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Review

Association between erythrocyte n-3 polyunsaturated fatty acids and biomarkers of inflammation and oxidative stress in patients with and without depression

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ABSTRACT

Associations between n-3 polyunsaturated fatty acids (PUFAs), inflammation, oxidative stress and the risk of depression have been suggested. We hypothesize that erythrocyte n-3 PUFAs are inversely associated with biomarkers for inflammation and oxidative stress in Koreans with and without depression. Study participants comprised 80 cases diagnosed with depression based on the Center for Epidemiological Studies Depression Scale Korea version (CES-D-K) scores ≥ 25 and psychiatrist confirmation and 80 age- and sex-matched healthy controls without histories of depression. Depressed patients had lower levels of n-3 PUFAs and higher circulating levels of inducible nitric oxide synthase (iNOS), superoxide dismutase, interferon-γ, and nitrotyrosine compared to the controls. CES-D-K scores and levels of iNOS and tumor necrosis factor (TNF)-α were negatively associated with Omega-3 Index (erythrocyte levels of eicosapentaenoic acid and docosahexaenoic acid) after adjusting for confounding factors. Concentrations of iNOS, TNF-α, thiobarbituric acid reactive substances, and nitrotyrosine were negatively correlated with erythrocyte levels of n-3 PUFAs, but positively with erythrocyte levels of n-6 PUFAs. Erythrocyte levels of n-3 PUFAs were inversely associated with circulating markers of inflammation and oxidative stress in Koreans with and without depression in this case control study. Future randomized controlled trials are needed to determine whether dietary or supplemental n-3 PUFAs can reduce inflammation and oxidative stress, and reduce depressive symptoms in humans.

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1. Introduction

Depression is associated with considerable morbidity, and has been projected by the World Health Organization to become the second most common cause of disability by 2020 [1]. Moreover, suicide has dramatically increased in Korea and is strongly associated with mental disorders such as depression [2].

Depression is accompanied by activation of the inflammatory response system indicated by an increased production of inflammatory cytokines and oxidative biomarker [3,4]. Cytokine production is accompanied by increased oxidative stress leading to elevated production of reactive oxygen species (ROS) and nitric oxide (NO), or decreased antioxidant defense such as superoxide dismutase (SOD) and glutathione peroxidase [4]. Oxidative stress also causes neuronal damage and plays a role in major depression via both the peripheral and central nervous systems [5].

On the other hand, inflammatory cytokines were found to be negatively associated with consumption of fish rich in n-3

polyunsaturated fatty acid (PUFA) such as eicosapentaenoic acid (EPA; 20:5n3) and docosahexaenoic acid (DHA; 22:6n3) in the Nurses' Health study [6] and plasma levels of n-3 PUFA in the InCHIANTI study [7] and the Heart and Soul Study [8]. Epidemiological studies also showed that low intake [9,10] and blood [11–13] levels of n-3 PUFAs are associated with an increased risk for being diagnosed with major depressive disorder. Clinical benefits of n-3 PUFA supplements have also been reported in several [14,15], but not all [16,17] randomized controlled trials. N-3 PUFA-induced suppression of eicosanoids has been shown to be involved in anti-inflammatory effects, particularly in the inhibition of tumor necrosis factor (TNF)-α and interleukin (IL)-6 [18]. We previously suggested that Omega-3 Index, erythrocyte levels of EPA and DHA could be a useful marker for depression in Koreans [11]. Baghai et al. [19] also reported that Omega-3 Index was lower in patients with major depressive disorder and were inversely associated with IL-6 levels. However, there is no other study investigating the association between blood levels of n-3 PUFAs and biomarkers of inflammation and particularly, oxidative stress in depressed patients.

Our previous study showed that the average Omega-3 Index was approximately 10% among Koreans, which was higher than in

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the Western populations [11,20]. The Korean National Health and Nutrition Examination survey consistently reported that Korean adults consumed higher amounts of fish, 50 g/d than the Western population [2]. Thus, we hypothesize that erythrocyte levels of n-3 PUFAs are negatively associated with biomarkers of inflammation and oxidative stress in Koreans with and without depression. The objectives of the present study were to: (1) Assess whether depressed participants had lower erythrocyte levels of n-3 PUFAs and n-3 PUFA/n-6 PUFA and higher circulating levels of inflammatory and oxidative stress biomarkers compared to the controls; (2) Explore whether erythrocyte levels of n-3 PUFAs and n-3 PUFA/n-6 PUFA were associated with the degree of depressive symptomatology and biomarkers of inflammation and oxidative stress; and (3) Explore whether individual fatty acids and composite fatty acid indices were correlated with biomarkers of inflammation and oxidative stress.

2. Patients and methods

2.1. Participants

This study protocol adhered to the guidelines laid out in the Declaration of Helsinki, and all protocols involving human participants were approved by the Institutional Review Board of Hanyang University Seoul and Kuri Hospital. Written informed consent was obtained from all participants. Participants were recruited consecutively from depressed patients who visited Hanyang University Seoul and Kuri Hospitals between September 2007 and December 2010.

The 80 cases consisted of depressed patients diagnosed according to the Center for Epidemiological Studies Depression Scale Korea version (CES-D-K) score ≥ 25 with confirmation by a psychiatrist according to the Diagnostic and Statistical Manual of Mental Disorders (DSM) IV [21] with careful attention to culturally different modes of expressing depressive feelings and thoughts [22]. Reliability, validity, and the optimal cutoff point for this scale were estimated. The receiver operating characteristic (ROC) curve analysis revealed two optimal cutoff points: 24/25, the point that best corresponded to the clinical diagnosis of depression, and 20/21, which most effectively detects and covers depressive symptoms

during screening. The fact that these cutoff points are higher than those in the Western countries may be due to different ways of affect expression, especially the suppression of positive affect, in cultures that are based on Confucian ethics. Eighty age- and sex-matched controls without a history of depression were recruited from patients visiting Hanyang University Seoul between September 2007 and December 2010.

A participant was excluded if he or she was pregnant, breastfeeding, under the age of 18 or over the age of 80. Information about age, gender, body mass index (BMI), family history of depressive disorders, exercise habits, cigarette smoking, alcohol intake and supplementation were obtained from interviews.

2.2. Biomarkers of inflammation and oxidative stress

Blood samples were taken in EDTA and SST blood tubes, and aliquots of serum and erythrocytes were stored at $-80\,^{\circ}\mathrm{C}$. Serum levels of TNF-α (Quantikine High Sensitivity Human TNF-α ELISA Kit, R&D Systems, Minneapolis, MN, USA), thiobarbituric acid reactive substances (TBARS Assay Kit, Cayman Chemical Company,

Table 1
Characteristics and erythrocytes fatty acid composition of participants with and without depression.[a]

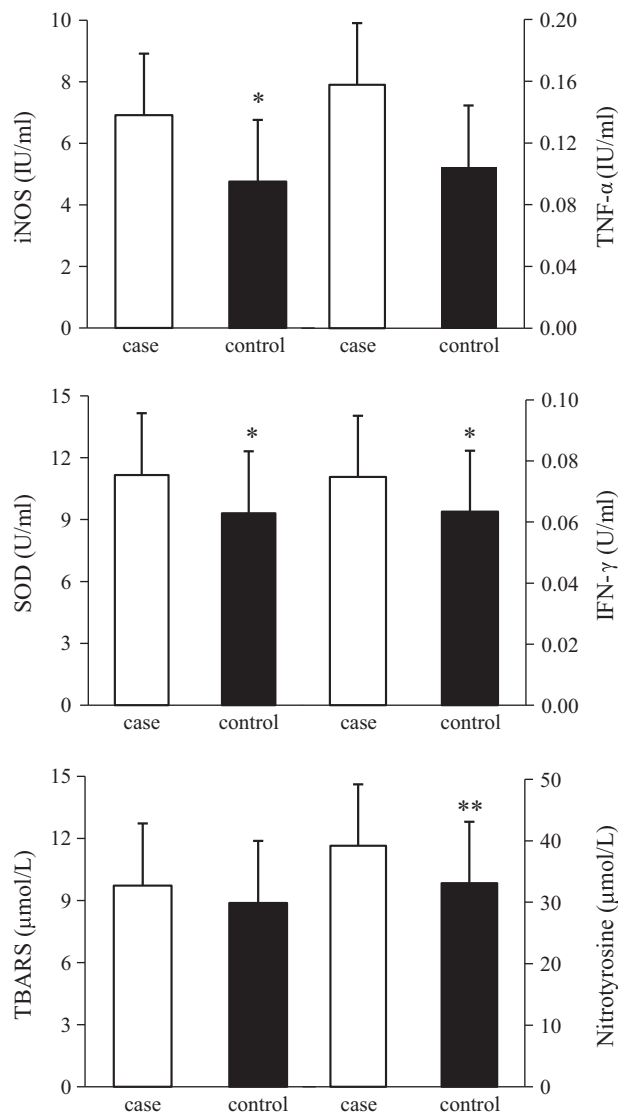|	Cases ($n=80$)	Controls ($n=80$)	P-value
Age (yr)	44.85 ± 1.77	44.47 ± 1.63	0.641
BMI (kg/m²)	22.62 ± 0.36	22.70 ± 0.22	0.982
Female, n (%)	59 (73.75)	52 (65.00)	0.136
Exercise, n (%)	30 (37.50)	27 (33.75)	0.193
Smoking, n (%)	23 (28.75)	25 (31.25)	0.665
Drinking, n (%)	41 (51.25)	55 (68.75)	0.051
CES-D-K score	35.41 ± 0.78	6.22 ± 0.50	< 0.001
16:0 (%)	21.51 ± 0.27	23.01 ± 0.21	0.025
18:0 (%)	16.25 ± 0.37	17.98 ± 0.15	0.001
16:1n7 (%)	0.90 ± 0.19	0.28 ± 0.02	0.001
18:2n6 (%)	12.86 ± 0.52	12.30 ± 0.43	0.159
20:4n6 (%)	14.84 ± 0.21	14.90 ± 0.28	0.844
18:3n3 (%)	0.39 ± 0.03	0.28 ± 0.01	< 0.001
20:5n3 (%)	1.12 ± 0.07	1.48 ± 0.05	< 0.001
22:6n3 (%)	7.49 ± 0.21	7.99 ± 0.01	0.059
Omega-3 Index (%)	8.61 ± 0.24	9.47 ± 0.20	0.006
16:1t (%)	0.25 ± 0.03	0.17 ± 0.02	0.054
18:1t (%)	0.39 ± 0.04	0.28 ± 0.03	0.035
18:2t (%)	0.29 ± 0.03	0.15 ± 0.02	< 0.001

[a] Values are means ± SEM or number of participant (percentage distribution), as appropriate; CES-D-K, Center for Epidemiological Studies Depression Scale Korea version; Omega-3 Index, sum of 20:5n3 and 22:6n3.

Fig. 1. Comparison of inflammatory and oxidative biomarker levels between cases and controls. An independent t-test was used to compare cases and controls. iNOS, inducible nitric oxide synthase; TNF-α, tumor necrosis factor alpha; IFN-γ, interferon gamma; SOD, superoxide dismutase; TBARS, thiobarbituric acid reactive substances; $n=160$. *$P < 0.05$, **$P < 0.01$.