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Fat food for a bad mood. Could we treat and prevent depression in Type 2 diabetes by means of ω-3 polyunsaturated fatty acids? A review of the evidence

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Abstract

Aims Evidence strongly suggests that depression is a common complication of Type 2 diabetes mellitus. However, there is considerable room to improve the effectiveness of pharmacological antidepressant agents, as in only 50–60% of the depressed subjects with diabetes does pharmacotherapy lead to remission of depression. The aim of the present paper was to review whether polyunsaturated fatty acids (PUFA) of the ω-3 family could be used for the prevention and treatment of depression in Type 2 diabetes.

Methods MEDLINE database and published reference lists were used to identify studies that examined the associations between ω-3 PUFA and depression. To examine potential side-effects, such as on glycaemic control, studies regarding the use of ω-3 supplements in Type 2 diabetes were also reviewed.

Results Epidemiological and clinical studies suggest that a high intake of ω-3 PUFA protects against the development of depression. There is also some evidence that a low intake of ω-3 is associated with an increased risk of Type 2 diabetes, but the results are less conclusive. Results from randomized controlled trials in non-diabetic subjects with major depression show that eicosapentaenoic acid is an effective adjunct treatment of depression in diabetes, while docosahexanoic acid is not. Moreover, consumption of ω-3 PUFA reduces the risk of cardiovascular disease and may therefore indirectly decrease depression in Type 2 diabetes, via the reduction of cardiovascular complications.

Conclusions Supplementation with ω-3 PUFA, in particular eicosapentaenoic acid, may be a safe and helpful tool to reduce the incidence of depression and to treat depression in Type 2 diabetes. Further studies are now justified to test these hypotheses in patients with Type 2 diabetes.

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Keywords diabetes, depression, omega-3 polyunsaturated fatty acids, phospholipids, metabolic syndrome

Abbreviations AA, arachidonic acid; ALA, alpha-linolenic acid; DHA, docosahexanoic acid; EPA, eicosapentaenoic acid; PUFA, polyunsaturated fatty acids

Introduction

Both Type 2 diabetes and depression are major healthcare problems throughout the world. It is expected that the number of patients with diabetes will increase by 42% in the developed countries from 51 million in 1995 to 72 million in 2025, and

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by 170% in developing countries from 84 to 227 million, with the majority of these patients having Type 2 diabetes [1]. With respect to depression, the Global Burden of Disease Study reported that major depression was the fourth leading cause of worldwide disability in 1990 and predicted that it would be the second leading cause by the year 2020 [2]. Evidence gathered during the past decades strongly suggests that Type 2 diabetes and depression are positively associated. The presence of Type 2 diabetes at least doubles the odds of comorbid depression [3,4]. Depression was also found to be an independent risk factor for Type 2 diabetes in recent studies [5–7], but one study did not confirm this association [8]. Depression in Type 2 diabetes can be effectively treated, but there is still considerable room for improvement. For example, in only 50–60% of the depressed subjects with diabetes does pharmacotherapy lead to remission of depression [9].

The mechanisms that account for the associations between Type 2 diabetes and depression are still poorly understood [10]. Depression may occur secondary to the burden of advanced diabetes and its complications, but also to diabetes-related abnormalities in neurohormonal or neurotransmitter function. The enhanced release of counterregulatory hormones in response to psychological stress in patients with a depressive disorder may be a link between depression and diabetes [11]. Interestingly, it has recently been hypothesized that the high prevalence of depression in chronic diseases such as cardiovascular disease, osteoporosis, multiple sclerosis and diabetes may be related to the impaired fatty acid metabolism that often accompanies these conditions [12,13]. Depression and Type 2 diabetes may both be a result of a relatively low intake of essential polyunsaturated fatty acids (PUFA) of the ω-3 family. This innovative idea was not discussed in any of the reviews regarding diabetes and depression [3,10,11,14,15] and deserves more attention.

In the present paper, we therefore set out to review the evidence regarding the associations between ω-3 PUFA and depression, the main purpose being to discuss whether ω-3 PUFA could aid in the prevention and/or treatment of depression in Type 2 diabetes. Furthermore, we examine possible side-effects of ω-3 PUFA in Type 2 diabetes.

Methods

Medline was used to identify studies published between January 1975 and September 2004 that reported an association between ω-3 fatty acids and depression and between ω-3 fatty acids and insulin resistance, onset of Type 2 diabetes, glycaemic control, dyslipidaemia and cardiovascular disease. We used the words 'omega-3', 'n-3', 'fish' or 'polyunsaturated' for our literature search, each in combination with one of the following terms: 'depression', 'type 2 diabetes', 'diabetes', 'glycaemic', 'adverse effects', 'side-effects', 'dyslipidaemia', 'cardiovascular' or 'review'. Subsequently, the reference lists of these articles were examined to identify additional studies. Studies were limited to articles published in peer-reviewed journals in the English language.

Results

Background information about essential polyunsaturated fatty acids

PUFA are classified according to the position of the first double bond. For example, ω-3 fatty acids have their first double bond between the third and fourth carbon atoms in the chain, whereas ω-6 fatty acids have the first double bond between carbon atoms six and seven. These chemical differences determine important biological properties of PUFA. Examples of the ω-3 class are: alpha-linolenic acid (ALA, 18:3n-3), eicosapentaenoic acid (EPA, 20:5n-3) and docosahexanoic acid (DHA, 22:6n-3). Common ω-6 PUFA are: linoleic acid (LA, 18:2n-6), gamma-linolenic acid (GLA, 18:3n-6) and arachidonic acid (AA, 20:4n-6). ALA, for example, can be found in large amounts in flaxseed and walnuts and in smaller amounts in soybeans and green leafy vegetables. ALA can be converted in the human body to longer chain (LC) PUFA such as EPA and DHA by means of δ-6 and δ-5 desaturase. However, this step is slow and rate limiting, particularly in humans. Therefore, the main source of LC ω-3 PUFA such as EPA and DHA is marine food, in particular fatty fish such as salmon, mackerel and herring. ω-6 PUFAs are found mainly in oils from seeds (e.g. corn, sunflower or safflower) and meat.

In recent decades, Western diets have replaced ω-3 PUFA from fish, nuts and leaves with ω-6 PUFA, which are now widely available as a result of modern industrial production techniques to obtain oil from seeds such as corn and sunflower [16]. Humans originally consumed a diet richer in ω-3 PUFA and low in saturated fatty acids because wild and free-range food animals and also wild plants have much higher contents of ω-3 PUFA than the present day commercial livestock and crop. These dietary changes have resulted in an increase of the ratio of ω-6 to ω-3 PUFA from about 2 : 1 to an estimated present ratio for most western people of about 15 : 1, reflecting a relative deficiency of the ω-3 [16].

Long chain ω-3 PUFA and depression

Observational studies

Seventeen observational, non-randomized studies have described associations between ω-3 PUFA and depression (Table 1). In countries where fish consumption is high, the prevalence of depression is significantly lower [17]. In a population-based adult sample, infrequent fish consumers were found to have a 31% higher likelihood of mild to severe depression than frequent fish consumers and also had a significantly higher risk of having suicidal ideation [18,19]. Mildly depressed subjects had reduced levels (−35%) of DHA in adipose tissue when compared with non-depressed subjects [20]. In the community-dwelling sample of elderly subjects from the Rotterdam Study, subjects with depressive disorder had significantly lower levels of DHA than non-depressed subjects [21]. Among patients with lung cancer, highest intake of ω-3 ALA was significantly

Table 1 Description of observational, non-randomized studies into the associations between ω-3 polyunsaturated fatty acids and depression

Ref.	Authors	Year	*N* subjects	Sex, F/M	Assessment of depression	Study design	Outcomes
17	Hibbeln *et al.*	1998	35 000	?	Structured diagnostic interview	Cross-sectional, multinational	High fish consumption is associated with lower annual prevalence of major depression ($r = -0.84$, $P < 0.005$)
18	Tanskanen *et al.*	2001	1767	?	BDI (self-reported depression)	Cross-sectional	Risk of being depressed was significantly lower among frequent fish consumer compared with less frequent consumers (OR 0.57, CI 0.35, 0.95)
19	Tanskanen *et al.*	2001	3204	?	BDI (self-reported depression)	Cross-sectional	Risk of being depressed was significantly lower among frequent lake-fish consumers compared with infrequent consumers (OR 0.63, CI 0.43, 0.94)
20	Mamalakis *et al.*	2002	247	101 F 146 M	Zung's SDS (self-reported depression)	Cross-sectional	Mildly depressed subjects had significantly lower (−34.6%) adipose tissue DHA levels than non-depressed subjects
21	Tiemeier *et al.*	2003	3884	59% F	CESD (self-reported depression) and diagnostic interview DSM-IV when screened positive	Cross-sectional	Levels of AA were higher and levels of DHA were significantly lower in subjects with a depressive disorder than in non-depressed control subjects, and the ratio of ω-6/ω-3 PUFA was significantly higher in subjects with depressive disorders (effect was probably not secondary to inflammation as the association became stronger with lower CRP concentrations)
22	Suzuki *et al.*	2004	771	215 F 556 M	HADS (self-reported depression)	Cross-sectional	Risk of depression among Japanese patients with newly diagnosed lung cancer was significantly lower in subjects with the highest intake of alpha-linolenic acid (OR 0.58, CI 0.38, 0.87) and also lower in patients with the highest total ω-3 intake (OR 0.55, CI 0.35, 0.88)
23	Jacka *et al.*	2004	755	755 F	Self-reported depression symptoms	Cross-sectional	No significant differences in self-reported dietary intakes of fish oil and seafood were identified between depressed = 0.09 g/day (0.04–0.18) vs. non-depressed = 0.11 g/day (0.05–0.22, $P = 0.3$)
24	Hakkarainen *et al.*	2004	29 133	29 133 M	Self-reported depression; hospital treatment for MDD, death from suicide	Cross-sectional	Dietary intake of ω-3 PUFA showed no association with mood
25	Timonen *et al.*	2004	5689	2721 M 2968 F	HCSL-25 depression subscale (self-report)	Cross-sectional	Risk of depression increased in women who were rare fish eaters: OR 2.6 (CI 1.4, 5.1) compared with regular fish eaters. No effect of fish consumption on depression in men
26	Mamalakis *et al.*	2004	150	150 M	GDS-15 (self-reported depression)	Cross-sectional	Depressed subjects had significantly higher ω-6/ω-3 ratio in adipose tissue, compared with nondepressed subjects. Of the individual ω-3 PUFA, only high alpha-linolenic acid was significantly associated with less depression (B = −0.30, $t = -2.45$, $P < 0.017$).
27	Frasure-Smith	2004	54	20/34	DSM-IV BDI	Cross-sectional case–control	Depressed patients had significantly lower concentrations of total ω-3 PUFA and DHA and higher ratios of AA/DHA, AA/EPA than controls
28	Adams *et al.*	1996	20 depressed		HDRS self-reported depression	Cross-sectional	Significant positive correlation between AA/EPA (ω-6/ω-3) ratio and severity of depression, and lower levels of erytrocyte EPA were associated with more depression
29	Maes *et al.*	1996	36 MDD 14 MinD 24 healthy	25 F/11 M 9 F/5 M 2 F/12 M	DSM III-R criteria	Cross-sectional	MDD subjects had significantly lower total ω-3 PUFA in cholesteryl esters and lower EPA in serum cholesteryl esters and phospholipids than minor depressed subjects and healthy controls

Table 1 *Continued*

Ref.	Authors	Year	*N* subjects	Sex, F/M	Assessment of depression	Study design	Outcomes
30	Edwards *et al*.	1998	10 MDE 14 healthy	8 F/2 M 12 F/2 M	DSM IV criteria, major depressive episode	Cross-sectional	Depressed subjects had lower levels of ω-3 PUFA in their red blood cell membranes. Lower levels of ω-3 PUFA in red cell membrane controls were associated with more depression symptomatology ($r = -0.75$, $P = 0.03$)
31	Peet *et al*.	1998	15 MDE 15 healthy controls	7 F/8 M 7 F/8 M	DSM-IV criteria, major depressive episode	Cross-sectional	Depressive patients showed significant depletions of total ω-3 PUFA, particularly DHAin red cell membranes, compared with healthy controls
32	Maes *et al*.	1999	34 MDD 14 healthy		HDRS Self-reported depression DSM-III-R criteria	Cross-sectional	MDD was associated with an increased ω-6/ω-3 ratio in phospholipids and cholesteryl esters and with lower fractions of EPA and DHA. It is suggested that lowered serum Zink, which is required as a cofactor by desaturase-enzymes, could explain the decreases in long-chain ω-3 PUFA in depression
33	Assies *et al*.	2004	44 patients Recurrent MDD	34 F/10 M	DSM-IV criteria	Cross-sectional	Compared wiith normal reference values, patients with recurrent MDD had decreased levels of docosapentaenoic acid and DHA and higher levels of gamma-linoleic acid. No significant associations between ω-3 PUFA in plasma/erythrocyte membranes and depressive status

HDRS, Hamilton Depression Rating Scale; MADRS, Montgomery–Asberg Depression Rating Scale; BDI, Beck Depression Inventory; HADS, Hospital Anxiety and Depression Scale; SDS, Zung's Self-rating Depression Scale; CESD, Center of Epidemiological Studies Depression Scale; MDD, major depressive disorder; HCSL, Hopkins Symptom Checklist; GDS, Geriatric Depression Scale; DSM, Diagnostic and Statistical Manual of Mental Disorders; DHA, docosahexanoic acid; AA, arachidonic acid; PUFA, polyunsaturated fatty acids; EPA, eicosapentaenoic acid.

associated with a lower risk of depression, while the intake of EPA or DHA was not significantly associated with depression [22]. In contrast, an Australian study found no significant differences between depressed and non-depressed subjects [23]. A recent very large Finnish study [24] also reported no significant association between self-reported dietary intake of ω-3 PUFA and depressed mood, major depressive episodes or suicide. Women who were rare fish eaters were at an increased risk of depression [25], while in men no effect of fish consumption on depression was found. Depressed subjects had higher ω-6/ω-3 PUFA than non-depressed subjects [26]. Moreover, of the ω-3 PUFA, only high intake of ALA was significantly associated with depression, while DHA and EPA were not [26]. In a case–control study in 54 age- and sex-matched pairs, 2 months after an acute coronary syndrome, depressed patients had significantly lower concentrations of total ω-3 and DHA than controls [27].

Severity of depression was positively associated with the AA/EPA ratio and lower levels of erythrocyte EPA correlated with more depression [28]. Maes *et al*. [29] described that subjects with major depressive disorder had significantly lower levels of ω-3 PUFA in cholesteryl esters than subjects with minor depression and healthy control subjects. In a small study of 10 depressed patients and 14 matched healthy control subjects, a diet higher in ω-3 PUFA was associated with less depression [30]. Depressed subjects also had significant depletions of ω-3 PUFA in red cell membranes, which was not due to reduced calorie intake and thus did not simply reflect loss of appetite due to more severe depression [30,31]. In another study [32], major depression was associated with an increased AA/EPA ratio in phospholipids and cholesteryl esters, depletions of EPA and DHA in phospholipids and depletions of ALA, EPA and DHA in cholesteryl esters. Finally, in the study by Assies *et al*. [33], subjects with recurrent major depressive disorder appeared to have decreased levels of DHA and DPA compared with reference values, but ω-3 PUFA did not correlate with depressive status.

Randomized placebo-controlled trials

Five randomized controlled trials have recently tested the effect of ω-3 PUFA in mood disorders (Table 2). Stoll and colleagues [34] conducted a 4-month, double-blind, placebo-controlled study, comparing ω-3 PUFA (9.6 g/day) vs. placebo (olive oil), in addition to usual treatment, in 30 patients with bipolar disorder (which is a mood disorder like major depression). The authors concluded that the ω-3 PUFA patient group had a significantly longer period of remission than the placebo group. In a second study, 20 patients with major depressive disorder participated in a 4-week double-blind trial, comparing placebo with ethyl-EPA, in addition to ongoing antidepressant therapy [35]. Ethyl-EPA had significant beneficial effects on core depressive symptoms such as depressed mood, guilt feelings and worthlessness as well as insomnia. Depressed patients who were treated with ethyl-EPA had a mean reduction of Hamilton depression scale score of 12.4 points, compared with 1.6 in patients receiving placebo. This reduction was clinically meaningful: six of 10 patients receiving ethyl-EPA but only one in 10 receiving placebo achieved a 50% reduction in Hamilton depression score. No clinically relevant side-effects were reported [35]. In a third, larger randomized controlled trial, 70 patients with treatment-resistant depression were randomized on a double-blind basis to placebo or to 1 g/day, 2 g/day or 4 g/day of ethyl-EPA in addition to unchanged antidepressant medication [36]. In that trial, 53% of the patients consuming 1 g/day of ethyl-EPA achieved a statistically significant and clinically relevant reduction of 50% on the Hamilton Depression Rating Scales, compared with 29% of patients in the control group. Only one study investigated the effects of DHA monotherapy (2 g/day) for 6 weeks compared with placebo in 36 subjects with major depression [37]. In that study, no significant effects of DHA were found: 28% in the DHA group and 24% in the placebo group had at least a 50% reduction in the score on the Montgomery–Asberg Depression Rating Scale. A fourth double-blind, placebo-controlled trial compared the effects of menhaden fish oil (rich in both EPA and DHA) in 28 patients with major depressive disorder, in addition to usual treatment [38]. The ω-3 capsules contained 4.4 g EPA/day and 2.2 g DHA/day with 2 mg/g tocopherols added as antioxidants. Results showed that after 8 weeks, subjects in the ω-3 group had significantly lower scores on the Hamilton Rating Scale for Depression compared with those in the placebo group [38].

ω-3 PUFA may also play an important role in the aetiology of schizophrenia [39]. Results from four out of five placebo-controlled, double-blind trials of EPA in the treatment of schizophrenia have given positive findings [40].

In summary, there is good evidence from epidemiological and clinical studies that consumption of ω-3 PUFA is associated with less depression. Moreover, the results from randomized controlled trials suggest that EPA in particular enhances the effect of antidepressants. It is important to emphasize that the relationship between ω-3 PUFA and depression has not been demonstrated in people with Type 2 diabetes. Further studies are thus needed to define whether EPA is an effective antidepressant in subjects with Type 2 diabetes mellitus, as a sole treatment or in addition to standard antidepressants.

ω-3 PUFA and depression: possible physiological mechanisms

Lipids, most of which are phospholipids, constitute about 60% of the solid mass of the brain and are therefore an absolute requirement for normal brain structure and function [36]. In the brain, the main ω-6 fatty acid is AA, while the main ω-3 PUFAs are DHA and EPA. These fatty acids have important roles in membrane fluidity and neuronal signal transduction processes. One mechanism linking ω-3 PUFA intake and depression may be the regulation of serotonergic and adrenergic nervous system function. Lower serotonergic activity has been well established in the pathophysiology of depression. Each step in biogenic amine function, including neurotransmitter

Table 2 Description of randomized trials testing the effects of supplementation with ω-3 polyunsaturated fatty acids on depression in humans

Ref.	Authors	Year	*N* subjects	Sex F/M	Assessment of depression	Study design	Outcomes
34	Stoll *et al.*	1999	30 patients bipolar disorder	20 F/10 M	DSM-IV criteria for bipolar disorder type I or II HDRS	Randomized, double-blind placebo-controlled trial	Four-month trial, comparing fish oil (EPA 6.2 g/day, DHA 3.4 g/day) vs. placebo (olive oil), in addition to usual treatment. Patients in the fish oil group had a significantly longer period of remission than the control group and also had significantly lower depression scores than the control group
35	Nemets *et al.*	2002	20 patients with MDD	17 F/3 M	DSM-IV criteria	Randomized, double-blind placebo-controlled trial	Four-week trial, comparing ethyl-EPA (2 g/day) with placebo as adjunct to antidepressant treatment. Ethyl-EPA supplementation improved depression at weeks 2, 3 and 4. No clinical side-effects of ethyl-EPA were found
36	Peet and Horrobin	2002	70 patients persistent depression	59 F/11 M	HDRS, MADRS, BDI	Randomized, double-blind placebo-controlled trial	Twelve-week dose-ranging trial, comparing 1, 2 or 4 g/day of ethyl-EPA with placebo in addition to ongoing treatment with a standard antidepressant, in subjects with persistent depression. 1 g/day of E-EPA was effective in treating depression, while 2 g/day and 4 g/day did not differ significantly from placebo
37	Marangell *et al.*	2003	36 patients with MDD	28 F/8 M	DSM-IV criteria	Randomized, double-blind placebo-controlled trial	Six-week trial: no effect of DHA monotherapy (2 g/day) vs. placebo in subjects with major depression
38	Su *et al.*	2003	22 patients with MDD	18 F/4 M	DSM-IV criteria	Randomized, double-blind placebo-controlled trial	Eight-week trial, comparing fish oil capsules (total: 4.4 g/day EPA and 2.2 g/day DHA) with placebo (olive oil ethyl esters), in addition to ongoing antidepressant medication. Patients in the fish oil group had significantly greater reduction in depression scores from week 4 to week 8 compared with patients in the placebo group

HDRS, Hamilton Depression Rating Scale; MADRS, Montgomery–Asberg Depression Rating Scale; BDI, Beck Depression Inventory; HADS, Hospital Anxiety and Depression Scale; MDD, major depressive disorder; DSM, Diagnostic and Statistical Manual of Mental Disorders; EPA, eicosapentaenoic acid; DHA, docosahexanoic acid.

synthesis, degradation, release, reuptake, and binding, is potentially influenced by membrane essential fatty acids [12]. An increased intake of ω-3 PUFA such as EPA and DHA increases membrane fluidity [41]. Decreased plasma membrane fluidity was associated with impaired 5-HT transport by endothelial cells, which might account for symptoms of depression [42]. Membrane fatty acids also modulate the activity of tryptophan hydroxylase, the rate-limiting enzyme in 5-HT synthesis, and the brain concentrations of 5-HT and 5-hydroxyindolacetic acid, the major 5-HT metabolite [32,42]. In healthy subjects, ω-3 PUFA (particularly DHA) predicted concentrations of 5-hydroxyindoleacetic acid in cerebrospinal fluid, a metabolite of serotonin and an indicator of brain serotonin turnover [43]. Another major function of ω-3 PUFA involves their role in the metabolism of eicosanoids and cytokines. Eicosanoids derived from the ω-3 PUFA have less (often 10–100-fold less) biological potency for inducing cellular responses than those derived from AA (ω-6 PUFA) and are therefore usually associated with decreased inflammatory responses. Eicosanoids also alter cytokine production and intracellular signalling. ω-3 PUFA consumption was found to decrease secretion of inflammatory cytokines that can provoke symptoms of depression [44].

ω-3 PUFA and glucose metabolism

In a recent review of the role of different types of fat and carbohydrate on the development of Type 2 diabetes, the authors conclude that a lower intake of saturated and trans-fatty acids and a higher intake of polyunsaturated fat and possibly ω-3 PUFA could improve glucose metabolism and insulin resistance [45]. There are several studies that provide support for that conclusion. For example, in the Seven Counties Study and in a Dutch study of 175 elderly men and women, a high intake of fish was associated with a reduced risk of impaired glucose tolerance and Type 2 diabetes [46,47]. After adjustment for age and other risk factors (but not physical activity), the odds ratio for glucose intolerance was 0.47 [95% confidence interval (CI) 0.23, 0.93] for participants consuming any fish (mean intake 24.2 g/day) [47]. In Inuit populations who traditionally have a high consumption of fatty fish and seal meat, the intake of long-chain ω-3 fatty acids was associated with better glucose tolerance [48,49]. In the Nurses Health Study, in 84 204 women aged 34–59 years, with no diabetes or cardiovascular disease or cancer at baseline, the incidence of diabetes was determined in a 14-year follow-up study [50]. Subjects with the highest consumption of ω-3 PUFA had a significantly lower risk for having Type 2 diabetes at 14-year follow-up [relative risk (RR) 0.80, 95% CI 0.67, 0.95]. The results of the Iowa's Women's Health Study showed that self-reported consumption of ω-3 PUFA showed a small and positive association with the incidence of Type 2 diabetes (RR 1.15, 95% CI 1.0, 1.33), but only vegetable fat remained significantly inversely related to diabetes risk, after simultaneous adjustment for other dietary fats [51]. However, in the San Luis Valley Diabetes Study and the Health Professionals Follow-up Study, two large prospective studies, intake of ω-3 PUFA was not associated with fasting plasma insulin concentrations or development of Type 2 diabetes [52,53]. One reason for these findings may be that the median intake of long-chain ω-3 PUFA is usually relatively low in US populations. For example, even in the highest quintile of estimated intake, the median intake of long-chain ω-3 PUFA was 0.57 g/day in the Health Professionals Follow-up Study and 0.39 g/day in the Iowa's Women Health Study, which is very low compared with 14 g daily in some Eskimo populations [48]. However, findings of a recent randomized controlled trial [54] have shown that that fish oil consumption was not associated with insulin sensitivity or insulin secretion in subjects without diabetes.

Finally, recent reviews of studies on the impact of the consumption of ω-3 PUFA on glycaemic control concluded that glucose metabolism is not likely to be adversely affected by the use of ω-3 PUFA supplements [55–57].

ω-3 PUFA and cardiovascular complications of diabetes mellitus

A review of the literature regarding the association between ω-3 PUFA and triglycerides concluded that there is a large body of evidence that consistently demonstrates that both EPA and DHA lower serum triglycerides [58]. Furthermore, a meta-analysis of 17 controlled clinical trials of ω-3 PUFA supplementation showed that supplementation with relatively high doses of ω-3 PUFA (more than 3 g/day) is associated with clinically relevant blood pressure reductions in individuals with untreated hypertension [59]. Epidemiological studies and randomized controlled trials have demonstrated that ω-3 PUFA supplements can reduce cardiac events (e.g. death, non-fatal myocardial infarction and non-fatal stroke) and decrease the progression of arteriosclerosis in patients with coronary artery disease [60]. The American Heart Association therefore recommends that people without documented coronary heart disease should eat a variety of (preferably oily) fish at least twice a week and should include oils and foods rich in ALA. Patients with documented coronary heart disease are advised to consume 1 g/day of ω-3 PUFA [61]. Cardiovascular disease is an important risk factor for depression. While 17–27% of patients with coronary artery disease have major depression, a significantly larger percentage has subsyndromal symptoms of depression [62]. Thus, increased consumption of ω-3 PUFA may have an indirect effect on depression, via the prevention of cardiovascular complications. Long-term consumption of ω-3 PUFA may decrease the risk of cardiovascular complications, and this may have beneficial effects on the health-related quality of life of patients, which in turn may protect against symptoms of depression.

Discussion

We have reviewed the associations between ω-3 PUFA and depression with the main objective of discussing whether ω-3

PUFA could aid in the prevention and/or treatment of depression in Type 2 diabetes. Studies regarding the use of ω-3 supplements in Type 2 diabetes were also reviewed in terms of potential side-effects of these supplements. The results of our review suggest that consumption of ω-3 PUFA has direct beneficial effects on mood. First, we found substantial evidence from epidemiological and clinical studies in non-diabetic subjects showing that a high intake of ω-3 PUFA is associated with lower levels of symptoms of depression. Second, three randomized controlled trials in depressed, non-diabetic subjects recently showed that daily supplementation with ethyl-EPA in addition to standard antidepressants significantly reduced symptoms of depression in many depressed patients. However, one study in depressed, non-diabetic subjects demonstrated that monotherapy with DHA was not effective in reducing depression. Third, results regarding the associations between ω-3 PUFA and cardiovascular disease suggest that there may also be an indirect beneficial effect of increased ω-3 PUFA consumption on depression via the reduction of cardiovascular complications.

These heterogeneous results may to some extent reflect differences in the method of assessment of depression, e.g. self-report vs. standardized psychiatric diagnostic interview, and/or ω-3 fatty acids, e.g. self-reported consumption vs. ω-3 PUFA in erythrocyte membranes, in plasma or adipose tissue. Sample differences may also play a role, e.g. community vs. clinical samples or socio-cultural differences between samples. Prevalence rates were found to be two to three times higher in studies using self-report measures vs. diagnostic interviews, and substantially higher prevalence rates are obtained in clinical samples compared with community samples. As a result, 'depressed subgroups' in studies where self-report instruments are used are more likely to have a less severe form of depression and this may have influenced the results of the studies. The gold standard for a diagnosis of depression is a standardized psychiatric diagnostic interview such as the Structural Clinical Interview Schedule (SCID) or the Composite International Diagnostic Interview (CIDI). Because of the time and the expense required to administer such an interview, epidemiological studies often use self-report measures. All studies mentioned in Tables 1 and 2 used validated self-report questionnaires for the assessment of depression [63].

There is evidence to suggest that a low intake of ω-3 PUFA contributes to depression, but also to the development of dyslipidaemia, insulin resistance, hypertension and cardiovascular disease (well-known components of the metabolic syndrome). This may partly explain why depressed patients (with or without diabetes) are at higher risk of cardiovascular disease and diabetes [64,65] but also of Type 2 diabetes [5–7]. Low consumption of ω-3 PUFA may thus be an underlying factor that precedes both depression and the metabolic syndrome. This may partly explain why depression is common in subjects with diabetes and/or cardiovascular disease. Furthermore, depressed mood was an important predictor of morbidity and mortality in patients with coronary disease, particularly after myocardial infarction, independent of previous cardiac history or coronary artery disease severity [66]. In patients with pre-existing diabetes, depression is an independent risk factor for coronary heart disease and appears to accelerate its presentation [67,68].

With the results of the present review in mind, we consider ω-3 PUFA supplements could prove to be effective in the prevention and treatment of depression in Type 2 diabetes, in addition to psychotherapy and pharmacotherapy. However, randomized controlled trials are needed to test this hypothesis. Although pharmacotherapeutic agents and psychotherapy have both proved to be effective in the treatment of depression in depressed diabetes patients, many patients do not respond to treatment [9]. Diabetes patients with treatment-resistant depression might respond to supplementation with ω-3 PUFA. There is also evidence to suggest that depression is more recurrent in patients with diabetes [69]. Thus, more optimal therapies that improve depression in diabetes are still being sought and we hope that the present review will inspire researchers to initiate new studies that can increase our knowledge of the effects of ω-3 PUFA on depression in Type 2 diabetes.

One advantage of ω-3 PUFA is that they are relatively inexpensive and generally well tolerated by patients. Adverse effects of ω-3 supplementation are mostly related to increased intestinal gas and these effects were more prominent with high doses of fish oil (10 g/day), whereas moderate doses of < 3 g/day were well tolerated [58]. Research into the long-term safety of ω-3 PUFA supplementation has demonstrated that these moderate amounts are safe [58,70,71].

Future directions for research

No studies, to date, have investigated the effects of supplementation with ω-3 PUFA on depression in Type 2 diabetes. It is important to emphasize that the randomized controlled trials that have been conducted to test the effect of EPA on depression in non-diabetic subjects were short-term studies: between 4 and 12 weeks for depression, 16 weeks for bipolar disorder. Depression is often of a chronic nature, i.e. highly recurrent, and was found to be even more recurrent in subjects with diabetes compared with non-diabetic depressed control subjects [69,72]. Moreover, most of the participants in the trials were women, and therefore we agree with Peet and Horrobin [36], who concluded that it is not yet possible to draw conclusions about the effect of EPA on depression in male patients.

To enhance our understanding of the associations between ω-3 PUFA, depression and Type 2 diabetes, large and longer-term studies (> 6 months) in people with Type 2 diabetes are now warranted. We propose a prospective, population-based epidemiological study to determine whether ω-3 PUFA are associated with depression in Type 2 diabetes and whether controlling for PUFA eliminates or decreases the relationship between depression and Type 2 diabetes. Biological studies are needed to increase our knowledge of factors that could be associated with improvement of affect, such as platelet activation,

heart rate variability, inflammation markers, and the immune system [60]. The strongest evidence can be provided by large-scale, placebo-controlled, double-blind trials comparing ω-3 polyunsaturated fatty acids with placebo. These studies should include enough male and female depressed subjects to study the effects of EPA in both men and women. In a group of subjects with Type 2 diabetes, the effects of ω-3 PUFA on the prevention of depression in Type 2 diabetes, either directly and/or via the prevention of cardiovascular complications, could be studied.

Future studies should preferably use a psychiatric diagnostic interview, the gold standard for depression diagnosis, along with a validated self-report instrument such as the Center of Epidemiological Studies Depression Scale (CESD) to measure change in symptoms of depression.

The results of a large number of studies show that there are various risk factors for depression, such as having chronic stress (e.g. due to life events, having a chronic disease such as diabetes, suffering from disabling complications of diabetes, job stress or marital problems), lack of social support and genetic factors. Future studies are needed to compare the relevance of ω-3 PUFA in the face of these other relevant predictors for depression.

One essential methodological issue concerns the use of fish oils. Fish oils have highly variable proportions of DHA and EPA and therefore it is very important that researchers do not use fish oils, but compare the effects of different purified and standardized ω-3 PUFA. EPA may be more effective in the treatment of depression than DHA [36]. As a mechanism, Peet and Horrobin describe that in depression, production of prostaglandins from AA by the cyclooxygenase system has consistently been found to be elevated. Interestingly, EPA but not DHA is an effective substrate for cyclooxygenase and can compete with AA at this point. Moreover, in some phospholipase A2 assays EPA, but not DHA, has been reported to be an effective inhibitor. Researchers should also carefully study the effects of the amount of ω-3 PUFA given to subjects. In the study of Peet and Horrobin [36], 1 g/day was effective while 2 or 4 g/day of ethyl-EPA showed little evidence of efficacy. In contrast, in the study of Nemets and colleagues [35], 2 g/day was effective. We suggest that 1 g/day should be compared with 2 g/day and placebo. This amount of PUFA is sufficient to influence several aspects of Type 2 diabetes, such as hypertriglyceridaemia and cardiovascular complications. The smallest amount of ω-3 PUFA to lower triglycerides is probably 1 g/day of fish oil [58].

Conclusions

In the recent evidence-based nutrition principles and recommendations for the treatment and prevention of diabetes and related complications, it is concluded that increased intake of the ω-3 PUFA eicosapentaenoic acid and docosahexanoic acid can be useful for patients with diabetes, as they lower triglycerides and have cardioprotective benefits [73]. The results of the present review suggest that these ω-3 PUFA may have other beneficial effects for patients with Type 2 diabetes: they may be helpful in the prevention and treatment of depression, a common and burdensome complication of Type 2 diabetes mellitus. Observational studies and randomized, double-blind, placebo-controlled trials are now justified to test these promising hypotheses.

Competing interests

None declared.

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