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Omega-3 fatty acids in major depressive disorder A preliminary double-blind, placebo-controlled trial

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Abstract

Patients with depression have been extensively reported to be associated with the abnormality of omega-3 polyunsaturated fatty acids (PUFAs), including significantly low eicosapentaenoic acid and docosahexaenoic acid in cell tissue contents (red blood cell membrane, plasma, etc.) and dietary intake. However, more evidence is needed to support its relation. In this study, we conducted an 8-week, double-blind, placebo-controlled trial, comparing omega-3 PUFAs (9.6 g/day) with placebo, on the top of the usual treatment, in 28 patients with major depressive disorder. Patients in the omega-3 PUFA group had a significantly decreased score on the 21-item Hamilton Rating Scale for Depression than those in the placebo group ($P<0.001$). From the preliminary findings in this study, omega-3 PUFAs could improve the short-term course of illness and were well tolerated in patients with major depressive disorder.

Keywords: Omega-3 polyunsaturated fatty acids; Major depressive disorder; Taiwan; Fish intake; Nutrition therapy; Diet

1. Introduction

WHO (World Health Organization) estimates that major depressive disorder will become the second leading cause of disability worldwide by 2020, which is only second to ischemic heart disease, and the leading cause in developing regions (Murray and Lopez, 1997). The annual prevalence of major depressive disorder shows nearly a 60-fold variation across countries (Weissman et al., 1996). It is similar to the cross-national difference in mortality from coronary artery disease, which might suggest that similar dietary risk factors could be important (Hibbeln, 1998). Based on the epidemiological data, societies with a high consumption of fish, which contain more omega-3 PUFAs, appear to have a lower prevalence of major depressive disorder (Hibbeln, 1998; Tanskanen et al., 2001).

Polyunsaturated fatty acids (PUFAs) have been reported recently to be effective in treatment of various psychiatric disorders. A mixture of eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) in a high dosage was effective in a case of a pregnant schizophrenic woman (Su et al., 2001). EPA has been reported to have positive effects for patients with schizophrenia in several studies (Peet et al., 2001; Peet and Horrobin, 2002a; Emsley et al., 2002). However, one study on EPA (Fenton et al., 2001) and the arm of DHA in another study (Peet et al., 2001) showed no effect. In their preliminary trial, Stoll et al. (1999) concluded that omega-3 PUFAs could improve the 4-month course of illness in patients with bipolar disorder. We further found, from Stoll's data, that omega-3 PUFAs seem to prevent depression but not mania among the patients with bipolar disorder (Su et al., 2000).

The PUFAs are classified mainly into omega-3 (or $n-3$) and omega-6 (or $n-6$) groups, of which the parent

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essential fatty acid is α-linolenic acid (ALA; C18:3*n*−3) and linoleic acid (LA; C18:2*n*−6). As we know that cerebral cell membranes are composed of certain PUFAs, which cannot be synthesized and must be obtained from the diet. Therefore, the abnormalities of PUFA composition in cell membranes can alter membrane microstructure, and then result in abnormal signal transduction and immunological regulation. There are studies revealing abnormalities in PUFA composition may vary in different major psychiatric disorders (Chiu et al., 2003a). In depressive disorders, the major abnormality is seen as lower erythrocyte membrane omega-3 PUFAs, including significant decrease of EPA and DHA levels (Adams et al., 1996; Maes et al., 1996, 1999; Edwards et al., 1998; Peet et al., 1998). EPA monotherapy was then reported its antidepressant effect in a case of treatment-resistant major depressive disorder (Puri et al., 2002). Benefits of omega-3 PUFAs augmentation with antidepressant medications were also reported in the recent studies (Nemets et al., 2002; Peet and Horrobin, 2002b), though the dietary frequency and erythrocyte omega-3 fatty acid composition were not measured then. In addition, we suggest that the patients in the placebo group should also receive tertiary butylhydroquinone and tocopherols as they did in the omega-3 fatty acids group, to avoid the possible therapeutic effect from these compound as a confounding factor (Su et al., 2000).

To provide more evidence to uncover the relation between pathogenesis in major depression and omega-3 PUFAs and then establish an efficient treatment for it, we conducted an 8-week, preliminary double-blind, placebo-controlled trial. Our hypothesis is that giving a high dosage of DHA and EPA is effective when treating depressive symptoms.

2. Method

Participants were outpatients, ranging from 18 to 60 years old, referred by Taipei Medical University–Wan Fang Hospital. They were enrolled if they met the following criteria: (1) they were diagnosed with DSM-IV as major depressive disorder and had no other comorbid Axis I or Axis II psychiatric disorders, (2) they were rated over 18 on the 21-item Hamilton Rating Scale for Depression (HRSD), (3) there was no change in their medications or psychotherapy 4 weeks before the enrollment, (4) they had to be physically healthy under comprehensive evaluations of medical history, physical examination and laboratory tests, and (5) they were competent to understand the study and were given written informed consents. The Institutional Review Board of Taipei Medical University–Wan Fang Hospital has approved this research before it underwent.

Before randomized grouping, all the qualified participants received single-blind placebo capsules for 1 week (in Week −1). Those who showed a decrease of 20% or more in HRSD score (placebo responders) were excluded. After placebo-lead-in phase, participants were randomized to receive five identical gelatin capsules containing either omega-3 fatty acids or placebo (olive oil ethyl esters) twice daily in Week 0. Each capsule of omega-3 fatty acid concentrate contains 440 mg of eicosapentanoic acid (C20:5ω3) and 220 mg of docosahexanoic acid (C22:6ω3). All capsules, either ω3 fatty acids or placebo, were vacuumed to deodorize, amended by blending with orange flavor, and supplemented with *tert*.-butylhydroquinone, 0.2 mg/g, and tocopherols, 2 mg/g, as antioxidants. The omega-3 fatty acid used in this study is made of the body oil of menhaden fishes, produced by China Chemical and Pharmaceutical Company in Taipei, Taiwan.

We performed the 21-item HRSD and the brief adverse-effect rating in Weeks −1 (placebo-lead-in phase), 0 (baseline), 2, 4, 6, and 8. We applied dietary frequency rating scales, recorded food diary and took the blood samples for RBC omega-3 PUFA analysis in Weeks −1 and 8. Participants, receiving medications when entering this study, continued the same medications in constant dosages whether they were in the therapeutic range. The only medication allowed for addition were oral sedatives/hypnotics (lorazepam or zolpidem) for intolerable anxiety and insomnia. Participants on any antipsychotics or mood stabilizers are excluded in this study.

Data were analyzed with the SPSS statistical software. The effect of the addition of omega-3 PUFAs was examined by repeated-measures analysis of variance with time as repeated factor, treatment (placebo or omega-3 PUFAs) as independent factor, and clinical data (age, onset of age, body mass index, duration of current episode, numbers of previous depressive episodes, duration of antidepressant treatment before enrollment, dose of antidepressants at inclusion, and RBC omega-3 PUFA compositions) as covariates. Treatment differences in the score of severity were assessed by Mann–Whitney test (Wilcoxon signed rank test). The difference is considered statistically significant if P value is equal to or greater than 0.05.

3. Results

Thirty-two patients were enrolled in this study, but four were excluded at the stage of placebo lead-in. Twenty-eight patients were randomized to either omega-3 PUFAs ($n=14$) or placebo ($n=14$), while 22 patients (12 of the omega-3 group and 10 of the placebo group) completed this 8-week study. Six patients dropped out prior to Week 8. Of the six, two received omega-3 (one was lost in follow-up and the other was lost due to noncompliance), and four received placebo (three were lost in follow-up and the other was lost due to noncompliance). Table 1 shows no statistical differences in demographic, clinical characteristics or omega-3 PUFA composition in RBC. There was one participant in each group, who was free

Table 1
Demographic and clinical characteristics of patients who received omega-3 PUFA treatment (ω3) or placebo

	ω3[a] (n=12)	Placebo[a] (n=10)	P
Age (years)	35.2±11.6	42.3±10.7	0.25
Sex (no. F:M)	10:2	8:2	0.92
Body mass index	21.4±4.6	23.0±2.7	0.10
Age of onset (years)	30.6±10.7	35.1±8.6	0.31
Duration of current episode (weeks)	22.8±15.5	21.5±13.0	0.97
No. of previous depressive episodes	2.5±1.0	2.3±1.2	0.54
Duration of antidepressant treatment before enrollment	9.3±4.9	10.4±7.5	0.87
Dose of antidepressants while being enrolled (fluoxetine equivalent)[b]	23.0±8.2	17.1±4.9	0.19
RBC omega-3 PUFA compositions			
EPA	3.0±3.2	4.4±3.4	0.46
DHA	2.9±2.8	2.2±2.0	0.78
HRSD score[c]			
Pretreatment (week 0)	22.5±3.9	22.1±3.9	0.77
Posttreatment (week 8)	8.9±3.7	15.7±3.2	0.001

[a] Mean±SD unless otherwise specified. Mann–Whitney U-test, except where otherwise noted.
[b] The antidepressant doses are converted into fluoxetine equivalents according to practice guideline by American Psychiatric Association (2000).
[c] HRSD, Hamilton Rating Scale for Depression.

from medications. The dosages of fluvoxamine (n=2, 1 in omega-3 group), trazodone (n=2, 1 in omega-3 group), or moclobemide (n=5, 3 in omega-3 group) used were converted into fluoxetine (n=11, 6 in omega-3 group) equivalents (American Psychiatric Association, 2000), and there were no difference in the doses of antidepressant use. There is no difference in the dietary frequency on fish intake or total unsaturated fatty acids in 24-h dietary recall and 3-day dietary record of participants in both groups as well.

As shown in Fig. 1, participants in omega-3 PUFA group had significant differences in the HRSD score from the fourth week after treatment. The percentage of reducing HRSD total scores in omega-3 PUFA group was significantly much greater than that of in placebo group. The difference was unrelated to the demographic and clinical covariates. One participant (in omega-3 PUFA group) had mild excitement during Weeks 1 and 2, another one (in omega-3 PUFA group) had mild diarrhea during Weeks 2 and 4, and one (in placebo group) had insomnia during Weeks 2 and 4. None of them did have any major adverse effects, such as abnormal bleeding time.

The effect of omega-3 PUFA and placebo supplement on RBC fatty acid composition were also examined. The RBC fatty acid composition of both pre- and post-treatment was available only for seven participants in omega-3 PUFA group and six participants in the control group. The mean post-treatment value±S.D. of DHA (5.8±3.4, n=7) of patients in omega-3 PUFA group was significantly much higher (P=0.03) than that of (2.4±2.6, n=7) in the period of pre-treatment. The mean post-treatment value±S.D. of EPA (2.7±2.5, n=7) of patients in omega-3 PUFA group is not significantly different (P=0.87) from that of in the period of pre-treatment (2.5±3.1, n=7). There is no significant difference between pre- and post-treatment levels of DHA or EPA for participants in placebo group (n=6).

4. Discussion

Although this study is limited by its small sample size and the possible confounding factor of uncontrolled combined medications, the findings do provide a rationale perspective to conduct further large-scale trials of omega-3 PUFAs monotherapy.

It is interesting to notice that EPA, but not DHA, improves schizophrenic symptoms (Peet et al., 2001; Peet and Horrobin, 2002a; Emsley et al., 2002) and major depressive disorder (Marangell et al., 2000; Nemets et al., 2002; Peet and Horrobin, 2002b) as well. Furthermore, EPA, but not DHA, has been reported to be an effective substrate for cyclooxygenase and inhibitor for phosphlipase A2, which may play an important role in psychophysiology of depression (Peet and Horrobin, 2002b). However, Maes et al. (1996, 1999) reported that patients with major depression had a lower level of EPA and total $n-3$ PUFAs and elevated ratio of ecosapentaenoic acid (EPA; 20:5$n-3$)/docosahexaenoic acid (DHA; 22:6$n-3$) in serum cholesteryl esters and phospholipids. Similar findings were revealed in terms of fatty acid compositions on erythrocyte membrane (Adams et al., 1996; Edwards et al., 1998; Peet et al., 1998). These results implied that the deficiency of DHA is more prominent than that of EPA. Furthermore, EPA exists with a very small quantity in neuronal membranes, while DHA is a major constituent of neuronal membrane phospholipid, and it plays an important role in functioning of neurotransmitters, including serotonin (Hibbeln and Salem, 1995, Hibbeln et al., 1998). In the frontal cortex, rats with low brain concentrations of DHA were found to have a 44% increase in serotonin-2A receptor number (Delion et al., 1994), which is a potential marker of reduced serotonin function. In this study, it is rational to use combination for omega-3 fatty acid treatment. However, it needs further investigation to see if EPA is more effective than DHA or EPA/DHA combination when using as antidepressants.

With the previous findings of abnormal PUFA levels in depressive patients (Adams et al., 1996; Maes et al., 1996, 1999; Edwards et al., 1998; Peet et al., 1998) and epidemiological findings (Hibbeln, 1998; Tanskanen et al., 2001), hopefully, the positive outcome of our study would

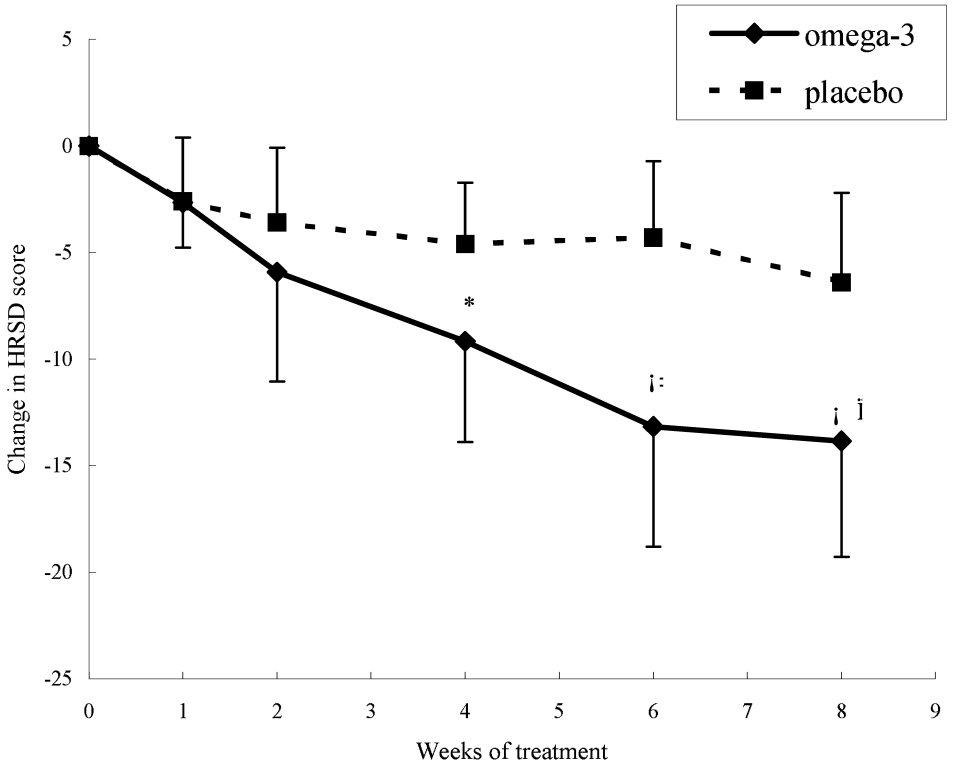

Fig. 1. Evolution of the 21-item Hamilton Rating Scale for Depression (HAM-D) score in depressive patients treated additionally with omega-3 PUFAs or placebo during the trial period. The significant differences were noted at week 4 ($z=-2.04$, $P=0.0043$)*, 6 ($z=-3.20$, $P=0.001$)[§] and week 8 ($z=-3.34$, $P=0.001$)[†] by Mann–Whitney U-test. The rate of reduction in HRSD total scores in omega-3 PUFA group is significantly greater than that in placebo group ($F=6.62$, $P=0.024$) by repeated-measures analysis of variance.

provide more evidences to support phospholipid hypothesis in depression (Horrobin and Bennett, 1999).

The mechanism of omega-3 PUFA augmentation effect on depression is still unknown. One of the hypotheses is that omega-3 PUFAs can normalize the altered membrane microstructure and neurotransmission in patients with depression. For example, the changes in brain fatty acid concentration, induced by chronic dietary omega-3 fatty acid deficiency alter serotonergic and dopaminergic neurotransmission (Delion et al., 1994) and induces an increase in 5-HT_2 and decrease in D_2 frontal cortex receptor density (Delion et al., 1996). The upregulation of 5-$HT_{2A/C}$ is thought to play a role in the pathophysiology of depression (Maes and Meltzer, 1995). Biochemical studies have shown that omega-3 PUFAs increased CSF 5-HIAA concentrations and somatotrophin release (Nizzo et al., 1978), which is usually seen with the improvement of depressive symptoms. The other hypothesis is that omega-3 PUFAs play an important role in the mechanism of mood stabilization by targeting parts of the 'arachidonic acid cascade' (Rapoport and Bosetti, 2002).

Although there is not much incentive for pharmaceutical companies to support a research of a non-patentable compound, such as omega-3 PUFAs, further data collection are crucial for both humanistic and scientific reasons because omega-3 PUFAs are favorable for the safety and lack of teratogenicity. Hopefully, the clinical trial of omega-3 PUFAs may help shed some light on the understanding of the disease pathophysiology of major depressive disorder and may benefit special psychiatric populations, such as pregnant and lactating women (Su et al., 2001; Chiu et al., 2003b).

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