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Improvement of major depression is associated with increased erythrocyte DHA

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Abstract

The aim of this study was to determine if changes in omega-3 polyunsaturated fatty acid status following tuna oil supplementation correlated with changes in scores of depression. A total of 95 volunteers receiving treatment for major depression were randomised to consume 8 × 1 g capsules per day of HiDHA (2 g DHA, 0.6 g EPA and 10 mg Vitamin E) or olive oil (placebo) for 16 weeks, whilst undergoing weekly counseling sessions by trained clinical psychologists using a standard empirically validated psychotherapy. Depression status was assessed using the 17 item Hamilton rating scale for depression and the Beck Depression Inventory by a psychodiagnostician who was blind to the treatment. Blood was taken at baseline and 16 weeks (n = 48) for measurement of erythrocyte fatty acids. With HiDHA supplementation, erythrocyte DHA content rose from 4.1 ± 0.2 to 7.9 ± 0.4 % (mean ± SEM, $p < 0.001$) of total fatty acids but did not change (4.0 ± 0.2 to 4.1 ± 0.2 %) in the olive oil group. The mean changes in scores of depression did not differ significantly between the two groups (-12.2 ± 2.1 for tuna oil and -14.4 ± 2.3 for olive oil). However, analysis of covariance showed that in the fish oil group there was a significant correlation ($r = -0.51$) between the change in erythrocyte DHA and the change in scores of depression ($p < 0.05$). Further study of the relationship between DHA and depression is warranted.

Keywords

erythrocyte, dha, increased, associated, improvement, depression, major

Disciplines

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Improvement of major depression is associated with increased erythrocyte DHA

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Abstract

The aim of this study was to determine if changes in omega-3 polyunsaturated fatty acid status following tuna oil supplementation correlated with changes in scores of depression. A total of 95 volunteers receiving treatment for major depression were randomised to consume 8 x 1g capsules per day of HiDHA (2g DHA, 0.6g EPA and 10mg Vitamin E) or olive oil (placebo) for 16 weeks, whilst undergoing weekly counseling sessions by trained clinical psychologists using a standard empirically validated psychotherapy. Depression status was assessed using the 17-item Hamilton Rating Scale for Depression and the Beck Depression Inventory by a psychodiagnostician who was blind to the treatment. Blood was taken at baseline and 16 weeks (n=48) for measurement of erythrocyte fatty acids. With HiDHA supplementation, erythrocyte DHA content rose from 4.1±0.2% to 7.9±0.4% (mean ± SEM, $p<0.001$) of total fatty acids but did not change (4.0±0.2% to 4.1±0.2%) in the olive oil group. The mean changes in scores of depression did not differ significantly between the two groups (-12.2±2.1 for tuna oil and –14.4±2.3 for olive oil). However, analysis of covariance showed that in the fish oil group there was a significant correlation (r=-0.51) between the change in erythrocyte DHA and the change in scores of depression ($p<0.05$). Further study of the relationship between DHA and depression is warranted.

Abbreviations

PUFA	Polyunsaturated fatty acid(s)
EPA	Eicosapentaenoic acid (20:5n-3)
DPA	Docosapentaenoic acid (22:5n-3)
DHA	Docosahexaenoic acid (22:6n-3)
LC n-3 PUFA	Long chain omega-3 polyunsaturated fatty acids

Introduction

There is considerable putative evidence suggesting a relationship between long chain omega-3 polyunsaturated fatty acid (LC n-3 PUFA) intake derived from fish and depression. A significant negative correlation exists between fish consumption and the prevalence of depression, indicating that countries or populations with higher fish intake have considerably reduced rates of depression [1-4].

Fish and seafood is rich in LC n-3 PUFA [5]. People with major depression have been found to have depleted levels of LC n-3 PUFA levels in cross-sectional trials relative to controls [6, 7]. Randomised controlled trials using EPA rich fish oils in addition to antidepressant therapy resulted in improved response [8-10], and as a monotherapy showed significant improvement in one study [11] but a trend ($p=0.087$) towards improvement in another study [12]. Randomised controlled trials using a mix of EPA and DHA fish oils in addition to antidepressant therapy resulted in improved response [10] or no response [13].

Most of the randomized controlled trials to date have used EPA rich fish oils, although DHA is the predominant LC n-3 PUFA obtained by eating fish [5] and is therefore likely to account for the negative correlation between fish consumption and depression. Moreover, DHA is the major fatty acid component of brain phospholipids and is essential for normal brain development [14]. Hence a DHA-rich fish oil supplement might be expected to be even more efficacious than EPA-rich fish oil in counteracting depression.

Therefore we conducted a double blinded, placebo controlled randomised trial to see if DHA rich tuna oil has any additional benefit to conventional outpatient treatment in people diagnosed with major depression. This study showed that there was no additional benefit of fish oil supplementation over and above their weekly counseling session with clinical psychologists, as both groups improved in their scores of depression [15]. However, the primary aim of this subset analysis was to determine if the changes to the scores of depression were associated with the change in erythrocyte DHA and secondary aims were to determine if the changes to the scores of depression were associated with the change in erythrocyte EPA and total LC n-3 PUFA..

Methods

Study participants (age range 18-75 years) with major depression were recruited from outpatients seeking treatment at Northfields Clinic at the University of Wollongong, south of Sydney, Australia and details of the entry criteria into this double blind placebo controlled trial and the study design are published elsewhere [15]. Inclusion criteria were primary diagnosis of major depression with Hamilton Depression Rating Scale (HDRS) score greater than 16 to ensure depression severity [15]. All study participants accepted into the trial received weekly counseling sessions by trained doctoral-level clinical psychologists using a standard empirically validated psychotherapy for depression [16]. All study participants gave informed consent following ethics approval for the study.

Study participants consumed eight 1-gram identical soft-gel capsules per day of either pure south pacific tuna oil (HiDHA, Clover Corporation; each 1 gram capsule yielding 250mg DHA and 70 mg EPA stabilised with 10mg Vitamin E) or olive oil (placebo; matched for vitamin E content) for 16 weeks intervention. Compliance with the trial protocol was assessed using fortnightly capsule counts. Blood samples were taken at baseline and 16 weeks to assess erythrocyte fatty acid levels. Fatty acids were analysed based on the method by Lepage and Roy [17] as described by Sullivan et al [18]. Depression was assessed using the Hamilton Depression Rating Scale (HDRS) and the Beck Depression Inventory (BDI) [15, 19].

The sex, age and changes in EPA, DPA, DHA, EPA plus DHA, total LC n-3 PUFA were included as predictor variables, change in the residualised scores of depression (BDI) was included as the response variable and standard least squares was performed using JMP 5.1 [SAS Institute Inc., Cary, NC, USA].

Results

183 study participants were assessed; 83 who met the inclusion criteria were randomly assigned to placebo (n=43) and fish oil (n=40); 60 study participants (placebo n=28 and fish oil n=32) completed the study [15]. Reasons for withdrawing included time commitment/constraints, moving out of the area and being hospitalized [15].

Both intervention groups receiving weekly counseling improved their scores of depression. This combined treatment may have created a ceiling effect (effect size of 2.73) such that there was no additional variance for fish oil supplementation to show superiority [15]. However, in the treatment group there were significant increases in erythrocyte levels of DHA (3.8% of total fatty acids) and LC n-3 PUFA (4.0% of total fatty acids), which displaced arachidonic acid (-3.0% of total fatty acids) and total n-6 PUFA (-4.3% of total fatty acids) after fish oil supplementation for 16 weeks (figures 1 and 2). There were no significant changes of fatty acids in the placebo (olive oil) group.

Even though the changes in depression scores did not differ between the olive oil and fish oil groups in that both groups improved from a mean HDRS score of 23.5 at baseline to 10.7 after 4 months intervention [15], there was a significant negative correlation the change in the residualised BDI score of depression and the change in erythrocyte DHA level (16 weeks minus baseline DHA levels) in the fish oil group ($r = -0.51$, $p=0.01$) (Figure 3a). When assessing erythrocyte EPA plus DHA the correlation was slightly stronger ($r = -0.54$, $p=0.01$) (Figure 3b) but EPA alone was not a significant correlate. Similar correlations were seen when using the HDRS (data not shown).

Discussion

Compliance with the trial protocol was excellent as assessed by capsules count [15] and supported by significant increases in DHA and LCn-3 PUFA by 3.8, and 4.0% respectively, and concomitant decreases in arachidonic acid (3.0%) and total omega-6 fatty acids (4.6%) for the fish group compared to placebo (figures 1 and 2). The diet history and food records indicated that baseline diet did not change during the intervention trial (data not shown).

Adipose tissue fatty acids are reflective of long-term dietary intake of fatty acids [20] and epidemiological studies show populations with high seafood intake have lower rates of depression [1]. As the duration of our trial (16 weeks) approximates the half-life of erythrocytes [21], the LC n-3 PUFA contents of erythrocyte membranes is a good indicator of intakes during the trial. Despite no differences in changes of depression scores between the control and fish oil groups [15], it is interesting that the changes in the residualised scores of depression were associated with the changes in erythrocyte DHA levels (Figure 3) in this study ($r = -0.51$, $p<0.001$). Our results are consistent with cross-sectional studies that found that adipose tissue DHA was inversely associated with depression [22, 23] In the study by Su et al [10], people with major depression were randomly assigned to LC n-3 PUFA (2.2g EPA plus 1.1g DHA) or placebo (olive oil) for 8 weeks duration. Even though their supplement had twice as much EPA as DHA, their erythrocyte DHA levels doubled and there were no significant increases in erythrocyte EPA [10]. Nevertheless, they significantly improved in their scores of depression [10], suggesting that DHA is important.

In our study the change in EPA was not significantly associated with the change in the residualised scores of depression, however the change in EPA plus DHA correlated with the change in the residualised scores of depression with a slight improvement over DHA alone ($r = -0.54$ versus $r = -0.51$, $p<0.001$), suggesting that both EPA and DHA have an effect. While DHA is an essential fatty acid component of brain tissue required for neurotransmission, EPA may possibly influence central nervous system activity by influencing cerebral blood flow through endothelial vasodilator mechanisms [24]. DHA is incorporated into phosphatidyl-ethanolamine and phosphatidyl-serine in the gray matter of the brain [25] and phosphatidyl-serine-DHA has been linked to neuronal cell survival [26, 27]. EPA may exert its effects through increased cerebral blood flow [28] and increased glucose supply to the brain [27, 29, 30]. A meta-analysis suggests that EPA may be more effective than DHA in treating

depression [31]. Of the more recent studies that compared EPA and DHA, one study showed that EPA was effective but not DHA in people with mild to moderate depression [32], whilst another showed both EPA and DHA to be effective in people with mild cognitive impairment when assessing their depression with the Geriatric Depression Scale [33]. However more research is required to determine the relative importance of EPA and DHA in acute regulation of brain function as opposed to structural development of the nervous system. The significance of these findings therefore lies in the intriguing links between mood, brain fatty acids, neurotransmission, blood flow and cognition.

Our study population was not deficient in their omega-3 status at the start of the study and this may have contributed to the lack of fish oil supplementation having an effect on scores of depression [15]. Published studies indicate that in normal healthy people erythrocyte LC n-3 PUFA expressed as percent of total fatty acids concentrations range from 5-9%; namely 5.51% [34], 7.48% [6], 8.5% [35], 8.87% [36] and 9.4% [37]. Other studies have reported EPA plus DHA levels expressed as percent of total fatty acids as 3.81% [38] and 5.57% [39]. One large case control study, which included 493 controls reported the erythrocyte EPA plus DHA quartiles as 3.3, 4.3, 5.0 and 6.5% [40]. Given our LC n-3 PUFA levels are comparable to healthy people; this could explain why there was no additional benefit of fish oil supplementation over and above counseling therapy.

Studies have shown that people with depression have lower erythrocyte EPA plus DHA (3.77%) compared to people without depression (4.45%) [6]. In light of this, the mean baseline erythrocyte EPA plus DHA level (5.0%) in our study population of people with depression is no lower than other studies in a normal healthy population. Furthermore, the Omega-3 Index (the sum of erythrocyte EPA plus DHA levels) has been postulated as a new cardiovascular disease risk factor, in which $\leq$4% is classified as high risk and $\geq$8% is classified as low risk [41]. If this omega-3 status is applied in our study population of people with depression, then our subjects would be classified as intermediate. As LC n-3 PUFA have been implicated to have a role in depression, the fact that our study population was not deficient in omega-3 could be another contributing factor for the inability of omega-3 supplementation to improve overall scores of depression. Moreover, at the end of our intervention, the DHA group's Omega-3 Index was 8.8%, which classifies them as low cardiovascular risk.

Another possible reason for our trial not to show beneficial effects of DHA [15]), was that all patients were receiving weekly counseling, and the effectiveness of this treatment resulted in no additional variance in which the fish oil condition may have showed superiority.

In conclusion, in people with major depression receiving weekly counseling, DHA supplementation did not confer any additional benefit; however individual changes in scores of depression were negatively correlated with changes in erythrocyte DHA levels, suggesting that DHA is important. Further research is required to assess the efficacy of DHA rich fish oil when more minimal treatments are used.

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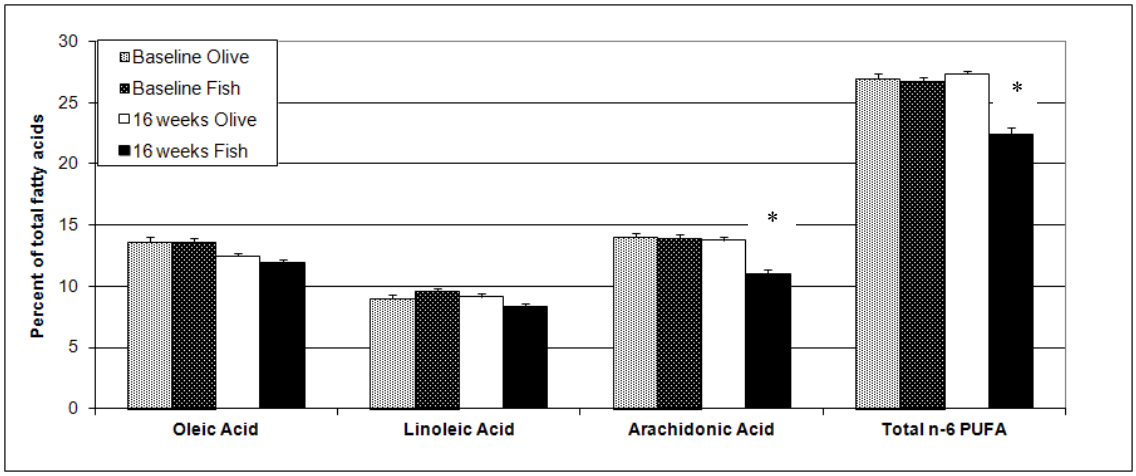
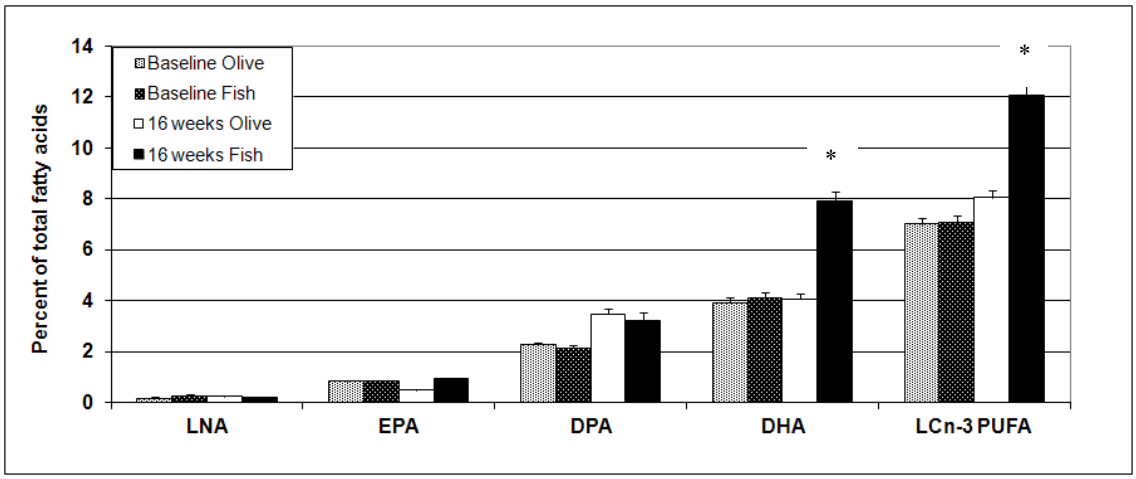
Figure 1



Erythrocyte oleic acid and omega-6 PUFA contents in both olive oil and fish oil groups at baseline and after 16 weeks intervention.
Baseline Olive oil group (▨); Baseline Fish Oil Group (▩); 16 weeks Olive Oil Group (□); 16 weeks Fish Oil Group (■).

* significantly different from baseline fish oil group, $p<0.05$

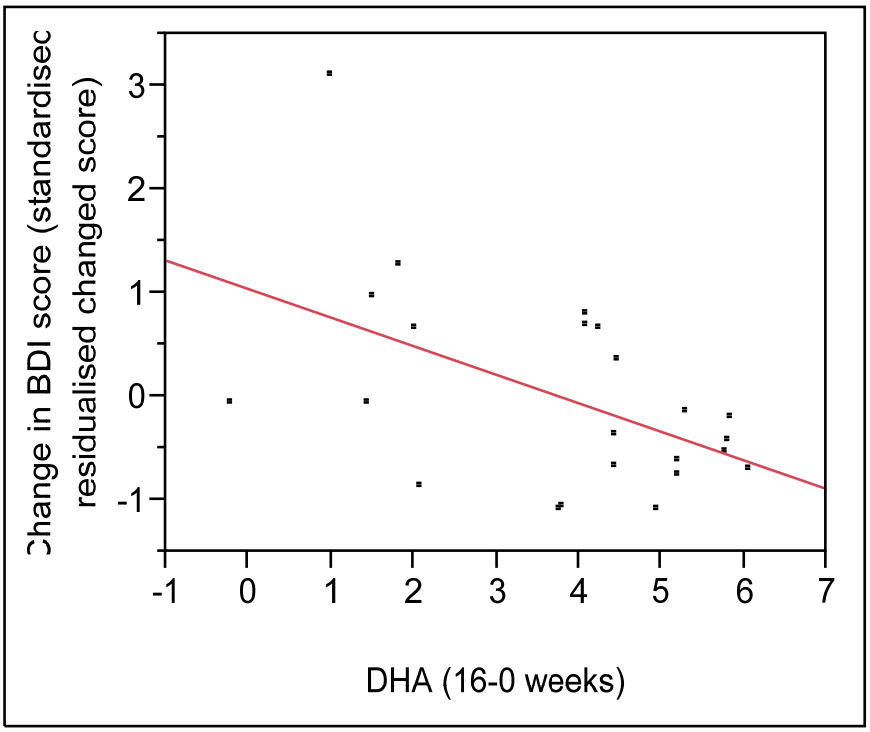
Figure 2



Erythrocyte omega-3 PUFA contents in both olive oil and fish oil groups at baseline and after 16 weeks intervention.
Baseline Olive oil group (▨); Baseline Fish Oil Group (▩); 16 weeks Olive Oil Group (□); 16 weeks Fish Oil Group (■).

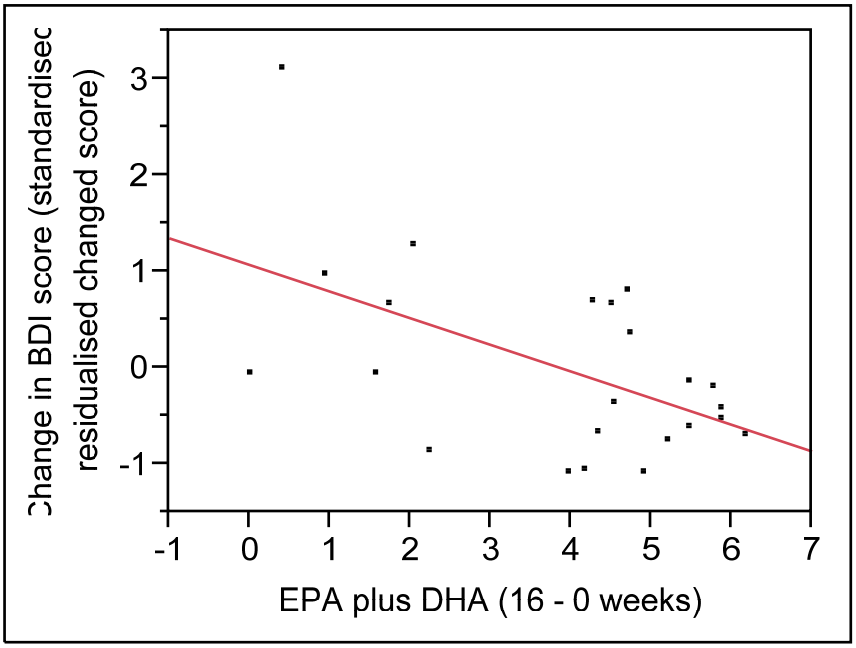
* significantly different from baseline fish oil group, $p<0.05$

Figure 3a.



Negative correlation (r = -0.51) between changes in the BDI score (residualised changed score) and changes in erythrocyte DHA levels (16 week minus baseline) in the fish oil group (n=24) (r^2 adjusted = 0.22, p = 0.0136).

Figure 3b.



Negative correlation (r = -0.54) between changes in the BDI score (residualised changed score) and changes in erythrocyte EPA plus DHA levels (16 week minus baseline) in the fish oil group (n=24) (r^2 adjusted = 0.25, p = 0.0082).