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Short Communication

Omega-3/omega-6 fatty acid ratios in different phospholipid classes and depressive symptoms in coronary artery disease patients ☆

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ABSTRACT

Depressive symptoms are highly incident among coronary artery disease (CAD) patients and increase mortality. Reduced ratios of eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) (omega-3 fatty acids) to arachidonic acid (AA, omega-6 fatty acid) concentrations have been linked with depressive symptoms in CAD. It remains unclear whether depressive symptoms are differentially associated with that ratio in different phospholipid classes, and this may have mechanistic implications. This study investigated associations between depressive symptoms in CAD patients and the EPA + DHA to AA ratio in the major phospholipid classes. This was a cross-sectional study of stable CAD patients. Sociodemographic, medical, medication, and cardiopulmonary fitness data were collected from each patient. Each patient was assessed for depressive symptoms using the 17-item Hamilton Depression Rating Scale (HAM-D). The percentage of EPA, DHA, and AA in each erythrocyte phospholipid class was determined using gas chromatography from fasting blood. Relationships between EPA + DHA to AA ratios and depressive symptoms were assessed using linear regression and were corrected for multiple comparisons. Seventy-six CAD patients were included (age = 61.9 ± 8.5, 74% male, HAM-D = 7.2 ± 5.9). In a backward elimination linear regression model, lower EPA + DHA to AA in erythrocyte phosphatidylinositol ($B = -12.71$, $\beta = -0.33$, $p < .01$) and sphingomyelin ($B = -2.52$, $\beta = -0.37$, $p < .01$) was associated with greater depressive symptom severity, independently of other known predictors. Other phospholipid classes were not associated with depressive symptoms. In conclusion, the relationship between EPA + DHA to AA ratios and depressive symptoms in CAD may not be consistent across phospholipid classes. Continued investigation of these potentially differential relationships may clarify underlying disease mechanisms.

1. Introduction

Depressive symptoms are highly incident among patients with coronary artery disease (CAD) Celano and Huffman (2011), may persist for longer than one year (Lauzon et al., 2003), and double the risk of mortality (Penninx et al., 2001).

Several studies have detected a relationship between lower ratios of omega-3 to omega-6 fatty acids and the presence of depressive symptoms in CAD patients (Chang et al., 2015; Frasure-Smith et al., 2004; Vollmer-Conna et al., 2015). It is noteworthy that those studies measured the percent composition of omega-3 and omega-6 fatty acids relative to all fatty acids, which largely reflects the major phospholipid classes, phosphatidylcholine (PC) and phosphatidylethanolamine (PE). However, the abundance of those two classes does not mean that they are the most mechanistically relevant classes to depressive symptoms.

Different phospholipid classes, such as the PC, PE, phosphatidylinositol (PI), phosphatidylserine (PS), sphingomyelin (of the sphingolipid class), and lysophospholipids (i.e. lysophosphatidylcholine (lyso-PC)) have diverse functional roles in membrane regulation and cellular signalling (van Meer et al., 2008). Among many processes, those diverse roles may have implications for the balance of pro- and anti-inflammatory signalling

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(Kita et al., 2006), which is a proposed contributor to depressive symptoms (Dowlati et al., 2010). As such, the omega-3 to omega-6 fatty acid ratio, particularly the ratio of eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) (omega-3 fatty acids) to arachidonic acid (AA, an omega-6 fatty acid), in different phospholipid classes may illuminate different signalling pathways implicated in the mechanisms of depressive symptoms in CAD.

This cross-sectional study investigated the relationships between depressive symptoms in CAD patients and EPA + DHA to AA ratios in each erythrocyte phospholipid class in order to clarify pertinent classes for future study.

2. Methods

2.1. Patients

Patients were approached at entry into a cardiac rehabilitation program at 2 centres in Toronto, Ontario. The study received ethics approval at both sites, as well as the study research centre, Sunnybrook Research Institute. Patients with CAD, as defined previously (Mazereeuw et al., 2015a), aged 45–80, who were 8–10 weeks post-acute coronary syndrome, spoke and understood English, and provided written and informed consent were included. Patients were excluded if they had a history of a neurological condition, an Axis I psychiatric disorder other than depression, a significant acute medical illness, or substance abuse. Patients using fatty acid supplements were excluded. Antidepressant use was permitted on the condition of dose stability throughout the previous 3 months.

2.2. Assessments

Demographic information, a detailed medical history, and concomitant medications were recorded. Depressive symptoms were assessed using the 17-item Hamilton Depression Rating Scale (HAM-D) Hamilton, 1960 in a structured manner (Williams, 1988), as recommended by consensus guidelines (Davidson et al., 2006). Whether or not each patient had experienced a previous depressive episode was also recorded. Global cognitive performance was assessed using the Standardized Mini-Mental State Examination (sMMSE) Molloy, 1999 and was included as a covariate in the analyses. The number of vascular risk factors affecting each patient (including hypertension, dyslipidemia, obesity, smoking, and diabetes mellitus) was recorded. Cardiopulmonary fitness, as measured by the peak volume of oxygen (VO_2 peak) utilized by a patient during an exercise stress test at entry to the cardiac rehabilitation program, was also collected by study staff. The collected patient characteristics were considered for inclusion as covariates in the study analyses. Fasting (12 h overnight) blood was collected for fatty acid analysis.

2.3. Fatty acid analysis

Erythrocyte percent composition of EPA, DHA, and AA is a stable measure reflecting long-term dietary intake (Harris and Von Schacky, 2004; Harris and Thomas, 2010). The percentage of EPA, DHA, and AA in each erythrocyte phospholipid class (PC, PE, PS, PI, SM, and lyso-PC) was determined by thin layer chromatographic separation of phospholipid classes followed by analysis of fatty acids by gas chromatography as has been previously described (Leslie et al., 2014). In each class, the percent composition of EPA and DHA was summed and divided by the percent composition of AA, yielding the EPA + DHA to AA ratio for that class. All analyses were performed blinded to patient characteristics.

2.4. Statistics

Statistical models were computed using SPSS statistical software, version 13.0, Chicago, IL, USA and all analyses were two-tailed. First, individual linear regressions were conducted to investigate the association between HAM-D total scores and the EPA + DHA to AA ratios in each phospholipid class. For those with an initial p-value <.05, interpretation of each regression was corrected for multiple comparisons using the false discovery rate (Benjamini and Hochberg, 1995).

Phospholipid classes remaining significant predictors of HAM-D total score were then investigated in the context of other known predictors of depressive symptoms in CAD patients using a backward elimination linear regression model. In addition to the phospholipid EPA + DHA to AA ratio predictor variable, additional variables entered into the model were: age, sex, living alone, history of a previous depressive episode, antidepressant use, cardiac event/intervention type, the number of vascular risk factors affecting each patient, sMMSE total score, and VO_2 peak. Collinear predictors were excluded from the model. Predictors below 5% significance were omitted from the model until all parameters met criteria for a significant predictor of HAM-D total score (exit criterion $p > .05$).

3. Results

3.1. Patient characteristics

Between August 2010 and February 2014, 76 CAD patients were enrolled (characteristics are presented in Table 1).

3.2. Depressive symptoms

Patients were all generally cognitively intact (mean sMMSE score = 28.8 ± 1.2). HAM-D scores ranged between 0 and 20 (mean = 7.2 ± 5.9). Twenty-eight (37%) patients had a history of a previous depressive episode.

Table 1
Patient characteristics.

Demographics	
Age, mean (SD)	61.9 (8.5)
Sex, male, *n* (%)	56 (74)
Caucasian, *n* (%)	57 (75)
Married/living with others, *n* (%)	65 (86)
Smoking history, *n* (%)	
Previous smoker	43 (57)
Current smoker	6 (8)
Cardiovascular characteristics	
CAD event, *n* (%)	
MI/IHD	27 (36)
PTCA	28 (37)
CABG	18 (24)
Other	3 (3)
Hypertension, *n* (%)	51 (67)
Diabetes, *n* (%)	21 (28)
Dyslipidemia, *n* (%)	56 (74)
BMI (kg/m^2) (SD)	28.5 (5.0)
Number of vascular risk factors (SD)	2.5 (1.3)
VO_2 peak fraction (%) (SD)	73 (23)
Concomitant medications, n (%)	
Acetylsalicylic acid	66 (87)
Antidepressant	9 (12)
Anxiolytic	5 (7)
β-adrenergic receptor blocker	56 (74)
Statin	74 (97)

Abbreviations: SD, standard deviation; MI, myocardial infarction; IHD, ischemic heart disease; PTCA, percutaneous transluminal coronary angioplasty; CABG, coronary artery bypass graft; BMI, body mass index; VO_2, volume of oxygen.