Psychotherapy and Psychosomatics

Published online: February 18, 2009

Psychother Psychosom 2009;78:125–127
DOI: 10.1159/000203118

Association between Omega–3 Fatty Acids and Depressive Symptoms among Patients with Established Coronary Artery Disease: Data from the Heart and Soul Study

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Depression is an established risk factor for the development of coronary heart disease (CHD) in healthy patients [1, 2] and for adverse cardiovascular outcomes in patients with existing CHD [3, 4]. A deeper biological understanding of the causes of depression in patients with cardiovascular disease is critical to improve the prevention and treatment of both conditions [5, 6]. Dietary factors resulting in lower levels of ω–3 fatty acids not only increase CHD risk [7, 8], but may also be involved in the pathophysiology of depression. Lower levels of ω–3 fatty acids, particularly docosahexaenoic acid (DHA) and eicosapentaenoic acid (EPA), have been associated with depression in both healthy adult populations [9, 10] and in patients with acute coronary syndrome [11, 12]. It is unknown whether low ω–3 fatty acid levels are associated with depression in patients with stable CHD.

We measured red blood cell levels of two ω–3 fatty acids, EPA and DHA, and assessed depressive symptoms in a cross-sectional study of 987 adults with CHD. The Heart and Soul Study is a prospective cohort study examining psychosocial factors and health outcomes in patients with established CHD. Detailed methods have previously been described [13]. Between 2000 and 2002, a total of 1,024 San Francisco area residents enrolled and completed a baseline study visit. Subjects without frozen blood samples (n = 37) were excluded, resulting in a final sample size of 987. ω–3 fatty acids were blindly measured in fasting venous blood samples using capillary gas chromatography to measure the fatty acid composition of red blood cell membranes. Red blood cell levels of EPA and DHA are presented as a percentage composition of total fatty acid methyl esters. We assessed current depression using the 9-item Patient Health Questionnaire [14], where a score $\geq$10 is consistent with major depression [15, 16]. Socioeconomic status (SES) was measured using both education and household income level as previously described [17].

We evaluated the association between ω–3 fatty acid levels and depressive symptoms as continuous variables using linear regression. We also examined the association of ω–3 fatty acid tertiles with depression as a dichotomous variable using χ^2 analysis and logistic regression. Multivariable models were sequentially adjusted for demographic factors and SES. All statistical tests were two-sided, and $p < 0.05$ was considered statistically significant. Analyses were performed with SAS version 9.1 (SAS Institute, Cary, N.C., USA).

The average age of the study participants was 67 $\pm$ 11 years, out of whom 804 study participants (approx. 80%) were men. Participants in the lowest tertile of ω–3 fatty acid levels (EPA + DHA) were less likely than participants in the highest tertile to be married, have a college degree or earn a household income over USD 20,000. These same participants were more likely to be Hispanic or black, have a history of hypertension, myocardial infarction or diabetes mellitus, to smoke, or to be physically inactive.

The prevalence of depression ranged from 23% in participants in the lowest tertile of ω–3 fatty acids (<3.1% of total blood fatty acids) to 13% in participants in the highest tertile (>4.3% of total blood fatty acids; p for trend = 0.004). Each unit decrease in EPA + DHA was inversely associated with depressive symptoms as a continuous variable, and these associations persisted after adjustment for age, sex and race (table 1). Similarly, each SD decrease in EPA + DHA was associated with significantly greater odds of depression as a dichotomous variable (Patient Health Questionnaire score $\geq$10; table 1). However, in both analyses, ω–3 fatty acid levels were no longer associated with depression after adjustment for education and household income level. Similar results were obtained for the analyses of EPA and DHA alone.

Prior studies have found an association between ω–3 fatty acids and depression in the general population [9]. A recent review of this literature concluded that a causal relationship likely exists between ω–3 fatty acids and depression but raised concerns that many studies had inadequate sample size and adjustment for potential confounders like SES [10]. There is a clear association between lower levels of ω–3 fatty acids and increased CHD risk [18], but the role of ω–3 fatty acids and depression in patients with CHD is not known. Two prior studies of acute coronary syndrome patients found an association between low ω–3 fatty acid levels and depression, suggesting that low ω–3 fatty acids may contribute to the development of depression in patients with heart disease [11, 12].

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Table 1. Association of EPA + DHA with depressive symptoms

	Depressive symptoms (continuous PHQ)		Depression (dichotomous PHQ ≥10)		
	β-coefficient ± SE	p value	OR	95% CI	p value
Unadjusted	−0.22 ± 0.07	0.002	1.3	1.1–1.5	0.006
Adjusted for age, sex and ethnicity	−0.14 ± 0.07	0.05	1.1	0.97–1.4	0.11
Adjusted for above plus income and education	−0.06 ± 0.07	0.42	1.0	0.87–1.2	0.68

Because EPA + DHA levels were not normally distributed, they were log-transformed. The β-coefficient was determined for the association of log EPA + DHA (entered as a continuous predictor variable) with depressive symptoms (log of PHQ score). The odds ratio (OR) was assessed for the association of EPA + DHA (entered as continuous predictor variables, per SD decrease) with depressive symptoms (dichotomous PHQ ≥10). PHQ = Patient Health Questionnaire; CI = confidence interval.

Our study extends this existing literature by finding a strong association between low ω–3 fatty acids and depression in outpatients with stable CHD, a population distinct from sicker, hospitalized patients with acute coronary syndrome. In addition, we examined the role of several important potential confounders and measured erythrocyte membrane levels of fatty acids rather than using less accurate serum measurements or dietary questionnaires. However, the cross-sectional nature of our study precluded us from making any definitive comments on causality. Additionally, our cohort participants were mostly older, urban men and thus are not entirely reflective of the general population.

In an effort to improve current cardiovascular prevention strategies, some have suggested providing ω–3 fatty acid supplements to CHD patients with a diagnosis of depression [11]. Because depression increases both cardiovascular risk and cardiovascular disease-related morbidity and mortality [1–4, 19–21], a potential reduction in the incidence of depression in patients with CHD by ω–3 fatty acid supplementation could lead to less adverse cardiac outcomes. However, given that differences in SES appeared to explain the association between ω–3 fatty acids and depression in our study, we are less confident that treatment with ω–3 fatty acids can improve depressive symptoms in patients with stable CHD. Since SES is an important risk factor for both poor diet and depression [22], it is possible that ω–3 fatty acid levels are not associated with depressive symptoms independent of SES [23]. To better understand the potential efficacy of ω–3 fatty acid supplementation for improving depressive symptoms in patients with CHD, future studies should carefully consider the role of SES in this association.

Acknowledgements

The Heart and Soul Study was funded by the Department of Veterans Affairs, Washington, D.C., the National Heart Lung and Blood Institute (R01 HL079235), Bethesda, Md., the American Federation for Aging Research (Paul Beeson Scholars Program), New York, N.Y., the Robert Wood Johnson Foundation (Faculty Scholars Program), Princeton, N.J., the Ischemia Research and Education Foundation, South San Francisco, Calif., and the Nancy Kirwan Heart Research Fund, San Francisco, Calif.

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Psychother Psychosom 2009;78:127–128
DOI: 10.1159/000203119

Light Therapy as a Treatment for Sexual Dysfunctions

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Seasonal trends have been demonstrated in reproduction and in sexual activities [1, 2] and the pineal gland, i.e. the light-regulated time keeper of our body, plays an important role in the neuroendocrine control of sexual function and reproductive physiology [2]. The retinohypothalamic tract brings information about light and dark cycles to the suprachiasmatic nucleus of the hypothalamus, which projects to the pineal gland and inhibits the production of melatonin. When these impulses stop (at night, when light no longer stimulates the hypothalamus), pineal inhibition ceases and melatonin is released. Although we are still far from knowing exactly where and how the pineal suppressive role is exerted, the fact that the gland exerts an inhibitory function on the reproductive axis is widely accepted [2]. In fact, the pineal seems to exert its hormonal effect at different levels of the reproductive axis, both at the hypothalamic-pituitary level (for instance via the inhibition of the hypothalamic pulsatile secretion of gonadotrophin-releasing hormone) [2, 3] and at the gonadal level, where melatonin receptors have also been found [2–4]. Furthermore, melatonin appears to increase prolactin secretion, which may contribute to sexual dysfunction [5].

Based on the observations mentioned above we hypothesized that an inhibition of pineal gland activity via a treatment with bright light could favorably influence sexual function and pilot-tested the usefulness of bright light therapy in a small sample of 9 male patients with nonorganic sexual dysfunction (table 1). Subjects (age 39–60) were consecutively recruited in the outpatient clinic of the Urology Department of the University of Siena Medical Center on the basis of a diagnosis of primary (i.e. not due to another illness or to a medication or a drug of abuse) hypoactive sexual desire disorder (HSDD, n = 2), sexual arousal disorder (SAD, n = 6), and orgasmic disorder (OD, n = 1) and the absence of a mood disorder, as assessed via the Mini International Neuropsychiatric Interview [6].

The University of Siena's biomedical institutional review board approved of all recruitment, assessment, and treatment procedures. All subjects provided written informed consent after receiving a complete description of the study and having the opportunity to ask questions. Subjects were randomly assigned to active light treatment (ALT) or placebo light treatment (L-PBO) and assessed at baseline (prior to starting ALT or L-PBO) and after 2 weeks of ALT/L-PBO treatment via the Structured Clinical Interview for DSM-IV-Sexual Disorders (SCID-S) and via a sex-

Table 1. Study outcomes

Treatment groups	Baseline diagnosis	Level of sexual satisfaction at baseline	Diagnosis after 2 weeks of ALT/L-PBO	Level of sexual satisfaction after 2 weeks of ALT/L-PBO
L-PBO				
Patient 1	HSDD	3	HSDD	4
Patient 2	SAD	2	SAD	2
Patient 3	SAD	4	SAD	4
Patient 4	SAD	2	SAD	2
ALT				
Patient 1	HSDD	2	HSDD	7
Patient 2	OD	4	none	7
Patient 3	SAD	3	SAD	8
Patient 4	SAD	3	none	9
Patient 5	SAD	2	none	9