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


Aim: Depression is common in individuals with diabetes. The present study is the first randomized controlled trial to test the efficacy of ω-3 ethyl-eicosapentaenoic acid (E-EPA) as an add-on to antidepressant medication in the treatment of depression in adults with diabetes mellitus.

Methods: In the VU University Medical Center, we conducted a 12-week, placebo-controlled, double-blind, parallel-group intervention study of E-EPA (1 g/day) versus placebo in 25 diabetes patients meeting DSM-IV criteria for major depressive disorder, who were already using antidepressant medication. The primary outcome was severity of depressive symptoms, assessed by the Montgomery Åsberg Depression Rating Scale (MADRS) at baseline and 12-week follow-up at two-weekly intervals. Blood samples were collected at baseline and at 12-week follow-up to determine EPA levels in erythrocyte membranes. Data were analyzed with ANOVA for repeated measures.

Results: Thirteen participants were randomly assigned to E-EPA; 12 participants were given placebo. At 12-week follow-up, erythrocyte membranes from patients receiving E-EPA contained tripled levels of EPA, while no changes were noted in participants receiving placebo. In both groups, depressive symptoms significantly decreased over time (F=21.14, p<0.001), yet no significant differences were found between those treated with E-EPA versus placebo (F=1.63, p=0.17).

Limitations: Although having sufficient study power, this study had a relatively small sample size. Small effects could not be detected, and dose-dependent effects could not be studied.

Conclusions: No evidence was found for the efficacy of adding E-EPA to antidepressants in reducing depressive symptoms in diabetic patients with co-morbid depression.

© 2010 Elsevier B.V. All rights reserved.

Keywords:
Depressive symptoms
Diabetes mellitus
Eicosapentaenoic acid
Major depressive disorder
Randomized controlled trial

1. Introduction

Depression is a common co-morbid disorder in both type 1 and type 2 diabetes mellitus, and is associated with impaired quality of life (Schram et al., 2009), poor glycemic control (Lustman et al., 2000), increased health care costs...
2. Methods

2.1. Study design and participants

Participants were recruited from the VUMC diabetes outpatient clinic and through advertisements on websites, in newspapers, and patient magazines. Patients were eligible if they were aged 18–75 years, diagnosed with diabetes (type 1 or type 2), and currently being on antidepressant medication for at least two months. Furthermore, participants had to meet the criteria for current Major Depressive Disorder (MDD), determined with the Composite International Diagnostic Interview (Andrews and Peters, 1998). Diabetes was stabilized with mixed tocopherols, and were produced by Minami Nutrition, Belgium. Patients were advised not to chew the capsules. Patients, research nurse and researchers were blinded toward treatment allocation until completion of the data collection.

2.2. Intervention

Patients were randomly allocated to 1 g/day E-EPA or to an equivalent dose of rapeseed oil + medium chain triglycerides (placebo) for 12 weeks. This dosage and duration are in line with other trials of ω-3 on depression (Appleton et al., 2010; Peet and Horrobin, 2002). Both intervention and placebo medication were provided in two soft gelatin capsules per day, stabilized with mixed tocopherols, and were produced by Minami Nutrition, Belgium. Patients were advised not to chew the capsules. Patients, research nurse and researchers were blinded toward treatment allocation until completion of the data collection.

2.3. Measurements

At baseline, demographic, anthropomorphic and health-related characteristics were assessed at the VUMC. Severity of depressive symptoms was assessed by the Dutch version of the 10-item Montgomery Åsberg Depression Rating Scale (MADRS) (Hartog and Goekoop, 1985), with a score range of 0–60. Higher scores reflect more severe depression. The MADRS was administered at seven times during the study by the research nurse. At baseline and in week 12, the MADRS was administered in the VUMC. In week 1, 3, 5, 7, and 9 measurements of the MADRS were obtained per telephone. A validation study showed that the MADRS can be reliably administered by telephone instead of face-to-face (Hermens et al., 2006).

Furthermore, in weeks 1, 3, 5, 7, 9 and 12 the research nurse assessed whether the patient experienced one of the following side effects: abdominal pain, belching, diarrhea, and nausea. Other side effects were also noted. To study concealment, patients were asked whether they thought to be allocated in the E-EPA group or the placebo group in week 12.

2.4. Blood samples

Blood was collected by venipuncture at baseline and in week 12 and analyzed by the National Institute for Public Health and the Environment. EPA levels in erythrocyte phospholipids were measured with a gas chromatograph (GC-3900, Varian Assoc., Palo Alto, USA). The EPA content was expressed as percentage of the total fatty acids present in the chromatogram. Hemoglobin A1c (HbA1c) is an indicator for glycemic control (normal values: 4.3–6.1%) (Jeffcoate, 2004) and was measured by a turbidimetric immuno inhibition method using an auto analyzer (LX20-Pro, Beckman-Coulter, Fullerton, USA).

2.5. Statistical analyses

Sample size was calculated with G*Power 3.0.10 for the within–between interaction in Analysis of Variance (ANOVA). Because we obtained seven repeated measures of depression...
symptom severity using the MADRS, 10 patients had to be included in each treatment arm to detect an effect size of 0.25 (power = 80%, two-sided \( \alpha = 0.05 \), correlation between repeated measures = 0.6 and non-sphericity correction \( \varepsilon = 0.6 \)). Assuming a drop-out rate of 20% we had to include a total of 25 patients.

Intention to treat analyses were conducted. Because MANOVA for repeated measures has low power in small samples (Stevens, 2002), the course of depression symptoms was compared between both groups using ANOVA for repeated measures by testing the significance of the interaction term treatment* time, adjusted for the Greenhouse–Geisser epsilon. Sensitivity analyses were performed by excluding one person who discontinued E-EPA treatment and two participants in the placebo arm who discontinued using antidepressants during the study. The standardized effect size was calculated by dividing the difference of change in MADRS scores (from baseline to 12-week follow-up) between the E-EPA and placebo group by their pooled standard deviations. In all analyses, a 2-sided \( p \) value of <0.05 was used to determine statistical significance. Statistical analyses were performed with SPSS version 16.0 for Windows.

3. Results

3.1. Participant flow

Fig. 1 presents the participant flow during enrollment, randomization and follow-up. Seventy-five patients were willing to participate in the study. Thirty-five patients declined after they had received more detailed information about the study. Furthermore, twelve patients were excluded because they did not meet the inclusion criteria. The 25 eligible persons for the trial were randomly assigned to either the E-EPA group (\( N = 13 \)) and the placebo group (\( N = 12 \)). One patient receiving E-EPA was lost to follow-up. From all other randomized patients, all follow-up measurements were available. One participant discontinued treatment during the trial due to an allergic reaction to E-EPA (see below). Two participants (both from the placebo group) ceased using antidepressants during the trial. Table 1 provides the baseline characteristics of the participants assigned to E-EPA and placebo.

3.2. EPA levels in erythrocyte membrane

From baseline to 12-week follow-up, the mean level of EPA in the erythrocyte membrane tripled in the E-EPA group (from 0.53% (±0.17) to (1.69%;±0.56)), whereas it remained stable in the placebo group (from 0.66% (±0.20) to (0.61%;±0.19)) supporting the integrity of the intervention arms.

3.3. Course of depression symptom severity measured with the MADRS

At baseline, the mean MADRS score was 26.3 (±8.2) in the E-EPA group and 26.4 (±8.7) in the placebo group. At 12-week follow-up, the mean MADRS scores dropped to
who discontinued using antidepressants marginally changed who ceased using E-EPA during the study and two patients (F = 1.63, df = 3.98, p = 0.31). Fig. 2 shows the development of the MADRS score to placebo in patients with diabetes and MDD during 12 weeks. This finding is not likely to be explained by a lack of contrast between the two groups, as we observed trippled levels of EPA in the erythrocyte membranes of diabetic depressed patients, yet significant heterogeneity in study design was noted. Our results are in line with a recent randomized controlled trial in coronary heart disease patients with major depression that did not find evidence that ω-3

| Table 1 Baseline characteristics of the 25 diabetes patients with major depressive disorder. |
|-----------------------------------------------|--------|--------|--------|--------|
| E-EPA (N = 13) | Placebo (N = 12) | p value |
| Age (years) a | Mean 53.1, SD 13.8 | Mean 55.0, SD 8.6 | 0.85 |
| Body Mass Index (kg/m²) | Mean 29.3, SD 5.1 | Mean 29.8, SD 4.8 | 0.80 |
| Waist circumference (cm) a | Mean 99, SD 15 | Mean 100, SD 14 | 0.98 |
| Women | N 8, % 62 | N 5, % 42 | 0.32 |
| Low educational level | N 3, % 23 | N 5, % 42 | 0.41 |
| Working full or part time | N 3, % 23 | N 5, % 42 | 0.41 |
| Living with a partner | N 7, % 54 | N 9, % 75 | 0.41 |
| Current smoker | N 0 | N 3, % 25 | 0.10 |
| Last month fish consumption ≥1 serving/week | N 3, % 23 | N 4, % 33 | 0.67 |
| Diabetes related | | | |
| Type 1 diabetes | N 5, % 38 | N 5, % 42 | 1.00 |
| Type 2 diabetes | N 8, % 62 | N 7, % 58 | 1.00 |
| One or more diabetes complications b | N 5, % 38 | N 2, % 17 | 0.38 |
| Treatment with diet | N 6, % 46 | N 2, % 17 | 0.20 |
| Treatment with oral blood glucose lowering drugs | N 7, % 54 | N 5, % 42 | 0.54 |
| Treatment with insulin | Mean 10.7, SD 3.4 | Mean 10.3, SD 3.0 | 0.97 |
| Duration of diabetes (years) | Mean 11.3, SD 10.7 | Mean 18.1, SD 12.4 | 0.19 |
| HbA1c (%) | Mean 6.9, SD 1.1 | Mean 6.9, SD 1.1 | 0.91 |
| Depression related | | | |
| MADRS score | Mean 26.3, SD 8.2 | Mean 26.4, SD 8.7 | 0.97 |
| Depression severity c | | | |
| Mild | N 1, % 7.7 | N 2, % 16.7 | 0.59 |
| Moderate | N 11, % 84.6 | N 7, % 58.3 | 0.20 |
| Severe | N 1, % 7.7 | N 3, % 25.0 | 0.32 |
| Treatment d | | | |
| Tricyclic antidepressant | N 2, % 17 | N 0, % 0 | 0.48 |
| Selective serotonin reuptake inhibitor | N 9, % 75 | N 10, % 91 | 0.64 |
| Noradrenergic and specific serotonergic antidepressant | N 1, % 8 | N 1, % 9 | 1.00 |

a Mann–Whitney U test. b Having nephropathy, retinopathy, diabetic foot, macrovascular complications, or neuropathy. c Depression severity according to MADRS score: 9–17 mild depression, 18–34 moderate depression, and ≥35 severe depression (Muller et al., 2000). d At 12-week follow-up. Treatment was not specified for 1 person in the E-EPA arm (loss to follow-up) and for 1 person in the placebo arm.

14.0 (±6.9) in the E-EPA group and to 11.6 (±9.1) in the placebo group (standardized effect size favoring placebo d = 0.29). Fig. 2 shows the development of the MADRS score for the E-EPA group and the placebo group over time. Repeated measures analysis revealed a statistically significant time effect: mean MADRS score decreased over time in both groups (F = 21.14, df = 3.98, p < 0.001). However, no significant effect of E-EPA treatment versus placebo over time was found (treatment*time interaction ANOVA F = 1.63, df = 3.98, p = 0.17). Excluding one participant who ceased using E-EPA during the study and two patients who discontinued using antidepressants marginally changed

4. Discussion

In the present randomized, double-blind placebo-controlled study, we found no evidence of a therapeutic effect of 1 g/day E-EPA as an add-on to antidepressant medication compared to placebo in patients with diabetes and MDD during 12 weeks. This finding is not likely to be explained by a lack of contrast between the two groups, as we observed trippled levels of EPA in the erythrocyte membranes of participants in the intervention group and no change in the placebo group.

In a recent meta-analysis, Appleton et al. (2010) concluded that ω-3 PUFAs showed antidepressant efficacy in non-diabetic depressed patients, yet significant heterogeneity in study design was noted. Our results are in line with a recent randomized controlled trial in coronary heart disease patients with major depression that did not find evidence that ω-3

![Fig. 2. Development of the MADRS score over time for the E-EPA (N = 12) and placebo group (N = 12). Error bars indicate 95% confidence interval. No significant treatment*time interaction (F = 1.63, df = 3.98, p = 0.17).](image-url)
PUFAs augmentation of sertraline was superior to sertraline plus placebo for the treatment of depression (Carney et al., 2009). However, there are clear differences between our study and the other studies in sample characteristics (diabetes patients vs. other patient groups) and the ω-3 PUFAs provided. Although EPA showed more promising results on depression than DHA monotherapy (Pouwer et al., 2005), it might be that a specific ratio of DHA and EPA is more effective.

Strengths of our study included the small number of loss to follow-up, the large number of follow-up measurements, and its double-blind, placebo-controlled design. However, the study is also subject to some limitations. Information about fish consumption was only assessed at baseline. Yet, there was no indication that the placebo group increased fish consumption as the level of EPA did not increase. Also, we had a heterogeneous sample of patients with respect to type of diabetes and antidepressant use. In the case that E-EPA would be more effective in either type of diabetes or as add-on to a specific type of antidepressant, our study sample was too small to detect these effects. Furthermore, the dose of fish oil in our study (1 g/day) and duration might not have been adequate for patients with diabetes. Although we could not find studies about the effect of the placebo (rapeseed oil) on mood, we cannot fully exclude the possibility that rapeseed oil has some beneficial effect on mood. Finally, although we assessed the power of our study rigorously, we are aware that our sample size is smaller than most other randomized controlled trials. Therefore, the results may be more sensitive for chance fluctuations and warrant future replication studies.

Clinical trials registration


Role of funding source

This study was supported by a grant from the Dutch Diabetes Research Foundation (grant number: 2004.11.002). This study was also financially supported by Minami Nutrition, Belgium, who freely provided both E-EPA supplements and placebo. We had complete freedom to direct analysis and reporting, without editorial direction or censorship from sponsors.

Conflict of interest

M. Bot, J. Assies, E.H.J.M. Jansen, F.J. Snoek, M. Diamant, A.T.F. Beekman, and P. de Jonge report no financial or other relationship relevant to the subject of this article. F. Pouwer received financial support and verum and placebo supplements from Minami Nutrition, Edegem, Belgium. This study was performed without editorial direction or censorship from sponsors.

Part of this paper was presented as an abstract at the scientific spring meeting of the Psychosocial Aspects of Diabetes Study Group; April 24–26, 2009, Dubrovnik, Croatia; and at the annual meeting of the European Diabetes Epidemiology Group; May 9–12, 2009, Wageningen, The Netherlands.

Acknowledgement

The authors would like to express their gratitude to the patients who participated in the randomized controlled trial.

References


