



Effects of eicosapentaenoic acid and fluoxetine on plasma cortisol, serum interleukin-1beta and interleukin-6 concentrations in patients with major depressive disorder

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ABSTRACT

Treatment studies have suggested that omega-3 fatty acids (ω -3 FAs) as monotherapy or adjunctive treatment have therapeutic effects in depression. The authors recently reported a study in which fluoxetine and eicosapentaenoic acid (EPA), which is an omega-3 fatty acid, appeared to be equally effective in controlling depressive symptoms and their combination was superior to either of them alone. Regulation of hypothalamus–pituitary–adrenal (HPA) axis activity and reduction of inflammatory cytokines are among several biological mechanisms which potentially explain the impact of ω -3 FAs on depression. In the present study, plasma cortisol and serum interleukin-1beta (IL-1 β) and interleukin-6 (IL-6) were measured in patients with a diagnosis of major depressive disorder (MDD) participating in aforementioned trial to determine the effects of 8 weeks of treatment of depression with 1000 mg EPA alone or in combination with 20 mg fluoxetine on HPA axis activity and inflammatory cytokine production and compare the changes in these variables with those of treating with 20 mg fluoxetine alone. Forty-two patients were included in analysis. Two-way repeated measures analysis of variance (ANOVA) showed that plasma cortisol decreased significantly after 8 weeks of intervention without significant difference among the groups. There was no interaction between group and response to treatment over time in the cortisol response based on three-way ANOVA. Serum concentrations of IL-1 β and IL-6 did not change significantly after intervention. In conclusion, EPA alone or in combination with fluoxetine, as well as fluoxetine alone decreased serum cortisol after 8 weeks of treatment in patients with major depression disorder (MDD) without any significant effect of response to treatment. Serum IL-1 β and IL-6 did not change significantly after intervention. These findings suggest that EPA may exert its therapeutic effects through reduction of cortisol.

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1. Introduction

Treatment studies have suggested that omega-3 fatty acids (ω -3 FAs) as monotherapy or adjunctive treatment have therapeutic effects in depression (Freeman et al., 2006; Lin and Su, 2007). The authors recently reported a study in which fluoxetine and eicosapentaenoic acid (EPA), which is an omega-3 fatty acid, appeared to be equally effective in controlling depressive symptoms (Jazayeri et al., 2008). Their combination was superior to either of them alone. It was

speculated that EPA may exert its therapeutic effects through reduction of hyperactivity of hypothalamus–pituitary–adrenal (HPA)-axis and production of inflammatory cytokines. Many previous studies have shown that antidepressants can normalise overactivity of HPA axis (Nikisch et al., 2005; Himmerich et al., 2006, 2007; Schule et al., 2009); in addition, it has been reported that most antidepressants have anti-inflammatory effects (Maes, 2008). Regulation of HPA-axis activity and reduction of inflammatory cytokines are among several biological mechanisms which potentially explain the impact of ω -3 FAs on depression (Freeman et al., 2006). Information regarding the effects of ω -3 FAs on HPA-axis activity and inflammatory cytokines in patients with major depressive disorder (MDD) is limited. In the present study, plasma cortisol and serum interleukin-1beta (IL-1 β) and interleukin-6 (IL-6) were measured in the subjects participating in the aforementioned trial (Jazayeri et al., 2008) to determine the effects of 8 weeks of

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Table 1
Demographic and disease characteristics of patients in study groups at the beginning.

	Fluoxetine (n = 14)	EPA ^a (n = 14)	Fluoxetine + EPA (n = 14)	P-value
Age (year)	37.00 ± 8.49	34.00 ± 8.46	33.86 ± 10.85	0.61 ^b
Gender (number, %)				
Male	4 (29%)	4 (29%)	6 (33%)	0.77 ^c
Female	10 (71%)	10 (71%)	8 (57%)	
BMI ^d (kg/m ²)	29.61 ± 6.16	26.61 ± 6.19	24.27 ± 7.30	0.11 ^b
Number of previous episodes	0.36 ± 1.08	0.21 ± 0.58	1.07 ± 2.61	0.36 ^b
Duration of recent episode (week)	14.00 ± 8.46	12.50 ± 8.72	9.64 ± 6.82	0.36 ^b
Age of onset (year)	34.64 ± 8.08	32.00 ± 8.87	29.14 ± 7.69	0.22 ^b
Baseline 24-HDRS ^e (score)	29.00 ± 6.93	29.29 ± 4.84	30.86 ± 5.41	0.66 ^b

^a Eicosapentaenoic acid.^b Analysis of variance.^c Fisher's exact test^d Body Mass Index.^e 24-item Hamilton Depression Rating Scale.

treatment of depression with EPA alone and in combination with fluoxetine on HPA-axis activity and inflammatory cytokine production and compare the change in these variables with those of treating with fluoxetine alone. The hypothesis of this study was that EPA as well as fluoxetine could reduce plasma cortisol and serum inflammatory cytokines and their combination would be more effective than either of them alone.

2. Methods

2.1. Patients

Eligible patients were referred from Roozbeh Hospital, Tehran, Iran to participate in the study. The study was explained to them and written informed consent was obtained. The protocol was prepared in accordance with the Helsinki declaration and approved by the Ethical Committee, Research Department of Tehran University of Medical Sciences. The patients were 20–59 years of age and met the Diagnostic and Statistical Manual of Mental Disorders, fourth edition (DSM-IV) criteria for MDD. Their scores on the 17-item Hamilton Depression Rating Scale (HDRS) were greater than 15 and they were free of medication for at least 6 weeks. The exclusion criteria were psychotic symptoms, co-morbid psychiatric disorders except for dysthymia and any anxiety disorder, medical illness established by medical history, physical examination or laboratory tests, suicidal thoughts, substance abuse, pregnancy and lactation, consumption of ω-3 FAs supplements in the previous year, dietary intake of more than one serving of fish per week and use of non-steroid anti-inflammatory drugs (NSAIDs) and other drugs two weeks before or during intervention.

2.2. Medication

Soft gels of 550 mg ethyl-EPA (500 mg pure EPA and 11 mg vitamin E as antioxidant) were supplied by Minami Nutrition, Belgium. The placebo soft gels, identical to the ethyl-EPA soft gels in appearance, contained 550 mg rapeseed oil and 11 mg vitamin E. Fluoxetine was provided as 20 mg capsules and its placebo contained starch and avicel.

2.3. Trial design

The trial was originally designed to compare therapeutic effects of EPA, fluoxetine and their combination in patients with major depressive disorder (Jazayeri et al., 2008). Sample size was calculated based on a final difference among the groups of >5 on the HDRS, $\alpha = 0.05$ and $\beta = 0.2$. In the present study, changes in plasma cortisol and serum IL-1 β and IL-6 were determined. Patients were randomly allocated into three groups according to pre-arranged balanced block randomisation to receive daily either two ethyl-EPA soft gels (1000 mg EPA) plus fluoxetine placebo, or one 20 mg fluoxetine capsule plus ethyl-EPA placebo or two ethyl-EPA soft gels (1000 mg EPA) plus one 20 mg fluoxetine capsule for 8 weeks. The study was double blind and because the fluoxetine capsule and EPA soft gel were not identical we used a double-dummy technique to blind patients and the physician who assessed them. The patients underwent psychiatric assessment by means of 24 item Hamilton Depression Rating Scale (24-HDRS) at baseline and at week 8. Fasting blood samples were obtained at 8:00 AM at baseline and after 8 weeks of intervention. Compliance was estimated by counting pills. Patients were considered compliant if they consumed more than 90% of the medication. Response to treatment was defined as $\geq 50\%$ reduction in baseline HDRS.

2.4. Laboratory methods

Plasma and serum were isolated and frozen at -70 °C until analysed. Cortisol was measured by radioimmunoassay with the commercially available kits (Immunotech, France). Serum concentrations of IL-1 β and IL-6 were determined by enzyme-linked immunosorbent assay (ELISA). ELISA kits were obtained from Bender Med system, Austria. Specimens were coded so the operator was blinded to treatment and other identifying characteristics. All samples were analysed in the same batch. The intra-assay coefficient of variation for cortisol was 5.8% and the sensitivity of cortisol kit was 10 nM/L. The intra-assay coefficients of variation for IL-1 β and IL-6 were 5.1% and 3.4%, respectively. The sensitivity for IL-1 β and IL-6 were 0.32 and 0.92 pg/ml respectively.

2.5. Statistical analysis

Kolmogorov–Smirnov test was used to verify normal distribution. Analyses of data were performed using SPSS version 13.5. Two-way analysis of variance with repeated measures (time as within subject and medication as between subject factor) was used to compare cytokines and cortisol levels before and after 8 weeks of treatment across treatment groups. Three-way analysis of variance (time as within subject and medication and response to treatment as between subject factor) was also performed to adjust for the effect of response to treatment. The tests were two-sided and *P*-value less than 0.05 was considered significant.

3. Results

Forty-two out of the sixty patients completed 8 weeks of the study and had blood measurements made at baseline and after 8 weeks of intervention. In the fluoxetine group one patient withdrew because of drowsiness after taking the medications, one was lost due to non-compliance and four were lost to follow-up. In the EPA group one patient was excluded due to developing suicidal ideation, one due to non-compliance, one because of steatorrhea after week 6 and three were lost to follow-up. In the group receiving EPA and fluoxetine combination one patient dropped out due to steatorrhea, one because of skin rash, one due to non-compliance, one was lost to follow-up, one refused to give blood after intervention and one used NSAID before giving blood at week 8. As shown in Table 1, there were

Table 2
Plasma cortisol and serum IL-1 β and IL-6 concentrations before and after 8 weeks of treatment of depression^a.

Parameter	Study group	Week 0	Week 8	Time		Time and group interaction	
				F	P-value	F	P-value
Cortisol (mM/L)	Fluoxetine	127.43 ± 42.54	113.71 ± 39.28	8.415	0.006 ^c	0.506	0.607
	EPA ^b	150.50 ± 59.08	129.71 ± 47.59				
	Fluoxetine + EPA	134.07 ± 49.76	101.57 ± 40.42				
IL-1 β (pg/mL)	Fluoxetine	4.21 ± 2.97	4.73 ± 3.37	0.759	0.389	1.301	0.284
	EPA	6.12 ± 3.56	5.31 ± 5.22				
	Fluoxetine + EPA	2.55 ± 2.84	5.03 ± 4.01				
IL-6 (pg/mL)	Fluoxetine	2.12 ± 2.34	1.83 ± 1.51	0.011	0.917	0.036	0.965
	EPA	2.11 ± 1.44	2.38 ± 2.21				
	Fluoxetine + EPA	4.21 ± 8.37	4.56 ± 7.28				

^a Two-way analysis of variance with repeated measures.^b Eicosapentaenoic acid.^c P-value is significant.

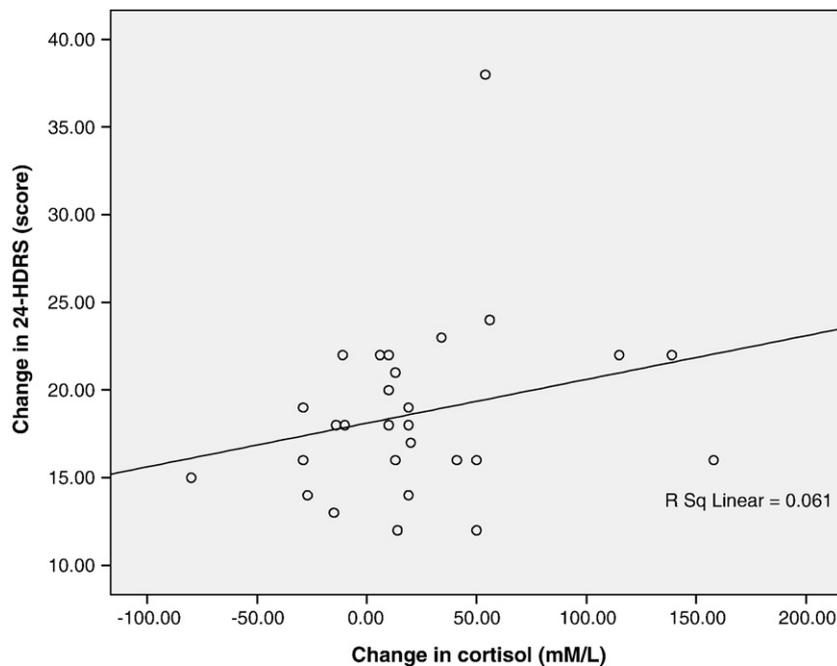


Fig. 1. Scatterplot of the change in cortisol (= T0weeks–T8) and the change in 24-HDRS (= T0weeks–T8) in 28 depressed patients who had response to treatment after 8 weeks of treatment with fluoxetine, eicosapentaenoic acid and EPA + fluoxetine. Pearson's correlation was 0.25 and *P*-value was 0.21. (24-HDRS: 24-item Hamilton Depression Rating Scale).

no significant differences in severity of depression, age of onset, duration of current episode, number of previous episodes, body mass index, gender and age among groups at the beginning.

Two-way repeated-measures analysis of variance (ANOVA) showed that plasma cortisol decreased significantly after 8 weeks of intervention without significant difference among groups (Table 2). As three-way ANOVA showed that there was no interaction between group and response to treatment over time in cortisol response ($F_{2,36}=0.675$, $P=0.52$), the decrease in plasma cortisol was not significantly different between responders and non-responders in each group. No association was found between 24-HDRS reduction and decline of cortisol secretion after 8 weeks of treatment in responders (Fig. 1). The change in HDRS score was 18.7 ± 5.1 in responders. Serum concentrations of IL-1 β and IL-6 did not change significantly after intervention based on repeated-measure ANOVA (Table 2). There was no interaction between group and response to treatment over time in IL-1 β and IL-6 response (P -value > 0.05). *Posteriori* power was calculated for all results. Maximum observed power was 0.80.

4. Discussion

Plasma cortisol concentration decreased significantly after 8 weeks in the three groups. Most previous studies have shown that treatment of depression with antidepressants can normalise hyperactivity of HPA axis or decrease plasma cortisol (Nikisch et al., 2005; Himmerich et al., 2006, 2007; Schule et al., 2009), although some findings are inconsistent (Kauffman et al., 2005; Marques-Deak et al., 2007). Certain antidepressants can enhance glucocorticoid receptor function (Pace et al., 2007). To the authors' knowledge, this is the first report of ω -3 FA effect on cortisol levels in patients with MDD, but it has been shown that after 3 weeks of a diet supplemented with fish oil, which is a rich source of ω -3 FAs, the stimulation by mental stress of plasma cortisol concentrations, was significantly blunted in healthy men (Delarue et al., 2003). In another study, 3–4 weeks of oral fish oil supplementation significantly blunted cortisol plasma levels in healthy subjects submitted to intravenous lipopolysaccharide challenge (Michaeli et al., 2007). A study in rats has shown that EPA can significantly reduce corticosterone concentrations induced by IL-1 through the suppression of phospholipase A2 (PLA2) expression

which then reduced prostaglandin E2 (PGE2) synthesis and corticosterone secretion (Song et al., 2007).

In the present study, cortisol decrease was not significantly different among treatment groups and between responders and non-responders and no association was found between 24-HDRS reduction and decline of cortisol secretion after 8 weeks of treatment; therefore, the overall decrease in HPA-axis activity was independent of improvement of depressive symptoms and may be related to treatment in each group. Normalising HPA can have a role in treating depression through decreasing CRF, which can induce a change in the serotonergic system contributing to the onset of depression (Leonard, 2005). This concept is in line with a recent review of two clinical studies of CRF1 receptor antagonists which reported that these compounds represent promising novel therapeutics in the psychopharmacology of depression (Holsboer and Ising, 2008). Furthermore, as corticosteroids negatively regulated transcription of serotonin1A (5HT1A) receptor gene, especially in limbic system (Lanfumeij et al., 2008), decreasing cortisol can potentially affect serotonin sensitivity and reduce depressive symptoms. As the cortisol decrease in EPA group was probably the effect of ω -3 FA and normalising HPA-axis hyperactivity can potentially improve depressive symptoms, the suggestion is that EPA may exert at least parts of its therapeutic effects through reduction of HPA-axis activity and plasma cortisol. Similarly, fluoxetine can decrease corticosteroids. Although in the EPA plus fluoxetine group the amount of cortisol decrease was larger than fluoxetine group, it was not statistically significant probably due to small sample size in each group. However, as in a previous study (Schule et al., 2009), the change in severity of depression was not correlated with the change in plasma cortisol. Since depression is a multi-factorial disease and several factors including HPA activity and inflammatory cytokines can cause depression (Leonard, 2007), cortisol levels may not necessarily correlate with depression, especially in this small sample size.

Serum concentrations of IL-1 β and IL-6 did not change significantly after intervention in the fluoxetine group. This was not consistent with most previous findings about anti-depressants effects on inflammatory cytokines (Leo et al., 2006; Tsao et al., 2006; Kim et al., 2007). In the previous studies, peripheral blood cell cytokine production or mRNA expressions of leucocytes were measured, while

in the present study serum concentrations of cytokines were measured similar to that of Eller et al. (2008) who did not find significant changes in IL-8 and TNF- α serum concentrations either after 12 weeks of treatment with escitalopram. Furthermore, the results may be non-significant because of the small sample size.

Serum concentrations of IL-1 β and IL-6 did not change significantly after intervention in the EPA group. To the authors' knowledge, there is no literature about the effects of ω -3 FAs on cytokines in patients with MDD, but a study in healthy subjects have shown that fish oil had no impact on cytokine production after endotoxin challenge (Michaeli et al., 2007). On the other hand, a cross-sectional study in MDD patients has shown that EPA to arachidonic (an omega-6 fatty acid) acid ratio is lower in MDD with non-response to treatment and arachidonic acid correlates with IL-6 (Dinan et al., 2009). A recent review has reported that in patients with inflammatory conditions, cytokine concentrations or production are influenced by ω -3 FAs supplementation in a relatively large number of studies (Sijben and Calder, 2007). Some of these studies suggest that local effects at the site of inflammation might be more pronounced than systemic effects, indicating that the presence of sensitised immune cells in inflammatory disorders might increase sensitivity to the immunomodulatory effects of long-chain ω -3 FAs (Sijben and Calder, 2007). As previous studies have shown that depression may be a low-grade inflammatory disease (Das, 2007) and glial cells can be a source of cytokines (Miller and O'Callaghan, 2005), we cannot rule out the possibility of a locally reduced production of cytokines due to effects of ω -3 FAs. Therefore measuring peripheral blood cell cytokine production or cerebrospinal fluid (CSF) concentration of cytokines can be useful in determining local effects of ω -3 FAs. Furthermore, as mentioned earlier, it is probable that the non-significant changes may be due to the small sample size.

The strength of the present study is that it is the first study assessing effects of ω -3 FAs on cortisol and cytokines in patients with MDD. Limitations of these findings which must be addressed are the small sample size and lack of a placebo group. As mentioned earlier, the study was originally designed to compare therapeutic effects of EPA and fluoxetine. The sample size was calculated based on a difference in HDRS score. If the sample size had been calculated based on cytokine and cortisol change after treatment and among groups, it would have been larger. Peripheral blood cell cytokine production was not measured in this study. The dexamethasone/CRH test was not performed to evaluate the HPA axis.

In conclusion, EPA alone or in combination with fluoxetine as well as fluoxetine alone decreased serum cortisol after 8 weeks of treatment in MDD patients. As response to treatment had no significant effect on the change in cortisol levels, probably the decrease was the effect of ω -3 FA and fluoxetine rather than improvement of depressive symptoms. Serum IL-1 β and IL-6 did not change significantly after intervention. These findings suggest that EPA may exert at least parts of its therapeutic effects through reduction of cortisol. More trials with larger samples, measuring peripheral blood cell cytokine production and comparison with placebo are needed to determine if supplementation with EPA can affect HPA-axis activity and production of cytokines.

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