendation of at least 500mg per day of omega-3 PUFAs i.e. two servings of fatty fish weekly. At six-year follow-up, those with adequate omega-3 PUFA intake at baseline had a 48% lower risk of developing diabetic retinopathy compared to those with inadequate intakes. However, researchers cautioned supplements would not necessarily yield the same benefits as dietary omega-3 PUFA as all factors influencing diabetic retinopathy in participants had not been accounted for. Clearly, more human studies of the effects of diet and omega-3 PUFAs on diabetic retinopathy in different populations consuming a range of background diets are warranted.

Mental Health and Cognition

Diabetes, cognitive problems, and mental disorders are frequently comorbid, and epidemiological evidence has demonstrated that individuals with glucose intolerance, obesity, and T2DM are at increased risk for brain disorders such as cognitive problems, dementia or depression [115-117]. Poor quality diets, such as Western style diets high in processed foods, added sugar and saturated fat have been associated with metabolic disease and obesity, which in turn are known risk factors for poor cognition and mental health [118-120]. While the underlying biological factors of this association are not completely understood, there are various neurological and peripheral mechanisms that are hypothesized in this relationship. As the primary energy source for the brain, glucose homeostasis and associated insulin signalling are important to neural health and function [121]. The poor glucose metabolism and impaired insulin signalling that is typical of T2DM may be associated with disrupted central nervous system function and as well as atrophy of the hippocampus and neurodegeneration [122, 123]. Additionally, poor regulation of blood glucose in T2DM may initiate acute changes in

cerebral blood flow, microvascular changes, and dysregulation of the HPA axis and subsequently, increase hippocampal exposure to glucocorticoids [124]. Further, hyperglycaemia and insulin resistance have been linked with inflammation and oxidative stress, both of which have been identified as risk factors and potential mechanisms associated with mood disorders [125, 126].

Omega-3 PUFAs are understood to have neuroprotective effects, and to promote healthy brain function, cognition, and mood [127-129]. Omega-3 PUFA supplementation has been associated with reductions in inflammation and oxidative stress [130-133]. Given that overweight/obesity and glucose intolerance are understood to contribute to inflammation, omega-3 PUFA supplementation may counteract peripheral inflammation and oxidative stress associated with T2DM [134], and may also act as a protective buffer against inflammation and dysregulated insulin activity, both peripherally and in the brain [135, 136]. Further, meta-analyses of RCTs suggest that omega-3 PUFA supplementation, particularly formulations with a high EPA to DHA ratio, may be protective against cognitive decline and risk of mood disorders [137-140]. While the effects of omega-3 PUFA supplementation on cognitive function and mental health have not been well studied specifically among populations with T2DM, the broader literature supporting the neuroprotective and anti-inflammatory benefits of omega-3 PUFA supplementation suggests that this may be a beneficial strategy among people with T2DM [141, 142]. However, recent literature has highlighted that individual characteristics, such as high or low baseline inflammation (as measured by interleukin-1ra, c-reactive protein, and adiponectin), may predict treatment response to omega-3 PUFAs and thus should be considered among this population [143]. Omega-3 PUFA supplementation, in combination with lifestyle modification (i.e. weight loss, reduction of saturated fat intake) may offer a low-risk neuroprotective strategy in T2DM, and this area warrants further investigation. While supplementation may not modulate glucose metabolism or insulin function directly, it may reduce the likelihood of comorbid psychiatric or neurodegenerative conditions that may complicate diabetes treatment or prognosis [144, 145].

Practical Considerations of Omega-3 PUFA Supplementation

To inform clinical use of omega-3 PUFA supplementation in the diabetic population, relevant practical issues need to be considered. These include patient's attitudes towards supplementation, the possibility of adverse events, issues related to supplement purity, dose, and cost of obtaining omega-3 PUFAs via supplementation versus food.

There is limited data on the use of omega-3 PUFA supplementation amongst populations with diabetes. The overall reported use of complementary and alternative medicine in diabetic populations ranges from 17% to 73% [146], which is comparable to usage rates in the general population [147, 148]. In the Freemantle Diabetes Study [147], up to 14% of patients with T2DM indicated that they had previously taken fish oil/omega 3 supplementation. Manya et al.[149] explored diabetic patients reasons for taking supplementation and found that only 3% of subjects currently using fish oil were doing so 'specifically to treat diabetes'. These results suggest that while people living with T2DM do not commonly use omega-3 PUFA supplements, they are open to supplement use in general.

Due to the increased risk of CVD associated with T2DM, patients with diabetes are frequently prescribed anti-coagulant medications such as aspirin. It has been postulated that omega-3 PUFA supplements and anticoagulant, and antihypertensive drugs are contraindicated [150]. Theoretically, bleeding could occur due to the anti-thrombotic properties of EPA and DHA [151]. However, a review[151] examining the safety of omega-3 PUFA supplements (0.03 – 1.86g EPA, 0.15-1.72 g DHA per day, taken for 6 to 52 weeks) failed to identify any severe adverse events (bleeding, death, bruising) that were likely to be attributable to omega-3 PUFA use. A related review on safety considerations with omega-3 fatty acid therapy, concluded that there is little evidence that either 'low–dose' (<1g/day) or 'high-dose' (typically 5-6g/day) omega-3 supplementation increase bleeding risks in patients being treated with antiplatelet or anticoagulant therapies [152]. Likewise, an RCT assessing fish oil supplementation (32% EPA; 23% DHA; dose 2.7g/day or 6.1g/day) in high-risk pregnancies found no evidence of increased risk of adverse events when the prophylactic (2.7g/day) and therapeutic (6.1g/day) trial arms were compared to an olive oil control group [153]. While the existing evidence does not support any clinically significant risks of bleeding with use of omega-3 PUFAs at standard doses, individuals with bleeding disorders may require additional monitoring and supervision [154]. Congenital bleeding disorders occur in approximately 1% of the population and are frequently undiagnosed [155].

Individuals commonly report gastrointestinal (GI) symptoms (especially eructation) with fish oil use. Five of the 17 studies in the review by Villani et al.[151] reported on GI symptoms. The prevalence of GI symptoms ranged from 3 – 53.8%; occurrence of GI symptoms did not appear to be affected by supplement dose or composition. The authors concluded that there is unlikely to be differences in GI disturbances between omega-3 PUFAs and placebo supplements (e.g. sunflower oil) [151].

Additional concerns specific to omega 3 PUFA supplementation relate to the stability and purity of commercial supplement products. Due to their long chain chemical structure, omega-3 PUFAs are prone to oxidation if exposed to excess heat and/or light. Improper storage of commercial omega-3 PUFA supplements may result in oxidised products and negate the potential beneficial health effects of supplementation. Two recent analyses of several commercial fish oil products have provided conflicting results with one analysis finding few products met recommendations of oxidation markers while the other study finding the opposite [156, 157]. Possible reasons for this conflict are due to the type of analysis and range of supplements tested. Furthermore, due to the bioaccumulation of heavy metals and organic pollutants in animal lipid reserves, marine sources of omega-3 PUFAs (e.g. fish oils) may contain significant levels of these compounds [158]. Previous studies that have investigated the content of various pollutants in marine omega-3 PUFAs have identified some products that exceeded recommended intakes of pollutants but most products were below the recommended levels [158, 159].

The common therapeutic dosages for omega-3 range from 1-4g/day [160]. For reference, two grams of omega-3 fatty acids can be obtained by eating around 100 g of Atlantic salmon [161] or taking 2 to 10 fish oil capsules. For many individuals, these amounts are difficult to achieve with food alone. While omega-3 supplements range in price, and fish oil supplements with higher concentrations of EPA and DHA tend to me more expensive [162, 163], economic analyses have demonstrated that, per mg, omega-3 PUFA supplements are always cheaper than food sources of omega-3 [162, 163]. Accordingly, supplements represent a viable and practical means of obtaining adequate omega-3 PUFAs. However, in the context of whole of diet patterns (such as the Dietary Approaches to Stop Hypertension [DASH] diet and the Mediterranean diet), dietary sources of omega-3 PUFAs such as fish and flax seeds also contain a wide range of compounds including taurine, polyphenols, selenium, and fibre that may provide unique health benefits. Furthermore, in contrast to the use of omega-3 PUFA supplements, consumption of a wholefood item rich in omega-3 PUFAs (e.g. fish) will improve overall diet quality by displacing a potentially low-nutrient density food item.[164] Therefore, whole food sources of omega-3 PUFAs should be encouraged and evidence-based omega-3 supplementation should be seen as an adjunct to, rather than replacement for food.

Future directions and conclusion

Despite promising animal studies, the current clinical evidence for the use of omega-3 supplementation for the management of T2DM and associated conditions is both limited and conflicting. Currently, the clinical evidence does not support the use of omega-3 PUFA supplementation for improving glycaemic control and there is insufficient evidence to make recommendations on the use of omega-3 PUFAs for diabetic nephropathy and retinopathy. While there is promising evidence for the use of omega-3 supplementation for NAFLD-related outcomes and mental health from non-diabetic populations, there is limited clinical evidence in diabetic populations to support its use. As discussed in detail in our recently published review on the controversies in omega-3 PUFA supplementation trials,[160] possible explanations for the conflicting evidence base are issues with study design such as inadequate intervention periods and sample size of studies, inadequate dose of supplements, variations in the ratio of EPA to DHA and clinical heterogeneity among diabetic populations (e.g. evaluating diabetic nephropathy in patients with microalbuminuria and macroalbuminuria). Meta-analyses of RCTs suggest that omega-3 PUFAs are effective in reducing triglycerides in T2DM. However, there is insufficient evidence to support the use of omega-3 PUFAs for other CVD risk factors (e.g. oxidative stress) and clinical endpoints in the T2DM context. Although omega-3 supplementation appears to be generally well-tolerated, clinicians should consider issues regarding possible contraindications as well as oxidation and impurity issues with some commercial products. Finally, omega-3 PUFA supplements are a cost-effective method of achieving therapeutic doses. However, due to the beneficial effect of dietary sources of omega-3 PUFAs in improving diet quality and improving intake of other beneficial nutrients, food sources of omega-3 PUFAs should be prioritised.

References

1. McCrimmon RJ, Ryan CM, Frier BM. Diabetes and cognitive dysfunction. The Lancet.379(9833):2291-9.
2. Pantalone KM, Hobbs TM, Wells BJ, Kong SX, Kattan MW, Bouchard J, et al. Clinical characteristics, complications, comorbidities and treatment patterns among patients with type 2 diabetes mellitus in a large integrated health system. BMJ Open Diabetes Research & Care. 2015;3(1).
3. Domingueti CP, Dusse LM, Carvalho M, de Sousa LP, Gomes KB, Fernandes AP. Diabetes mellitus: The linkage between oxidative stress, inflammation, hypercoagulability and vascular complications. Journal of diabetes and its complications. 2016;30(4):738-45.
4. International Diabetes Federation. IDF Diabetes Atlas. 7th ed. Brussels, Belgium: International Diabetes Federation; 2015.
5. Australian Institute of Health and Welfare. Diabetes expenditure in Australia 2008–09. Canberra, Australia Australian Institute of Health and Welfare; 2013.
6. Schwingshackl L, Missbach B, Konig J, Hoffmann G. Adherence to a Mediterranean diet and risk of diabetes: a systematic review and meta-analysis. Public health nutrition. 2015;18(7):1292-9.
7. Pitsavos C, Panagiotakos DB, Tzima N, Chrysohoou C, Economou M, Zampelas A, et al. Adherence to the Mediterranean diet is associated with total antioxidant capacity in healthy adults: the ATTICA study. Am J Clin Nutr. 2005;82(3):694-9.
8. Martinez-Gonzalez MA, de la Fuente-Arrillaga C, Nunez-Cordoba JM, Basterra-Gortari FJ, Beunza JJ, Vazquez Z, et al. Adherence to Mediterranean diet and risk of developing diabetes: prospective cohort study. Bmj. 2008;336(7657):1348-51.
9. Salas-Salvado J, Bullo M, Babio N, Martinez-Gonzalez MA, Ibarrola-Jurado N, Basora J, et al. Reduction in the incidence of type 2 diabetes with the Mediterranean diet: results of the PREDIMED-Reus nutrition intervention randomized trial. Diabetes Care. 2011;34(1):14-9.
10. Gebauer SK, Psota TL, Harris WS, Kris-Etherton PM. n−3 Fatty acid dietary recommendations and food sources to achieve essentiality and cardiovascular benefits. The American Journal of Clinical Nutrition. 2006;83(6):S1526-35S.
11. De Caterina R, Madonna R, Bertolotto A, Schmidt EB. n-3 Fatty Acids in the Treatment of Diabetic Patients. Biological rationale and clinical data. 2007;30(4):1012-26.
12. Watson H, Mitra S, Croden FC, Taylor M, Wood HM, Perry SL, et al. A randomised trial of the effect of omega-3 polyunsaturated fatty acid supplements on the human intestinal microbiota. Gut. 2017.
13. Oh DY, Talukdar S, Bae EJ, Imamura T, Morinaga H, Fan W, et al. GPR120 is an omega-3 fatty acid receptor mediating potent anti-inflammatory and insulin-sensitizing effects. Cell. 2010;142(5):687-98.
14. Vemuri M, Kelley DS, Mackey BE, Rasooly R, Bartolini G. Docosahexaenoic Acid (DHA) But Not Eicosapentaenoic Acid (EPA) Prevents Trans-10, Cis-12 Conjugated Linoleic Acid (CLA)-Induced Insulin Resistance in Mice. Metabolic syndrome and related disorders. 2007;5(4):315-22.
15. Feskens EJ, Bowles CH, Kromhout D. Inverse association between fish intake and risk of glucose intolerance in normoglycemic elderly men and women. Diabetes Care. 1991;14(11):935-41.
16. Lalia AZ, Lanza IR. Insulin-Sensitizing Effects of Omega-3 Fatty Acids: Lost in Translation? Nutrients. 2016;8(6).
17. Matsuura B, Kanno S, Minami H, Tsubouchi E, Iwai M, Matsui H, et al. Effects of antihyperlipidemic agents on hepatic insulin sensitivity in perfused Goto-Kakizaki rat liver. Journal of Gastroenterology. 2004;39(4):339-45.
18. Wu JHY, Micha R, Imamura F, Pan A, Biggs ML, Ajaz O, et al. Omega-3 fatty acids and incident type 2 diabetes: a systematic review and meta-analysis. Br J Nutr. 2012;107(S2):S214-S27.
19. Kuda O, Jelenik T, Jilkova Z, Flachs P, Rossmeisl M, Hensler M, et al. n -3 Fatty acids and rosiglitazone improve insulin sensitivity through additive stimulatory effects on muscle glycogen

synthesis in mice fed a high-fat diet. Clinical and Experimental Diabetes and Metabolism. 2009;52(5):941-51.
20. Rossi AS, Lombardo YB, Lacorte JM, Chicco AG, Rouault C, Slama G, et al. Dietary fish oil positively regulates plasma leptin and adiponectin levels in sucrose-fed, insulin-resistant rats. American journal of physiology Regulatory, integrative and comparative physiology. 2005;289(2):R486-r94.
21. Wu JHY, Micha R, Imamura F, Pan A, Biggs ML, Ajaz O, et al. Omega-3 Fatty Acids and incident Type 2 Diabetes: A Systematic Review and Meta-Analysis. The British journal of nutrition. 2012;107(0 2):S214-S27.
22. Flachs P, Rossmeisl M, Kopecky J. The effect of n-3 fatty acids on glucose homeostasis and insulin sensitivity. Physiological research. 2014;63 Suppl 1:S93-118.
23. Glauber H, Wallace P, Griver K, Brechtel G. Adverse metabolic effect of omega-3 fatty acids in non-insulin-dependent diabetes mellitus. Annals of internal medicine. 1988;108(5):663.
24. Friday KE, Childs MT, Tsunehara CH, Fujimoto WY, Bierman EL, Ensinck JW. Elevated Plasma Glucose and Lowered Triglyceride Levels From Omega-3 Fatty Acid Supplementation in Type II Diabetes. Diabetes Care. 1989;12(4):276-81.
25. Chen C, Yu X, Shao S. Effects of Omega-3 Fatty Acid Supplementation on Glucose Control and Lipid Levels in Type 2 Diabetes: A Meta-Analysis.(Report). 2015;10(10).
26. Coelho OGL, da Silva BP, Rocha D, Lopes LL, Alfenas RCG. Polyunsaturated fatty acids and type 2 diabetes: Impact on the glycemic control mechanism. Critical reviews in food science and nutrition. 2017;57(17):3614-9.
27. Antigoni ZL, Ian RL. Insulin-Sensitizing Effects of Omega-3 Fatty Acids: Lost in Translation? Nutrients. 2016;8(6):329.
28. Hartweg J, Perera R, Montori V. Cochrane Database Syst Rev: Omega-3 polyunsaturated fatty acids (PUFA) for type 2 diabetes mellitus. Alternative Medicine Review. 2008;13(2):171.
29. Mostad IL, Bjerve KS, Bjorgaas MR, Lydersen S, Grill V. Effects of n-3 fatty acids in subjects with type 2 diabetes: reduction of insulin sensitivity and time-dependent alteration from carbohydrate to fat oxidation. Am J Clin Nutr. 2006;84(3):540-50.
30. Farsi PF, Djazayery A, Eshraghian MR, Koohdani F, Saboor-Yaraghi AA, Derakhshanian H, et al. Effects of supplementation with omega-3 on insulin sensitivity and non-esterified free fatty acid (NEFA) in type 2 diabetic patients. Arquivos brasileiros de endocrinologia e metabologia. 2014;58(4):335-40.
31. Byelashov OA, Sinclair AJ, Kaur G. Dietary sources, current intakes, and nutritional role of omega-3 docosapentaenoic acid. Lipid technology. 2015;27(4):79-82.
32. Guo XF, Sinclair AJ, Kaur G, Li D. Differential effects of EPA, DPA and DHA on cardio-metabolic risk factors in high-fat diet fed mice. Prostaglandins, leukotrienes, and essential fatty acids. 2017.
33. Montori VM, Farmer A, Wollan PC, Dinneen SF. Fish Oil Supplementation in Type 2 Diabetes: A quantitative systematic review. Diabetes Care. 2000;23(9):1407.
34. Friedberg C, Heine R, Grobbee D. Fish oil and glycemic control in diabetes: A meta-analysis. Diabetes Care. 1998;21(4):494-500.
35. Leon BM, Maddox TM. Diabetes and cardiovascular disease: Epidemiology, biological mechanisms. 2015.
36. Shaw J, Tanamas S. Diabetes: the silent pandemic and its impact on Australia. Melbourne: Baker IDI Heart and Diabetes Institute. 2012.
37. Halter JB, Musi N, Horne FM, Crandall JP, Goldberg A, Harkless L, et al. Diabetes and cardiovascular disease in older adults: current status and future directions. Diabetes. 2014;63(8):2578-89.
38. Patel TP, Rawal K, Bagchi AK, Akolkar G, Bernardes N, da Silva Dias D, et al. Insulin resistance: an additional risk factor in the pathogenesis of cardiovascular disease in type 2 diabetes. Heart failure reviews. 2016;21(1):11-23.

39. Chen C, Yu X, Shao S. Effects of omega-3 fatty acid supplementation on glucose control and lipid levels in type 2 diabetes: a meta-analysis. PloS one. 2015;10(10):e0139565.
40. Montori VM, Farmer A, Wollan PC, Dinneen SF. Fish oil supplementation in type 2 diabetes: a quantitative systematic review. Diabetes care. 2000;23(9):1407-15.
41. Hartweg J, Perera R, Montori VM, Dinneen SF, Neil AH, Farmer AJ. Omega-3 polyunsaturated fatty acids (PUFA) for type 2 diabetes mellitus. The Cochrane Library. 2008.
42. Matheus ASdM, Tannus LRM, Cobas RA, Palma CCS, Negrato CA, Gomes MdB. Impact of Diabetes on Cardiovascular Disease: An Update. International Journal of Hypertension. 2013;2013:653789.
43. Hartweg J, Farmer AJ, Holman RR, Neil HAW. Meta-analysis of the effects of n-3 polyunsaturated fatty acids on haematological and thrombogenic factors in type 2 diabetes. Diabetologia. 2007;50(2):250-8.
44. Atar MJH, Hajianfar H, Bahonar A. The effects of omega-3 on blood pressure and the relationship between serum visfatin level and blood pressure in patients with type II diabetes. ARYA atherosclerosis. 2012;8(1):27.
45. Poudyal H, Panchal SK, Diwan V, Brown L. Omega-3 fatty acids and metabolic syndrome: effects and emerging mechanisms of action. Progress in lipid research. 2011;50(4):372-87.
46. Buckley JD, Howe PRC. Long-Chain Omega-3 Polyunsaturated Fatty Acids May Be Beneficial for Reducing Obesity—A Review. Nutrients. 2010;2(12):1212-30.
47. Kabir M, Skurnik G, Naour N, Pechtner V, Meugnier E, Rome S, et al. Treatment for 2 mo with n− 3 polyunsaturated fatty acids reduces adiposity and some atherogenic factors but does not improve insulin sensitivity in women with type 2 diabetes: a randomized controlled study. The American journal of clinical nutrition. 2007;86(6):1670-9.
48. Kojda G, Harrison D. Interactions between NO and reactive oxygen species: pathophysiological importance in atherosclerosis, hypertension, diabetes and heart failure. Cardiovascular research. 1999;43(3):652-71.
49. Rangel-Huerta OD, Gil A. Omega 3 fatty acids in cardiovascular disease risk factors: An updated systematic review of randomised clinical trials. Clinical Nutrition. 2017.
50. McDonald DM, O'Kane F, McConville M, Devine AB, McVeigh GE. Platelet Redox Balance in Diabetic Patients With Hypertension Improved by n-3 Fatty Acids. Diabetes Care. 2013;36(4):998-1005.
51. Pase MP, Grima NA, Sarris J. Do long-chain n-3 fatty acids reduce arterial stiffness? A meta-analysis of randomised controlled trials. British Journal of Nutrition. 2011;106(7):974-80.
52. Mita T, Watada H, Ogihara T, Nomiyama T, Ogawa O, Kinoshita J, et al. Eicosapentaenoic acid reduces the progression of carotid intima-media thickness in patients with type 2 diabetes. Atherosclerosis. 2007;191(1):162-7.
53. McVeigh GE, Brennan GM, Cohn JN, Finkelstein SM, Hayes RJ, Johnston GD. Fish oil improves arterial compliance in non-insulin-dependent diabetes mellitus. Arteriosclerosis, Thrombosis, and Vascular Biology. 1994;14(9):1425-9.
54. Sena CM, Pereira AM, Seiça R. Endothelial dysfunction — A major mediator of diabetic vascular disease. Biochimica et Biophysica Acta (BBA) - Molecular Basis of Disease. 2013;1832(12):2216-31.
55. Zehr KR, Walker MK. Omega-3 polyunsaturated fatty acids improve endothelial function in humans at risk for atherosclerosis: A Review. Prostaglandins & Other Lipid Mediators. 2017.
56. Siscovick DS, Barringer TA, Fretts AM, Wu JHY, Lichtenstein AH, Costello RB, et al. Omega-3 Polyunsaturated Fatty Acid (Fish Oil) Supplementation and the Prevention of Clinical Cardiovascular Disease: A Science Advisory From the American Heart Association. Circulation. 2017.
57. Investigators OT. n–3 Fatty acids and cardiovascular outcomes in patients with dysglycemia. N Engl J Med. 2012;2012(367):309-18.

58. Armitage J, Bowman L. Ascend–'a Study of Cardiovascular Events in Diabetes': a new large-scale randomised trial of aspirin and of omega-3 fatty acid supplementation for the primary prevention of cardiovascular disease in diabetes. Diabetic Medicine. 2005;22:59.
59. Rauch B, Schiele R, Schneider S, Diller F, Victor N, Gohlke H, et al. OMEGA, a randomized, placebo-controlled trial to test the effect of highly purified omega-3 fatty acids on top of modern guideline-adjusted therapy after myocardial infarction. Circulation. 2010:CIRCULATIONAHA. 110.948562.
60. Oikawa S, Yokoyama M, Origasa H, Matsuzaki M, Matsuzawa Y, Saito Y, et al. Suppressive effect of EPA on the incidence of coronary events in hypercholesterolemia with impaired glucose metabolism: Sub-analysis of the Japan EPA Lipid Intervention Study (JELIS). Atherosclerosis. 2009;206(2):535-9.
61. Kromhout D, Geleijnse JM, de Goede J, Griep LMO, Mulder BJ, de Boer M-J, et al. n-3 Fatty Acids, Ventricular Arrhythmia–Related Events, and Fatal Myocardial Infarction in Postmyocardial Infarction Patients With Diabetes. Diabetes care. 2011;34(12):2515-20.
62. National Heart Foundation of Australia and the Cardiac Society of Australia and New Zealand. Reducing risk in heart disease: an expert guide to clinical practice for secondary prevention of

coronary heart disease. Melbourne: National Heart Foundation of Australia, 2012.
63. Browning JD, Szczepaniak LS, Dobbins R, Horton JD, Cohen JC, Grundy SM, et al. Prevalence of hepatic steatosis in an urban population in the United States: impact of ethnicity. Hepatology. 2004;40(6):1387-95.
64. Younossi ZM, Gramlich T, Matteoni CA, Boparai N, McCullough AJ. Nonalcoholic fatty liver disease in patients with type 2 diabetes. Clinical gastroenterology and hepatology : the official clinical practice journal of the American Gastroenterological Association. 2004;2(3):262-5.
65. Buzzetti E, Pinzani M, Tsochatzis EA. The multiple-hit pathogenesis of non-alcoholic fatty liver disease (NAFLD). Metabolism. 2016;65(8):1038-48.
66. Uyeda K, Yamashita H, Kawaguchi T. Carbohydrate responsive element-binding protein (ChREBP): a key regulator of glucose metabolism and fat storage. Biochemical pharmacology. 2002;63(12):2075-80.
67. Neuschwander-Tetri BA, Clark JM, Bass NM, Van Natta ML, Unalp-Arida A, Tonascia J, et al. Clinical, laboratory and histological associations in adults with nonalcoholic fatty liver disease. Hepatology. 2010;52(3):913-24.
68. Zein CO, Unalp A, Colvin R, Liu Y-C, McCullough AJ, Network NSCR. Smoking and severity of hepatic fibrosis in nonalcoholic fatty liver disease. Journal of hepatology. 2011;54(4):753-9.
69. Targher G, Day CP, Bonora E. Risk of cardiovascular disease in patients with nonalcoholic fatty liver disease. New England Journal of Medicine. 2010;363(14):1341-50.
70. Wong VW-S, Wong GL-H, Choi PC-L, Chan AW-H, Li MK-P, Chan H-Y, et al. Disease progression of non-alcoholic fatty liver disease: a prospective study with paired liver biopsies at 3 years. Gut. 2010;59(7):969-74.
71. Calder PC. Marine omega-3 fatty acids and inflammatory processes: effects, mechanisms and clinical relevance. Biochimica et Biophysica Acta (BBA)-Molecular and Cell Biology of Lipids. 2015;1851(4):469-84.
72. Jump DB, Lytle KA, Depner CM, Tripathy S. Omega-3 polyunsaturated fatty acids as a treatment strategy for nonalcoholic fatty liver disease. Pharmacology & therapeutics. 2017.
73. Scorletti E, Byrne CD. Omega-3 fatty acids, hepatic lipid metabolism, and nonalcoholic fatty liver disease. Annual review of nutrition. 2013;33:231-48.
74. Neschen S, Morino K, Dong J, Wang-Fischer Y, Cline GW, Romanelli AJ, et al. n-3 Fatty acids preserve insulin sensitivity in vivo in a peroxisome proliferator-activated receptor-alpha-dependent manner. Diabetes. 2007;56(4):1034-41.
75. Takeuchi Y, Yahagi N, Izumida Y, Nishi M, Kubota M, Teraoka Y, et al. Polyunsaturated Fatty Acids Selectively Suppress Sterol Regulatory Element-binding Protein-1 through Proteolytic

Processing and Autoloop Regulatory Circuit. The Journal of Biological Chemistry. 2010;285(15):11681-91.
76. Ducheix S, Montagner A, Polizzi A, Lasserre F, Marmugi A, Bertrand-Michel J, et al. Essential fatty acids deficiency promotes lipogenic gene expression and hepatic steatosis through the liver X receptor. Journal of hepatology. 2013;58(5):984-92.
77. Kim HJ, Lee KT, Park YB, Jeon SM, Choi MS. Dietary docosahexaenoic acid-rich diacylglycerols ameliorate hepatic steatosis and alter hepatic gene expressions in C57BL/6J-Lepob/ob mice. Molecular nutrition & food research. 2008;52(8):965-73.
78. He X-X, Wu X-L, Chen R-P, Chen C, Liu X-G, Wu B-J, et al. Effectiveness of omega-3 polyunsaturated fatty acids in non-alcoholic fatty liver disease: a meta-analysis of randomized controlled trials. PloS one. 2016;11(10):e0162368.
79. Lu W, Li S, Li J, Wang J, Zhang R, Zhou Y, et al. Effects of omega-3 fatty acid in nonalcoholic fatty liver disease: a meta-analysis. Gastroenterology research and practice. 2016;2016.
80. Musso G, Gambino R, Cassader M, Pagano G. A meta-analysis of randomized trials for the treatment of nonalcoholic fatty liver disease. Hepatology. 2010;52(1):79-104.
81. Parker HM, Johnson NA, Burdon CA, Cohn JS, O'Connor HT, George J. Omega-3 supplementation and non-alcoholic fatty liver disease: a systematic review and meta-analysis. Journal of hepatology. 2012;56(4):944-51.
82. Dasarathy S, Dasarathy J, Khiyami A, Yerian L, Hawkins C, Sargent R, et al. Double blind randomized placebo controlled clinical trial of omega 3 fatty acids for the treatment of diabetic patients with nonalcoholic steatohepatitis. Journal of clinical gastroenterology. 2015;49(2):137.
83. Kelly JT, Rossi M, Johnson DW, Campbell KL. Beyond Sodium, Phosphate and Potassium: Potential Dietary Interventions in Kidney Disease. Seminars in Dialysis. 2017;30(3):197-202.
84. Shapiro H, Theilla M, Attal-Singer J, Singer P. Effects of polyunsaturated fatty acid consumption in diabetic nephropathy. Nature reviews Nephrology. 2011;7(2):110-21.
85. K/DOQI working group. K/DOQI clinical practice guidelines on hypertension and antihypertensive agents in chronic kidney disease. American journal of kidney diseases : the official journal of the National Kidney Foundation. 2004;43(5 Suppl 1):S1-290.
86. Johnson DW, Atai E, Chan M, Phoon RK, Scott C, Toussaint ND, et al. KHA-CARI Guideline: early chronic kidney disease: detection, prevention and management. Nephrology. 2013;18(5):340-50.
87. Luis D, Zlatkis K, Comenge B, Garcia Z, Navarro JF, Lorenzo V, et al. Dietary Quality and Adherence to Dietary Recommendations in Patients Undergoing Hemodialysis. J Ren Nutr. 2016;26(3):190-5.
88. Therrien M, Byham-Gray L, Denmark R, Beto J. Comparison of dietary intake among women on maintenance dialysis to a Women's Health Initiative cohort: results from the NKF-CRN Second National Research Question Collaborative Study. J Ren Nutr. 2014;24(2):72-80.
89. Khoueiry G, Waked A, Goldman M, El-Charabaty E, Dunne E, Smith M, et al. Dietary intake in hemodialysis patients does not reflect a heart healthy diet. J Ren Nutr. 2011;21(6):438-47.
90. Luttrell KJ, Beto JA, Tangney CC. Selected nutrition practices of women on hemodialysis and peritoneal dialysis: observations from the NKF-CRN Second National Research Question Collaborative Study. J Ren Nutr. 2014;24(2):81-91.
91. Lin J, Judd S, Le A, Ard J, Newsome BB, Howard G, et al. Associations of dietary fat with albuminuria and kidney dysfunction. The American Journal of Clinical Nutrition. 2010;92(4):897-904.
92. Huang X, Lindholm B, Stenvinkel P, Carrero JJ. Dietary fat modification in patients with chronic kidney disease: n-3 fatty acids and beyond. Journal of nephrology. 2013;26(6):960-74.
93. Shapiro H, Theilla M, Attal-Singer J, Singer P. Effects of polyunsaturated fatty acid consumption in diabetic nephropathy. Nature Reviews Nephrology. 2011;7(2):110-21.
94. Gopinath B, Harris DC, Flood VM, Burlutsky G, Mitchell P. Consumption of long-chain n-3 PUFA, α-linolenic acid and fish is associated with the prevalence of chronic kidney disease. British journal of nutrition. 2011;105(9):1361-8.

95. Lee CC, Sharp SJ, Wexler DJ, Adler AI. Dietary intake of eicosapentaenoic and docosahexaenoic acid and diabetic nephropathy: cohort analysis of the diabetes control and complications trial. Diabetes Care. 2010;33(7):1454-6.
96. Guebre-Egziabher F, Debard C, Drai J, Denis L, Pesenti S, Bienvenu J, et al. Differential dose effect of fish oil on inflammation and adipose tissue gene expression in chronic kidney disease patients. Nutrition. 2013;29(5):730-6.
97. Huang X, Lindholm B, Stenvinkel P, Carrero JJ. Dietary fat modification in patients with chronic kidney disease: n-3 fatty acids and beyond. Journal of nephrology. 2013;26(6):960-74.
98. Rossing P, Hansen BV, Nielsen FS, Myrup B, Hølmer G, Parving H-H. Fish oil in diabetic nephropathy. Diabetes Care. 1996;19(11):1214-9.
99. Miller ER, Juraschek SP, Anderson CA, Guallar E, Henoch-Ryugo K, Charleston J, et al. The effects of n-3 long-chain polyunsaturated fatty acid supplementation on biomarkers of kidney injury in adults with diabetes. Diabetes care. 2013;36(6):1462-9.
100. Alexopoulos E, Stangou M, Pantzaki A, Kirmizis D, Memmos D. Treatment of Severe IgA Nephropathy With Omega-3 Fatty Acids: The Effect of a "Very Low Dose" Regimen. Renal failure. 2004;26(4):453-9.
101. Christensen JH, Sølling J, Schmidt EB. The effect of n-3 fatty acids on plasma lipids and lipoproteins and blood pressure in patients with CRF. American journal of kidney diseases. 2004;44(1):77-83.
102. Miller ER, 3rd, Juraschek SP, Appel LJ, Madala M, Anderson CA, Bleys J, et al. The effect of n-3 long-chain polyunsaturated fatty acid supplementation on urine protein excretion and kidney function: meta-analysis of clinical trials. Am J Clin Nutr. 2009;89(6):1937-45.
103. Miller ER, Juraschek SP, Appel LJ, Madala M, Anderson CA, Bleys J, et al. The effect of n–3 long-chain polyunsaturated fatty acid supplementation on urine protein excretion and kidney function: meta-analysis of clinical trials. The American journal of clinical nutrition. 2009:ajcn. 26867.
104. Kabir M, Skurnik G, Naour N, Pechtner V, Meugnier E, Rome S, et al. Treatment for 2 mo with n 3 polyunsaturated fatty acids reduces adiposity and some atherogenic factors but does not improve insulin sensitivity in women with type 2 diabetes: a randomized controlled study. Am J Clin Nutr. 2007;86(6):1670-9.
105. SanGiovanni JP, Chew EY. The role of omega-3 long-chain polyunsaturated fatty acids in health and disease of the retina. Prog Retin Eye Res. 2005;24(1):87-138.
106. Hammes HP, Weiss A, Fuhrer D, Kramer HJ, Papavassilis C, Grimminger F. Acceleration of experimental diabetic retinopathy in the rat by omega-3 fatty acids. Diabetologia. 1996;39(3):251-5.
107. Connor KM, SanGiovanni JP, Lofqvist C, Aderman CM, Chen J, Higuchi A, et al. Increased dietary intake of omega-3-polyunsaturated fatty acids reduces pathological retinal angiogenesis. Nature medicine. 2007;13(7):868-73.
108. Yee P, Weymouth AE, Fletcher EL, Vingrys AJ. A role for omega-3 polyunsaturated fatty acid supplements in diabetic neuropathy. Invest Ophthalmol Vis Sci. 2010;51(3):1755-64.
109. Sapieha P, Stahl A, Chen J, Seaward MR, Willett KL, Krah NM, et al. 5-Lipoxygenase metabolite 4-HDHA is a mediator of the antiangiogenic effect of omega-3 polyunsaturated fatty acids. Sci Transl Med. 2011;3(69):69ra12.
110. Sapieha P, Chen J, Stahl A, Seaward MR, Favazza TL, Juan AM, et al. Omega-3 polyunsaturated fatty acids preserve retinal function in type 2 diabetic mice. Nutr Diabetes. 2012;2:e36.
111. Kowluru RA, Zhong Q, Santos JM, Thandampallayam M, Putt D, Gierhart DL. Beneficial effects of the nutritional supplements on the development of diabetic retinopathy. Nutr Metab (Lond). 2014;11(1):8.
112. Buhler AD, Bucher F, Augustynik M, Wohrl J, Martin G, Schlunck G, et al. Systemic confounders affecting serum measurements of omega-3 and -6 polyunsaturated fatty acids in patients with retinal disease. BMC Ophthalmol. 2016;16(1):159.

113. Hodge W, Barnes D, Schachter HM, Pan Y, Lowcock EC, Zhang L, et al. Effects of omega-3 fatty acids on eye health. Evid Rep Technol Assess (Summ). 2005(117):1-6.
114. Sala-Vila A, Diaz-Lopez A, Valls-Pedret C, Cofan M, Garcia-Layana A, Lamuela-Raventos RM, et al. Dietary Marine omega-3 Fatty Acids and Incident Sight-Threatening Retinopathy in Middle-Aged and Older Individuals With Type 2 Diabetes: Prospective Investigation From the PREDIMED Trial. JAMA Ophthalmol. 2016;134(10):1142-9.
115. Pasquier F, Boulogne A, Leys D, Fontaine P. Diabetes mellitus and dementia. Diabetes Metab. 2006;32(5 Pt 1):403-14.
116. Gunstad J, Paul RH, Cohen RA, Tate DF, Spitznagel MB, Gordon E. Elevated body mass index is associated with executive dysfunction in otherwise healthy adults. Compr Psychiatry. 2007;48(1):57-61.
117. Ali S, Stone MA, Peters JL, Davies MJ, Khunti K. The prevalence of co-morbid depression in adults with Type 2 diabetes: a systematic review and meta-analysis. Diabet Med. 2006;23(11):1165-73.
118. Hsu TM, Kanoski SE. Blood-brain barrier disruption: mechanistic links between Western diet consumption and dementia. Frontiers in Aging Neuroscience. 2014;6:88.
119. Lutsey PL, Steffen LM, Stevens J. Dietary intake and the development of the metabolic syndrome: the Atherosclerosis Risk in Communities study. Circulation. 2008;117(6):754-61.
120. Li Y, Lv MR, Wei YJ, Sun L, Zhang JX, Zhang HG, et al. Dietary patterns and depression risk: A meta-analysis. Psychiatry Res. 2017;253:373-82.
121. Gerozissis K. Brain insulin, energy and glucose homeostasis; genes, environment and metabolic pathologies. Eur J Pharmacol. 2008;585(1):38-49.
122. de la Monte SM, Wands JR. Review of insulin and insulin-like growth factor expression, signaling, and malfunction in the central nervous system: relevance to Alzheimer's disease. J Alzheimers Dis. 2005;7(1):45-61.
123. Lamport DJ, Lawton CL, Mansfield MW, Dye L. Impairments in glucose tolerance can have a negative impact on cognitive function: a systematic research review. Neurosci Biobehav Rev. 2009;33(3):394-413.
124. Strachan MW, Reynolds RM, Marioni RE, Price JF. Cognitive function, dementia and type 2 diabetes mellitus in the elderly. Nat Rev Endocrinol. 2011;7(2):108-14.
125. De La Monte SM. Metabolic derangements mediate cognitive impairment and Alzheimer's disease: role of peripheral insulin-resistance diseases. Panminerva Med. 2012;54(3):171-8.
126. Maes M. The cytokine hypothesis of depression: inflammation, oxidative & nitrosative stress (IO&NS) and leaky gut as new targets for adjunctive treatments in depression. Neuro Endocrinol Lett. 2008;29(3):287-91.
127. Lin PY, Su KP. A meta-analytic review of double-blind, placebo-controlled trials of antidepressant efficacy of omega-3 fatty acids. J Clin Psychiatry. 2007;68(7):1056-61.
128. Zhang W, Li P, Hu X, Zhang F, Chen J, Gao Y. Omega-3 polyunsaturated fatty acids in the brain: metabolism and neuroprotection. Front Biosci (Landmark Ed). 2011;16:2653-70.
129. Dyall SC. Long-chain omega-3 fatty acids and the brain: a review of the independent and shared effects of EPA, DPA and DHA. Front Aging Neurosci. 2015;7:52.
130. Wall R, Ross RP, Fitzgerald GF, Stanton C. Fatty acids from fish: the anti-inflammatory potential of long-chain omega-3 fatty acids. Nutr Rev. 2010;68(5):280-9.
131. Akinkuolie AO, Ngwa JS, Meigs JB, Djousse L. Omega-3 polyunsaturated fatty acid and insulin sensitivity: a meta-analysis of randomized controlled trials. Clin Nutr. 2011;30(6):702-7.
132. Nettleton JA, Katz R. n-3 long-chain polyunsaturated fatty acids in type 2 diabetes: a review. J Am Diet Assoc. 2005;105(3):428-40.
133. Calder PC. n-3 polyunsaturated fatty acids, inflammation, and inflammatory diseases. Am J Clin Nutr. 2006;83(6 Suppl):1505S-19S.

134. Figaro MK, Kritchevsky SB, Resnick HE, Shorr RI, Butler J, Shintani A, et al. Diabetes, inflammation, and functional decline in older adults: findings from the Health, Aging and Body Composition (ABC) study. Diabetes Care. 2006;29(9):2039-45.
135. Fotuhi M, Mohassel P, Yaffe K. Fish consumption, long-chain omega-3 fatty acids and risk of cognitive decline or Alzheimer disease: a complex association. Nat Clin Pract Neurol. 2009;5(3):140-52.
136. Mazza M, Pomponi M, Janiri L, Bria P, Mazza S. Omega-3 fatty acids and antioxidants in neurological and psychiatric diseases: an overview. Prog Neuropsychopharmacol Biol Psychiatry. 2007;31(1):12-26.
137. Karr JE, Alexander JE, Winningham RG. Omega-3 polyunsaturated fatty acids and cognition throughout the lifespan: a review. Nutr Neurosci. 2011;14(5):216-25.
138. Kraguljac NV, Montori VM, Pavuluri M, Chai HS, Wilson BS, Unal SS. Efficacy of omega-3 fatty acids in mood disorders - a systematic review and metaanalysis. Psychopharmacol Bull. 2009;42(3):39-54.
139. Sarris J, Murphy J, Mischoulon D, Papakostas GI, Fava M, Berk M, et al. Adjunctive Nutraceuticals for Depression: A Systematic Review and Meta-Analyses. The American journal of psychiatry. 2016;173(6):575-87.
140. Sublette ME, Ellis SP, Geant AL, Mann JJ. Meta-analysis of the effects of eicosapentaenoic acid (EPA) in clinical trials in depression. The Journal of clinical psychiatry. 2011;72(12):1577-84.
141. Hooper L, Thompson RL, Harrison RA, Summerbell CD, Ness AR, Moore HJ, et al. Risks and benefits of omega 3 fats for mortality, cardiovascular disease, and cancer: systematic review. BMJ. 2006;332(7544):752-60.
142. Fontani G, Corradeschi F, Felici A, Alfatti F, Migliorini S, Lodi L. Cognitive and physiological effects of Omega-3 polyunsaturated fatty acid supplementation in healthy subjects. Eur J Clin Invest. 2005;35(11):691-9.
143. Rapaport MH, Nierenberg AA, Schettler PJ, Kinkead B, Cardoos A, Walker R, et al. Inflammation as a predictive biomarker for response to omega-3 fatty acids in major depressive disorder: a proof-of-concept study. Mol Psychiatry. 2016;21(1):71-9.
144. Bot M, Pouwer F, Assies J, Jansen EHJM, Diamant M, Snoek FJ, et al. Eicosapentaenoic acid as an add-on to antidepressant medication for co-morbid major depression in patients with diabetes mellitus: A randomized, double-blind placebo-controlled study. Journal of Affective Disorders. 2010;126(1):282-6.
145. American Diabetes A. Standards of Medical Care in Diabetes-2016 Abridged for Primary Care Providers. Clin Diabetes. 2016;34(1):3-21.
146. Chang H-y, Wallis M, Tiralongo E. Use of complementary and alternative medicine among people living with diabetes: literature review. Journal of Advanced Nursing. 2007;58(4):307-19.
147. Harris PE, Cooper KL, Relton C, Thomas KJ. Prevalence of complementary and alternative medicine (CAM) use by the general population: a systematic review and update. International Journal of Clinical Practice. 2012;66(10):924-39.
148. Yeh GY, Eisenberg DM, Davis RB, Phillips RS. Use of complementary and alternative medicine among persons with diabetes mellitus: results of a national survey. American Journal of Public Health. 2002;92(10):1648-52.
149. Manya K, Champion B, Dunning T. The use of complementary and alternative medicine among people living with diabetes in Sydney. BMC Complementary and Alternative Medicine. 2012;12:2-.
150. Bishop FL, Yardley L, Lewith GT. A systematic review of beliefs involved in the use of complementary and alternative medicine. Journal of health psychology. 2007;12(6):851-67.
151. Villani AM, Crotty M, Cleland LG, James MJ, Fraser RJ, Cobiac L, et al. Fish oil administration in older adults: is there potential for adverse events? A systematic review of the literature. BMC geriatrics. 2013;13(1):41.

152. Bays HE. Safety Considerations with Omega-3 Fatty Acid Therapy. The American Journal of Cardiology. 2007;99(6, Supplement 1):S35-S43.
153. Olsen SF, Secher NJ, Tabor A, Weber T, Walker JJ, Gluud C. Randomised clinical trials of fish oil supplementation in high risk pregnancies. BJOG: An International Journal of Obstetrics & Gynaecology. 2000;107(3):382-95.
154. Braun L. Complementary medicine: Fish oils and bleeding: What's the risk? The Australian Journal of Pharmacy 2013;94(1119).
155. Mensah PK, Gooding R. Surgery in patients with inherited bleeding disorders. Anaesthesia. 2015;70 Suppl 1:112-20, e39-40.
156. Albert BB, Derraik JG, Cameron-Smith D, Hofman PL, Tumanov S, Villas-Boas SG, et al. Fish oil supplements in New Zealand are highly oxidised and do not meet label content of n-3 PUFA. Scientific reports. 2015;5:7928.
157. Nichols PD, Dogan L, Sinclair A. Australian and New Zealand Fish Oil Products in 2016 Meet Label Omega-3 Claims and Are Not Oxidized. Nutrients. 2016;8(11).
158. Bengtson Nash SM, Schlabach M, Nichols PD. A Nutritional-Toxicological Assessment of Antarctic Krill Oil versus Fish Oil Dietary Supplements. Nutrients. 2014;6(9):3382-402.
159. Covaci A, Voorspoels S, Vetter W, Gelbin A, Jorens PG, Blust R, et al. Anthropogenic and naturally occurring organobrominated compounds in fish oil dietary supplements. Environmental science & technology. 2007;41(15):5237-44.
160. Radcliffe JE, Thomas J, Bramley AL, Kouris-Blazos A, Radford BE, Scholey AB, et al. Controversies in omega-3 efficacy and novel concepts for application. Journal of Nutrition & Intermediary Metabolism. 2016;5(Supplement C):11-22.
161. Zealand FSAN. Nutrient tables for use in Australia (NUTTAB) Australia Food Standards Australia New Zealand 2015 [
162. Press R. The omega-3 fatty acid composition and cost analysis of fish oil supplements: fishing for the best deals: The Ohio State University; 2011.
163. Watters C, Edmonds C, Rosner L, Sloss K, Leung P. A cost analysis of EPA and DHA in fish, supplements and foods. J Nutr Food Sci. 2012;2(8):1-5.
164. Brazionis L, Ting E, Itsiopoulos C, Wilson A, Hodge A. The effects of fish or fish oil on the omega-3 index. Nutrition & Dietetics. 2012;69(1):5-12.

Highlights

- T2DM is a significant health burden with multiple associated comorbidities
- There are limited clinical data supporting omega-3 PUFA supplement use in T2DM
- There is consistent evidence for omega-3 PUFA in reducing elevated triglycerides
- Issues with omega-3 PUFA supplement use include safety, dose, and contraindications

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors. All authors declare no conflict of interest.