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A controlled study of plasma fatty acids in Indian patients with depressive episode

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ABSTRACT

Aim: To study the plasma omega 3 and omega 6 fatty acid levels in patients with depressive episode and in matched healthy controls.
Method: Thirty patients with first episode depression and thirty healthy matched control subjects were recruited from a tertiary care hospital setting. We measured plasma omega-3 and omega-6 fatty acid levels of the study and the control group.
Result: There were no significant differences in plasma omega 3 fatty acid levels between study group and control group. The plasma omega 6 fatty acid levels of study group were significantly less than that of control group.
Conclusions: The present study is an initial attempt to investigate the link between fatty acids and depression in a clinical setting in India. This comparative study with normal controls did not etiologically link these poly-unsaturated fatty acids in this sample of depressive disorder.

1. Introduction

Major depressive disorder is a common psychiatric illness with a high morbidity and mortality. Depression is the third leading contributor to the global burden of disease and the first in middle-income and high-income countries. It has been expected to be second leading cause of disability by 2020 (Ustün et al., 2004). The investigators of the Global Burden of Disease project predict that by 2030, depression will become one of the leading causes of disability worldwide (Mathers and Loncar, 2006). The Global Burden of Diseases, Injuries, and Risk Factors Study 2016 estimated depression as the fifth leading cause of YLDs in the year 2016 (Vos et al., 2016). The World Mental Health Survey found the life time prevalence of major depressive episode to be 14.6% in the 10 high-income countries, 11.1% in the 8 low- to middle- income countries and 9% in India (Bromet et al., 2011). For any true increase, numerous determinants could be proposed. In recent years, there has been considerable interest in a dietary contribution, particularly involving omega-3 fatty acids (Weissman et al., 1996).

The omega 3 fatty acids are alpha linolenic acid (ALA), eicosapentaenoic acid (EPA), docosahexaenoic acids (DHA) and omega 6 fatty acids are arachidonic acid (AA), gamma linolenic acid (GLA) and linoleic acid (LA). Because these essential fatty acids (EFAs) cannot be synthesized in the human body, they must be derived from dietary sources (Logan, 2004). They are important components of phospholipids and cholesterol esters, which are themselves integral to the neuronal cell membrane, especially synaptic and dendritic membranes, and intracellular membranes such as mitochondria and vesicles. If unavailable, they are replaced by non-essential fatty acids, changing the behavior of the phospholipid molecules and affecting the tertiary and quaternary structures of membrane-bound receptors and associated neurotransmitters (Hallahan and Garland, 2005).

Previous study investigating relationship between depression and omega-3 and omega-6 long-chain polyunsaturated fatty acids in plasma and erythrocyte phospholipids, reported a significant positive relation between depression severity and the ratio of erythrocyte phospholipids arachidonic acid to EPA and a negative relation between erythrocyte EPA, DHA and depression severity (Edwards et al., 1998; Peet et al., 1997). Depressed subjects also had significantly lower alpha-linolenic

Abbreviations: AA, arachidonic acid; AL, aalpha linolenic acid; ANCOV, aanalysis of covariance; BMI, body mass index; DHA, docosahexaenoic acids; EFA, essential fatty acids; EPA, eicosapentaenoic acid; FA, fatty acid; GC, gas chromatography; GHQ, general health questionnaire; GLA, gamma linolenic acid; HRSD, hamilton rating scale for depression; LA, linoleic acid; PUFA, polyunsaturated fatty acids

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acid and lower total omega-3 in serum cholesteryl esters and lower EPA in both serum cholesteryl ester and phospholipid fractions (Maes et al., 1996). These findings suggest an abnormal intake or metabolism of essential fatty acids in conjunction with decreased formation of cholesteryl esters in major depression. The depressed subjects had significantly lower adipose tissue DHA levels than the non-depressed subjects (Mamalakis et al., 2002). Meta-analytic studies show the levels of EPA, DHA, and total omega-3 polyunsaturated fatty acids (PUFA) were significantly low in depressive patients and omega-3 PUFAs have a significant antidepressant effect (Lin et al., 2010; Lin and Su, 2007).

Studies found that supplementation of omega-3 fatty acid in addition to standard psychiatric care had shown significant greater improvements in scores for depression (Jazayeri et al., 2008; Hallahan et al., 2007). Supplements containing EPA ≥60% of total EPA + DHA, in a dose range of 200 to 2200 mg/d of EPA in excess of DHA, are effective against primary depression (Sublette et al., 2011). Similar findings have also been reported in a review. In patients with depression, formulations > 50% EPA demonstrated clinical benefits compared with placebo whereas formulations > 50% DHA did not show any benefit (Hallahan et al., 2016). A number of studies have shown negative correlation between sea food consumption (which contains omega 3 fatty acids) and community rates of mood disorders (Cott and Hibbeln, 2001; Tanskanen et al., 2001). Recent metanalysis of 11 randomized clinical trials on patients with diagnosis of major depressive disorder and 8 randomized clinical trials on patients with depressive symptoms but no syndromal diagnosis depressive disorder found that significant clinical benefit of omega-3 PUFA treatment compared to placebo. Significant clinical efficacy was found in the use of omega-3 PUFA as adjuvant rather than mono-therapy (Grosso et al., 2014).

However, studies also found no beneficial effects of omega 3 fatty acids in depression and publication bias are also noted (Lucas et al., 2011; Appleton et al., 2010). A meta-analysis shows a small, non-significant benefit of omega-3 FAs for major depression (Bloch and Hannestad, 2011). Recent Cochrane review that includes 25 studies involving 1373 participants, omega 3 fatty acid supplementation results in a small to modest benefit for depressive symptomology, compared to placebo. And this effect is unlikely to be clinically meaningful. The authors also noted that this effect estimate was likely to be biased towards a positive finding for omega 3 fatty acids, and that the true effect was likely to be smaller (Appleton et al., 2015). Patients with depression only who have high biomarkers of inflammation respond to omega3 fatty acids (Rapaport et al., 2016). An older study has also found that omega 3 fatty acid levels were significantly greater in the subjects with depression compared with their controls (Ellis and Sanders, 1977).

The existing studies are primarily from western countries. There are differences in metabolism between Indian and the western population as Asian Indians compared to Caucasians have higher body fat, waist to hip ratio, intra-abdominal and subcutaneous fat; and lesser average body mass-index, waist and hip circumference and muscle mass (Banerji et al., 1999). There is difference in dietary habits between eastern and the western population. In rural India omega-6: omega-3 ratio of dietary fatty acid is 5–6.1, which is lower than that of western population and in urban India it is 38–50, which is higher than that of western population. The increased proportion of omega 6 fatty acids in diet is a risk factor for various non-communicable disease including depression (Fedacko et al., 2012). Also, the fatty acid compositions of plasma total lipids in Indian population is different than that of western population (Stark et al., 2016).

Though this is an important area of research, this aspect has not been studied in Indian population. From India, studies on essential poly unsaturated fatty acids have been carried out in patients with schizophrenia and bipolar affective disorder (Ranjekar et al., 2003) or in the animal model with depression (Lakhwani et al., 2007). As there has been no Indian study on plasma levels of essential fatty acids in patients with depressive disorder, a need was felt for a research study to assess the plasma fatty acid levels in patients with depression in the Indian perspective.

The aim of the present study was to determine plasma omega-3 and omega-6 fatty acid levels in Indian patients with depressive episode and healthy controls.

2. Methods

2.1. Study setting and sample collection

Patients were recruited from the outpatient and inpatient clinics of Department of Psychiatry of a tertiary care hospital in North-India (All India Institute of Medical Sciences, New Delhi). Drug naïve patients having the first episode of depression (F32) according to International Classification of Diseases, tenth revision, Diagnostic Criteria for Research (ICD-10- DCR) (WHO, 1993), were included in this study by non-random, non-stratified sampling.

Age and sex matched control subjects were selected from healthy volunteers. The controls were of either sex, had no current psychiatric diagnosis and scored less than 2 on General Health Questionnaire (GHQ). Thirty patients and thirty controls of age 18–65 years were included in this study.

The exclusion criteria for both cases and controls were current history of substance abuse (except nicotine), borderline personality disorder, psychosis or eating disorder, persons having known history of dyslipidaemia, persons who are under any treatment or diet or having illness known to interfere with lipid or omega-3 essential fatty acid metabolism and persons taking supplements containing omega-3 essential fatty acid or consuming fish more than once per week.

Informed consent was obtained from the subjects prior to inclusion in the study and clearance from institute ethics committee was taken.

2.2. Assessment

The ICD-10 Diagnostic Criteria for Research (DCR) was used to make the diagnosis. Socio-demographic and clinical details were recorded. Detailed nutritional history about fish intake and of alcohol or use of any drug treatment was enquired and recorded. The body mass index (BMI) was calculated using the mathematical formula: Body mass-index (BMI) = weight/height^2 (kg/m^2).

Depression was assessed through Hamilton Rating Scale for Depression (HRSD). It is not a diagnostic scale; rather measures the severity of depression where patient had received a diagnosis of depressive disorder. It is a 21-question multiple choice questionnaire rated on 0–4 likert scale used to rate the severity of depression (Hamilton, 1960). The General Health Questionnaire-12 (GHQ-12) is a distress and well being scale to measure psychological morbidity in normal population. The items were rated on a four-point likert scale (0–3). But while computing the scores, each item is scored as 0 or 1. Thus the total score varies from 0 to 12. A case score above 2 is considered as reflecting recognizable psychological problems (Jacob et al., 1997). The Hindi version of GHQ-12 was standardized and was found to be quite sensitive, reliable and valid instrument for screening psychiatric patients (Gautam et al., 1987).

2.3. Laboratory investigations

All the subjects and controls underwent estimation of their plasma omega-3 fatty acids (alpha linolenic acid, eicosapantanoic acid, docosahexaenoic acids, and plasma omega-6 fatty acids (arachidonic acid, gamma linolenic acid and linoleic acid). Blood was collected with subjects in the fasting under all aseptic measures. The blood was transported to the laboratory within 2 h of collection. The samples were stored at −70 °C till analysis. Then plasma was separated and processed for gas chromatography (GC). We carried out the fatty acid estimation in whole plasma. Briefly the method entailed converting the fatty acids