A Mini Analysis: Depression and Omega-3 Essential Fatty Acids

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Omega-3 polyunsaturated fatty acids have received a considerable amount of attention in a number of human pathologies, including inflammation, cardiovascular disease, behavioral or mental disease, and especially depression. They make up one component of mammalian brain tissue that includes the different saturated, monounsaturated, and polyunsaturated fatty acids (McNamara and Carlson, 2006).

Omega-3 fatty acids compose about 15% of the total fatty acid composition, and are essential long-chain polyunsaturated fatty acids concentrated in the human cental nervous system (CNS), retina, and testes (McNamara and Carlson, 2006). Omega-3 fatty acids are of particular interest in clinical psychiatric states, as they are selectively concentrated in neuronal synaptic membranes and regulate vascular and immune functions that affect the central nervous system (Freeman et al., 2006). These fatty acids are available only from dietary sources (fish oils, fish, and eggs), making it likely that insufficient intake of omega-3 fatty acids may be linked to maladaptive changes in CNS function, possibly contributing to the progression of depression (Freeman et al., 2006). Omega-3 fatty acids can also be obtained from plants (especially nuts): however, they come in the form of α-linolenic acids, of which only 10-15% are converted into omega-3 fatty acids (Su et al., 2003; Freeman et al., 2006).

Epidemiological data suggest that the lifetime prevalence of mental and behavioral disorders within the human population is 25%, most of which is thought to be due to depression (World Health Report, 2002). Depression is a common mental disorder currently causing a high level of burden, and it represents an active area of research. In trying to present a balanced analysis of the role of omega-3 fatty acids, I will be exploring two studies that support the role of omega-3 fatty acids in depression when used as an additional or adjunct treatment to current care (Hallahan et al., 2007; Su et al., 2003), as well as one study that does not support this evidence (Silvers et al., 2005).

The mechanism of how decreases in omega-3 fatty acid may lead to depression is not completely understood, but a number of theories exist. In brief, one mechanism involves the regulation of the serotonergic neurotransmitter system, which is supported in studies of humans and animals (Hibbeln et al., 1998). A second mechanism is supported by the "macrophage theory of depression," which derives from the fact that clinical depression is accompanied by overactivity of the inflammatory response of the immune system, namely, increased secretions of inflammatory cytokines (Maes et al., 1995). Omega-3 fatty acids have been shown to have important effects on inflammatory pathways by specifically reducing inflammation. The administration of the inflammatory cytokine, alpha-interferon, to human subjects provoked a range of psychiatric symptoms similar to those found in depression (Bonaccorso et al., 2001). The cAMP signal transduction hypothesis suggests that depression and bipolar disorder may be caused by an impaired phospholipid metabolism and impaired fatty acid related signal transduction and also attempts to explain associations between depression and cardiovascular disease and other autoimmune disorders (Horrobin and Bennett, 1999). These represent some of the plausible mechanisms and, as stated above, the exact etiology currently remains an area of ongoing research. The work described below attempts to elucidate the role of omega-3 fatty acids as an additional therapy to the standard of care for depression.

A double-blind randomized controlled trial was conducted to assess the efficacy of omega-3 fatty acid supplementation in improving psychological well-being in patients with recurrent self-harm (Hallahan et al., 2007). Self-harm, in this study, is utilized as a benchmark for depression as well as a measure of the severity of depression. The study included 49 patients recruited from an emergency department after trying to inflict self-harm, ranging in age from 16 to 64 years. Patients who had previous episodes of self-harm were the ones recruited for this study. Exclusion criteria were: current history of addiction, psychosis, or eating disorder, currently receiving psychotherapy, known history of dyslipidemia, or use of omega-3 fatty acid supplements. Patients in the study were given either omega-3 fatty acid supplements (1.2 grams [g] of EPA and 0.9 g of DHA) or placebo in addition to standard care, and six psychological domains were measured at baseline and at the twelve-week endpoint (Hallahan et al., 2007). It should be noted that the inclusion of a small amount of fish oil was added to the placebo tablets in order to maintain the integrity of the study by helping ensure that patients were not able to identify what group they may have been in. Significant improvements in the treatment arm in comparison to the placebo arm were

noted for depression, suicidality, and daily stresses. The authors note that larger studies are warranted, but the marked reduction in markers for suicidal behavior and improvement in well-being are significant. There seem to be clear benefits to adjunctive therapy with omega-3 supplements or dietary intake, and the authors state that omega-3 fatty acids may play a role in the psychological status of patients (Hallahan et al., 2007).

Prior to the aforementioned study, Su et al. (2003) conducted an eight-week, double-blind, placebo-controlled trial, comparing omega-3 fatty acids (4.4 g/day of EPA and 2.2 g/day of DHA) with placebo, in addition to the usual treatment, in patients with a diagnosis of major depressive disorder (Su et al., 2003). Additional criteria met by patients in the study included no change in medications or psychotherapy four weeks before enrollment, competency to understand study, and a rating of over 18 on the 21-item Hamilton Rating Scale for Depression (HRDS). This study showed improvement during the short-term course of the major depressive disorder illness in patients who were part of the treatment arm. The improvement in terms of the HRDS for depression was approximately -15 for the treated depressive patients receiving additional omega-3 fatty acids versus the placebo group, who had a score of approximately -5 (Su et al., 2003). This study was a clear indication that omega-3 fatty acids have a role in improving depression.

Silvers et al. (2005) published a randomized, double-blind, placebo-controlled study of fish oil versus placebo, showing no difference in mood or depression. This study was done in the presence of standard treatment, as were the two others described in this analysis. Seventy-seven participants were randomly assigned to receive 8 g of either fish or olive oil per day (the distribution of fatty acids for these oils is variant) in addition to their existing therapy. The participants were chosen from a community (outpatient) setting, where they were already being treated for a current depressive episode with no coexisting psychiatric disorders. Depression criteria were again met by the short form of the HRDS and not the DSM-IV, as in the previous study. The conclusions from this study showed no statistically significant differences between the groups, and the authors state that fish oil is no more effective than the control as an add-on therapy in a community setting, despite an increase of circulating omega-3 fatty acids in the treatment group (Silvers et al., 2005). However, it should be noted that not only is the population sample different from those in the other studies mentioned, but the total amount of omega-3 fatty acids in fish oil is highly variable. For these reasons, it may not be appropriate to compare supplementation with fish oil to supplementation with the pure omega-3 fatty acids that were used in the previously discussed studies. The previous two studies that supported supplementation of omega-3 fatty acids presented here are not normalized with regard to the dose of supplementation. Silvers et al. (2005) used natural sources (8 g of fish oil) for supplementation whereas Su et al. (2003) used 4.4 g/day of EPA and 2.2 g/day of DHA and Hallahan et al. (2007) used 1.2 g of EPA and 0.9 g of DHA of purified extract. Silvers et al. (2005) may reflect the dose dependence of omega-3 fatty acids on the efficacy of the treatment of depression as an adjunct therapy. The authors do discuss this in the article. They also argue that if the doses are normalized, their data show that omega-3 fatty acid adjunct supplementation may not be a good treatment for community based patients. Only patients who meet DSM-IV criteria for depression may actually be an appropriate target population (Silvers et al., 2005).

The studies mentioned here have a limited number of patients and, as such, larger-scale studies are warranted, especially if the specific questions raised above are to be answered. The underlying molecular mechanism is also unknown and presents a limitation to this body of research. However, the literature cited in this document is promising in terms of omega-3 fatty acid effects on depression as supplemental therapy to the current recommended regimens. The American Heart Association (AHA) has recommendations for omega-3 fatty acids for inflammation and coronary artery disease protection (Kris-Etherton et al., 2003). The AHA recommends eating fish (particularly fatty fish) at least two times a week (Kris-Etherton et al., 2003). The AHA comments on increased protective effects of diets high in omega-3 fatty acid content for coronary heart disease as well as efficacy in lowering triglyceride levels. Since there have been no reportable side effects, taking into account the data presented here, these same recommendations can be given to patients who suffer from psychiatric disorders. Two tuna fish sandwiches a week may be just what the doctor ordered!

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