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Oxidative stress predicts depressive symptom changes with omega-3 fatty acid treatment in coronary artery disease patients

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ABSTRACT

Background: Antidepressant efficacy of omega-3 polyunsaturated fatty acid (n-3 PUFA) treatment in coronary artery disease (CAD) patients remains unpredictable. N-3 PUFA can mitigate oxidative stress, which is common in CAD and may contribute to depressive symptoms. This study investigated whether greater pre-treatment oxidative stress, measured by the ratios of late-stage lipid peroxidation markers (malondialdehyde [MDA], 4-hydroxy-2-nonenal [4-HNE], and 8-isoprostane [8-ISO]) to an early-stage marker (lipid hydroperoxides [LPH]), predicted n-3 PUFA antidepressant benefits in CAD.

Methods: This was a secondary analysis of CAROTID (CAD Randomized Omega-3 Trial in Depression, NCT00981383). Patient demographics and medical characteristics were collected. Depressive symptoms were measured using the 17-item Hamilton Depression Rating Scale (HAM-D). Patients were then randomized to receive either 1.9 g/day n-3 PUFA or placebo for 12 weeks, after which HAM-D scores were reassessed. Baseline LPH, 4-HNE, 8-ISO, MDA and n-3 PUFA concentrations were analysed from fasting blood.

Results: Seventy-nine patients (age = 61.1 ± 8.5, 76% male, HAM-D = 7.5 ± 6.1) were included (n = 45 placebo, n = 34 n-3 PUFA). In the n-3 PUFA group, higher baseline ratios of MDA/LPH (primary analysis: $F_{1,33} = 6.20$, beta = −0.35, p = 0.018), 4-HNE/LPH (exploratory analysis: $F_{1,33} = 5.35$, beta = −0.32, p = 0.027), and 8-ISO/LPH (exploratory analysis: $F_{1,33} = 6.10$, beta = −0.33, p = 0.019), indicating higher oxidative stress, were associated with greater depressive symptom improvement. In each model, higher baseline EPA + DHA concentrations independently predicted depressive symptom improvement with n-3 PUFA (MDA/LPH: $F_{1,33} = 11.05$, p = 0.002; 4-HNE/LPH: $F_{1,33} = 11.36$, p = 0.002; 8-ISO/LPH: $F_{1,33} = 13.15$, p = 0.001). No associations were observed in the placebo group.

Conclusions: n-3 PUFA may be more likely to improve depressive symptoms in CAD patients with pre-treatment evidence of oxidative stress.

1. Introduction

Increased lipid peroxidation has been associated with the presence and severity of depressive symptoms (Mazereeuw et al., 2015). This may be particularly relevant to depressive symptoms among patients with coronary artery disease (**CAD**) given the involvement of oxidative stress in that condition (Negi and Anand, 2010).

In the early stage of lipid peroxidation, reactive oxygen species damage unsaturated lipids, producing lipid hydroperoxides (**LPH**). LPH may be neutralized by antioxidant defenses, or they may progress to later stages of lipid peroxidation if antioxidant defenses are overwhelmed (Forman et al., 2014). Late-stage lipid peroxidation markers include malondialdehyde (**MDA**), 4-hydroxy-2-nonenal (**4-HNE**), and 8-isoprostane (**8-ISO**), each of which has been previously associated with the presence of depressive symptoms (Mazereeuw et al., 2015).

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Increased oxidative stress appears to be more closely related to depressive symptoms in patients with deficits in omega-3 polyunsaturated fatty acids (**n-3 PUFA**) such as eicosapentaenoic acid (**EPA**) and docosahexaenoic acid (**DHA**) (Bigornia et al., 2016). Accordingly, n-3 PUFA have shown antioxidant effects against reactive oxygen species in clinical samples (Azizi-Soleiman et al., 2013; Lee et al., 2013), and these effects have been associated with reduced depressive-symptom like behaviour in animals (de Mello et al., 2014). As such, n-3 PUFA treatment of depressive symptoms may be particularly beneficial in patients with greater baseline evidence of oxidative stress; however, this has yet to be studied.

This study investigated whether the baseline severity of oxidative stress, as measured by the ratios of late-stage lipid peroxidation markers (MDA, 4-HNE, and 8-ISO) to an early-stage marker (LPH), was associated with improvement in depressive symptoms among n-3 PUFA treated CAD patients.

2. Methods

This was a secondary analysis of data from the CAD Randomized Omega-3 Trial in Depression (**CAROTID**), which was a randomized, double-blind, placebo-controlled trial investigating the antidepressant efficacy of 1.9 g/day n-3 PUFA treatment compared to placebo using a 12-week parallel arm design (Mazereeuw et al., 2016). This study was approved by the Research Ethics Boards of Sunnybrook Health Sciences Centre, University Health Network, and Trillium Health Partners, and was conducted according to the principles expressed in the Declaration of Helsinki.

2.1. Patients

Trial inclusion and exclusion criteria are detailed elsewhere (Mazereeuw et al., 2016). Briefly, patients enrolled in CAROTID were those with evidence of stable CAD (history of myocardial infarction, coronary artery bypass graft, percutaneous transluminal coronary angioplasty, or at least a 50% stenosis in one or more major coronary artery), aged 45–80 years, male or female, and the ability to speak and understand English. Excluded patients were those with a significant acute medical illness, clinically significant cognitive impairment, a neurological condition, unstable angina, or a contraindication to n-3 PUFA supplements. Antidepressant use was permitted if used at a stable dose for at least 3 months prior to the trial.

2.2. Design

Eligible patients consenting to participate in CAROTID were invited to a baseline visit, prior to treatment arm randomization. At baseline, patient demographic, anthropomorphic, medical, and medication information was documented. Whether or not a patient had previously experienced a depressive episode was also recorded.

Depressive symptoms were assessed using the 17-item Hamilton Depression Rating Scale (HAM-D) (Williams, 1988). Fasting (12 h overnight) blood was drawn and processed for analysis of serum lipid peroxidation markers and plasma n-3 PUFA. Patients were then randomized (1:1) to receive either 1.9 g/d n-3 PUFA supplements (1.2 g/d EPA + 0.6 g/d DHA + 0.1 g/d other n-3 PUFA) or placebo for 12 weeks. Depressive symptom severity was reassessed using the HAM-D at week 12.

2.3. Analysis of lipid peroxidation markers and n-3 PUFA

Serum concentrations of LPH were measured based on absorbance relative to hydroperoxide at 500 nm in spectrophotometry (Cayman; Item No. 705003). Serum concentrations of MDA (Cayman; item No. 700870) were measured based on the absorbance of reaction products with thiobarbituric acid reactive substances at 530 nm in spectrophotometry. Serum concentrations of 4-HNE (Cell Biolabs, Inc.; STA-338) and 8-ISO (Cayman; item No. 516351) were quantified by standard sandwich ELISA according to manufacturer's instructions.

Plasma EPA and DHA concentrations were measured by gas chromatography as previously described (Merino et al., 2011). The sum of baseline EPA and DHA concentrations (EPA + DHA, as a measure of plasma "omega-3 index" (Harris and Von Schacky, 2004)) were included as a planned covariate. All analyses were performed blinded to treatment allocation and patient characteristics.

2.4. Statistical analyses

Late-stage/early-stage ratios were calculated by dividing the concentrations of each of MDA, 4-HNE, and 8-ISO by the concentration of LPH, yielding the MDA/LPH, 4-HNE/LPH, and 8-ISO/LPH ratios. The MDA/LPH ratio was investigated in the primary analysis as MDA has been the most consistently measured marker in previous depression studies (Mazereeuw et al., 2015). The HNE/LPH and 8-ISO/LPH ratios were investigated in the exploratory analysis. The ratios were log-transformed to ensure consistent normality between them, and the resulting transformed values were used for analyses. Ratios of oxidative stress markers, including those comparing late-stage to early-stage lipid peroxidation, have been previously used to indicate the severity of oxidative stress (Scola et al., 2016; Andreazza et al., 2007).

The baseline MDA/LPH, 4-HNE/LPH, and 8-ISO/LPH ratios were assessed as predictors of depressive symptom change in both the n-3 PUFA and placebo groups using a repeated measures general linear model with HAM-D total score as the dependent variable with 2 observations (baseline and week 12). Predictive associations between those ratios and changes in depressive symptom scores over 12 weeks were also investigated using linear regression to provide context for the direction and increment of the association. Missing data were imputed using multiple imputation (Rubin, 1987). Planned covariates were age as well as baseline plasma concentrations of EPA + DHA due to their previously identified relationships with depressive symptom changes in CAD patients treated with n-3 PUFA (Carney et al., 2016) (Mazereeuw et al., 2016). *Post-hoc* analyses included exploration of the associations between each baseline ratio and depressive symptom changes with n-3 PUFA in a subgroup that completed the study protocol and a subgroup not using antidepressant maintenance medication. The presence of statistical outliers was determined using the interquartile range method and through visual inspection. Finally, the baseline ratios were deconstructed, and associations between individual lipid peroxidation markers and depressive symptom changes with n-3 PUFA were explored.

Statistical models were computed using SPSS statistical software, version 13.0, Chicago, IL, USA and all analyses were two-tailed.

3. Results

Between August 2010 and February 2014, 645 patients were assessed for CAROTID trial eligibility and 92 patients were enrolled into the randomization phase. As reported previously, compliance with n-3 PUFA supplements was good; however, n-3 PUFA treatment did not improve depressive symptoms over 12 weeks compared to placebo (Mazereeuw et al., 2016). Of the 92 patients enrolled in CAROTID, 79 patients (34 receiving n-3 PUFA and 45

Table 1
Baseline patient characteristics.

Characteristic	Patients (n = 79)	n-3 PUFA (n = 34)	Placebo (n = 45)	Significance		
				F/χ^2	*df*	*P*
Demographics						
Mean age (SD)	61.1 (8.5)	62.6 (8.9)	59.8 (8.1)	2.25	1	0.14
Sex, male, n	60	27	33	0.39	1	0.60
Cardiovascular characteristics (n)						
CAD event				0.74	3	0.86
MI/IHD	29	11	18			
PTCA	28	12	16			
CABG	20	10	10			
Other	2	1	1			
Smoking history				2.19	2	0.34
Previous smoker	42	19	23			
Current smoker	8	5	3			
Hypertension	51	23	28	0.25	1	0.62
Diabetes	19	11	8	2.25	1	0.19
Obese (BMI > 30)	27	11	16	0.09	1	0.81
Dyslipidemia	61	28	33	0.90	1	0.42
Psychometric characteristics						
HAM-D_{17} total score, mean (SD)	7.5 (6.1)	7.3 (6.7)	7.6 (5.6)	0.05	1	0.83
History of depression, n	32	14	18	0.11	1	0.92
Biochemical characteristics						
Plasma EPA + DHA (μg/ml), mean (SD)	73.8 (32.0)	64.1 (22.2)	81.3 (36.4)	6.10	1	0.016
Serum LPH (μM), mean (SD)	17.9 (12.6)	17.7 (12.5)	18.2 (12.8)	0.03	1	0.88
Serum 4-HNE (fmol/μg), mean (SD)	45.6 (15.5)	44.5 (16.8)	46.4 (14.7)	0.27	1	0.60
Serum 8-ISO (pg/mL), mean (SD)	0.11 (0.07)	0.11 (0.06)	0.12 (0.08)	1.35	1	0.25
Serum MDA (uM), mean (SD)	0.04 (0.02)	0.04 (0.02)	0.04 (0.02)	0.01	1	0.91

Abbreviations: SD, standard deviation; df, degrees of freedom; n-3 PUFA, omega-3 polyunsaturated fatty acid; MI, myocardial infarction; IHD, ischemic heart disease; PTCA, percutaneous transluminal coronary angioplasty; CABG, coronary artery bypass graft; BMI, body mass index; HAM-D, 17-Item Hamilton Depression Rating Scale; EPA, eicosapentaenoic acid; DHA, docosahexaenoic acid; LPH, lipid hydroperoxides; 4-HNE, 4-hydroxy-2-nonenal; 8-ISO, 8-isoprostane; MDA, malondialdehyde.

receiving placebo) provided baseline serum lipid peroxidation samples and were included in the present study.

Patient characteristics are summarized in Table 1. There were no differences in the history of CAD, cardiovascular risk factors, history or severity of depression, or concomitant medications used between the treatment groups. The majority of patients were using statins (99%), acetylsalicylic acid (86%), and antihypertensives (75%), whereas few patients were using anti-inflammatory agents (4%), anxiolytics (6%), or antidepressants (14%). Baseline (prior to treatment) plasma EPA + DHA concentrations were greater in the placebo group than in the n-3 PUFA group.

3.1. Lipid peroxidation and depressive symptom outcomes

There were no differences in the baseline raw concentrations of the lipid peroxidation markers between the treatment groups [Table1]. In the primary analysis, a greater baseline MDA/LPH ratio was significantly associated with depressive symptom improvement over 12 weeks with n-3 PUFA treatment [Table 2, Fig. 1]. In exploratory analyses, greater baseline ratios of 4-HNE/LPH and 8-ISO/LPH each significantly predicted greater improvement in depressive symptoms over 12 weeks of n-3 PUFA treatment [Table 2, Fig. 1].

These ratios remained significant predictors of improvement with treatment after adjusting for age and for the baseline plasma concentration of EPA + DHA [Table 2]. Greater baseline EPA + DHA concentrations were an independent predictor of improvement with treatment in each model (MDA/LPH model: $F_{1,33} = 11.05$, $p = 0.002$; 4-HNE/LPH model: $F_{1,33} = 11.36$, $p = 0.002$; 8-ISO/LPH model: $F_{1,33} = 13.15$, $p = 0.001$).

Neither the baseline lipid peroxidation ratios [Table 2] nor the baseline plasma EPA + DHA concentrations were associated with depressive symptom changes over 12 weeks in the placebo group in either the unadjusted or adjusted models.

3.2. Post-hoc analyses

In the per-protocol subgroup of patients treated with n-3 PUFA (n = 29), greater baseline ratios of MDA/LPH (adjusted: $F_{1,28} = 5.88$, $p = 0.024$), 4-HNE/LPH (adjusted: $F_{1,28} = 9.12$, $p = 0.006$), and 8-ISO/

Table 2
A greater baseline ratio of late-stage/early-stage lipid peroxidation predicts changes in HAM-D total scores with n-3 PUFA treatment, but not with placebo.

Outcome	$F_{1,33}$[a]	n-3 PUFA (n = 34)			$F_{1,44}$[a]	Placebo (n = 45)		
		B (SE)[b]	β[b]	*P*[a]		B (SE)[b]	β[b]	*P*[a]
Unadjusted models								
MDA/LPH (primary)	11.93	−3.10 (0.99)	−0.50	*0.001*	0.12	0.06 (1.74)	−0.01	0.73
4-HNE/LPH	9.29	−3.65 (1.38)	−0.44	*0.005*	0.46	−0.45 (2.09)	−0.03	0.50
8-ISO/LPH	8.37	−2.65 (1.11)	−0.42	*0.007*	2.36	−2.15 (1.41)	−0.22	0.13
Adjusted models								
MDA/LPH (primary)	6.20	−2.17 (1.04)	−0.35	*0.018*	0.12	0.09 (1.78)	0.01	0.73
4-HNE/LPH	5.35	−2.60 (1.41)	−0.32	*0.027*	0.40	−0.58 (2.13)	−0.04	0.53
8-ISO/LPH	6.10	−2.07 (1.11)	−0.33	*0.019*	2.69	−2.41 (1.48)	−0.25	0.11

Italicized values indicates statistical significance.

[a] Repeated measures linear regression models were used for the main analysis. The *p* value represents that of the repeated measures regression.

[b] B (SE) and β coefficients from linear regression were included to present the direction of the observed associations. The adjusted models included age and baseline plasma EPA + DHA concentrations as covariates.

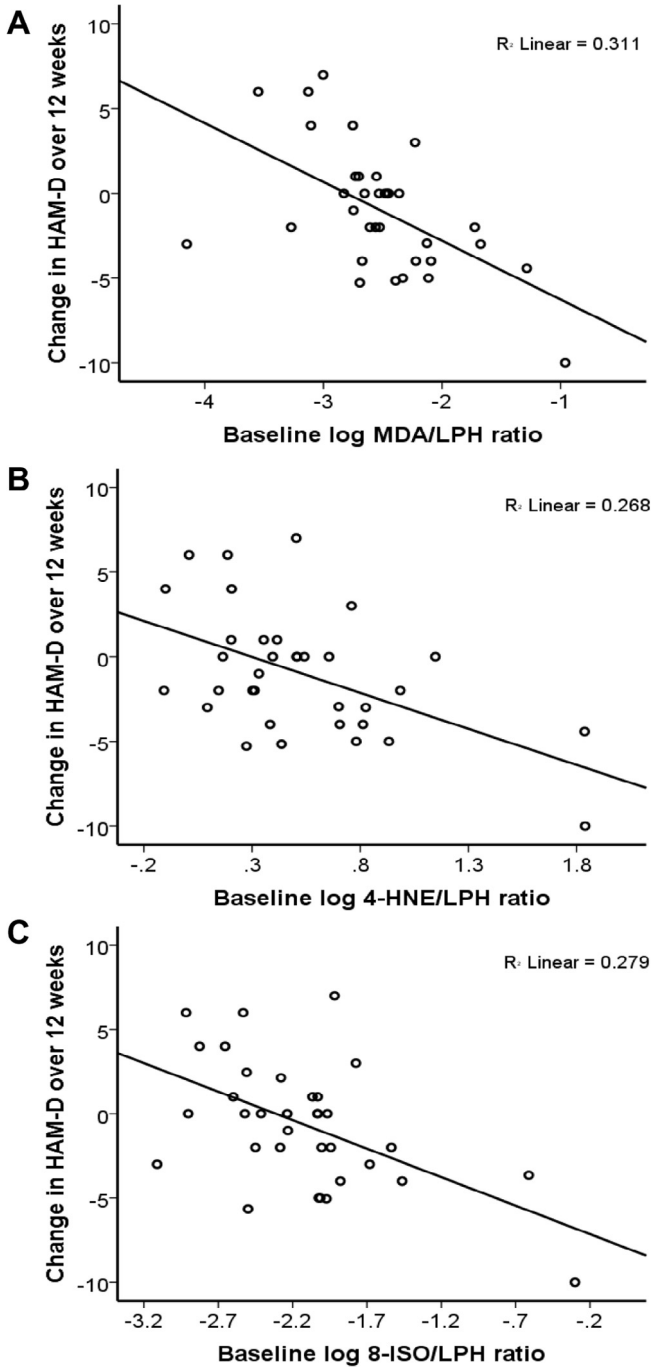

Fig. 1. Associations between late-stage/early-stage ratios and change in depressive symptoms with 12 weeks of n-3 PUFA treatment. All associations were statistically significant in both unadjusted and adjusted models (refer to Table 2 for summary statistics). None of the data points in each plot (A, B, or C) were determined to be outliers (interquartile range method). After removal of two visually extreme points from the 4-HNE/LPH (B) and 8-ISO/LPH (C) ratio data, relationships between those baseline ratios and depressive symptom changes were no longer significant (refer to *post-hoc* sensitivity analyses).

LPH (adjusted: $F_{1,28} = 12.64$, $p = 0.002$) remained significant predictors of improvement in depressive symptoms over 12 weeks.

Similarly, after excluding n-3 PUFA treated patients using antidepressant maintenance medication throughout the trial ($n = 6$, resulting subgroup $n = 28$), greater baseline ratios of MDA/LPH (adjusted: $F_{1,27} = 6.12$, $p = 0.019$), 4-HNE/LPH (adjusted: $F_{1,27} = 7.16$, $p = 0.013$), and 8-ISO/LPH (adjusted: $F_{1,27} = 8.48$, $p = 0.007$) remained significant predictors of improvement in depressive symptoms over 12 weeks.

Deconstructing the baseline lipid peroxidation ratios revealed that none of LPH ($F_{1,33} = 2.35$, $p = 0.13$), MDA ($F_{1,33} = 2.26$, $p = 0.14$), 4-HNE ($F_{1,33} = 1.31$, $p = 0.26$), or 8-ISO ($F_{1,33} = 0.92$, $p = 0.34$) were independently associated with improvement in depressive symptoms with n-3PUFA after adjusting for covariates.

Although no statistical outliers were found, visual inspection suggested that the associations between depressive symptom changes and the 4-HNE/LPH and 8-ISO/LPH ratios may have been driven by two data points. After removal of those points in sensitivity analyses, neither association (adjusted models, 4-HNE/LPH: $F_{1,31} = 0.86$, $p = 0.36$; 8-ISO/LPH: $F_{1,31} = 1.05$, $p = 0.31$) remained significant. Visual inspection did not suggest removal of any data points from the MDA/LPH ratio.

4. Discussion

Greater baseline ratios of late-stage lipid peroxidation markers to early-stage lipid peroxidation markers in serum were associated with a greater improvement of depressive symptoms with 12 weeks of n-3 PUFA treatment. As lipid peroxidation markers reflect oxidative damage to lipids, this finding suggests that increased oxidative stress may generally be a pre-treatment predictor of n-3 PUFA antidepressant efficacy. This interpretation is supported by the finding that oxidative stress was not associated with depressive symptom changes in the placebo group.

Though the mechanisms by which n-3 PUFA, particularly EPA and DHA, which were the active ingredients in the formulation used in this study, mediate antioxidant effects remain unclear, several possibilities have been reviewed (Giordano and Visioli, 2014). For example, EPA and DHA have been shown to form micelles which scavenge free radicals, and to reduce hydroxyl radical and superoxide radical production. EPA and DHA have also been shown to downregulate the expression of NADPH oxidase, a major contributor to oxidative stress. Beyond oxidative stress, EPA and DHA are associated with downregulation of redox-sensitive transcription factors such as NF-κB, which increase the synthesis of pro-inflammatory cytokines associated with depression (Dowlati et al., 2010; Palanisamy et al., 2015). Consistent with these mechanisms, the antioxidant effects of n-3 PUFA have been regularly demonstrated in clinical samples (Azizi-Soleiman et al., 2013; Lee et al., 2013; Duffy et al., 2015).

As we postulated, a greater MDA/LPH ratio might indicate a greater conversion of early-stage lipid peroxidation products such as LPH to later-stage products such as MDA. This implication is supported by the relationships between the 4-HNE/LPH and 8-ISO/LPH ratios and depressive symptom change with n-PUFAs observed in exploratory analyses. High ratios in certain patients may indicate a high level of oxidative stress and overwhelmed antioxidant defenses, which may be amenable to n-3 PUFA treatment. The lack of significant relationships between individual late-stage or early-stage markers and depressive symptom changes suggests that the degree of conversion from early-stage to late-stage lipid peroxidation may be more relevant than the absolute concentrations of lipid peroxidation markers. It also suggests that these ratios were not driven by a significant relationship between LPH, their common denominator, and depressive symptom changes.

The conditions under which an early-stage marker such as LPH might transform into a particular late-stage marker such as MDA rather than another late-stage marker such as 4-HNE, *in vivo*, remain unclear. This study included multiple late-stage markers to evaluate a variety of potential late-stage/early-stage ratios, which appeared to similarly predict depressive symptom changes in this study. These findings suggest that the late-stage/early-stage ratio of lipid peroxidation may be reflected using any of

MDA, 4-HNE, or 8-ISO as the late-stage marker, although results of our sensitivity analysis indicate that MDA may be more robust than the others. These findings should be confirmed by future studies.

Oxidative stress has yet to be reported as a predictor of depressive symptom changes with n-3 PUFA treatment in CAD or other populations; however, previous studies have implicated inflammatory biomarkers as a predictor of antidepressant treatments. Elevated inflammatory activity, which is closely related to oxidative stress activity (Maes et al., 2011), has been shown to predict improvements in depressive symptoms among patients treated with n-3 PUFA (Rapaport et al., 2016). Inflammation may also differentially predict response to selective serotonin reuptake inhibitors and anti-inflammatory therapies. For example: while elevated baseline concentrations of circulating inflammatory markers such as C-reactive protein, interleukin-6, and tumor necrosis factor may not be associated with response to sertraline (Bot et al., 2011) or may predict non-response to escitalopram (Eller et al., 2008), they appear to predict the antidepressant efficacy of the tumor necrosis factor-antagonist infliximab (Raison et al., 2013) and exercise interventions (Rethorst et al., 2013) in patients with major depressive disorder, both of which have anti-inflammatory effects (Swardfager et al., 2012). These findings support the interpretation of the late-stage/early-stage lipid peroxidation ratios as favourable inflammatory/oxidative stress predictor of improvement in depressive symptoms with n-3 PUFA treatment.

This study also identified that greater baseline plasma concentrations of EPA + DHA were a significant predictor of improvement in depressive symptoms with n-3 PUFA treatment, but not with placebo. This finding contrasts with the hypothesis that n-3 PUFA deficits might indicate a state of increased responsiveness to n-3 PUFA treatment (McNamara, 2015). Rather, it is in line with previous evidence that greater baseline n-3 PUFA concentrations predict greater n-3 PUFA treatment response (Carney et al., 2016). Plasma and erythrocyte n-3 PUFA may indicate the level of biological n-3 PUFA reserves available to a patient in the midst of depressive symptoms, CAD, and the increased oxidative stress associated with those conditions (Mazereeuw et al., 2015; Negi and Anand, 2010). Consistent with this, cross-sectional studies have shown inverse relationships between oxidative stress markers and n-3 PUFA in those with depression (Bigornia et al., 2016; Baek and Park, 2013). Taken together, our findings suggest that adequate plasma n-3 PUFA concentrations and high oxidative stress prior to treatment may be favourable predictors of n-3 PUFA treatment benefit.

These findings invite future study along several lines. The utility of lipid peroxidation ratios may be better appreciated in models including inflammatory markers previously shown to predict n-3 PUFA antidepressant effects. The mechanisms by which LPH may convert into MDA, 4-HNE, or 8-ISO may elucidate underlying disease mechanisms which remain poorly understood. Finally, measurement of lipid peroxidation end-products may add mechanistic insight into the observed relationships between oxidative stress and n-3 PUFA in this study.

4.1. Limitations

The small sample size in the n-3 PUFA group limited the analyses to the inclusion of only 2 covariates. A larger sample size would have permitted the inclusion of other patient characteristics such as concomitant medications or cardiovascular risk factors. A larger sample size would have also permitted a well-powered investigation of a treatment X late-stage/early-stage ratio interaction incorporating both the n-3 PUFA and placebo groups in the same model. While there was an imbalance in the number of patients between the n-3 PUFA and placebo groups, the placebo group was used only as a comparison for the positive findings observed in the n-3 PUFA group. The similarities of patient characteristics in the n-3 PUFA and placebo groups suggest that patient factors were unlikely to be responsible for the different findings between them.

Plasma measurements of EPA and DHA have been shown to be more variable than measurements from erythrocytes (Harris and Thomas, 2010) and may reflect more recent EPA and DHA intake. The associations between baseline EPA + DHA concentrations and depressive symptom improvement with n-3 PUFA should be interpreted with this in mind. However, these associations are consistent with those recently observed using erythrocyte measurements (Carney et al., 2016).

As established normal ranges for serum concentrations of LPH and other markers have yet to be established, we could not determine whether the high concentrations measured in this study were truly high and whether the low concentrations were truly low in the broader population of persons with CAD. This limited the interpretation of the early-stage and late-stage markers individually and encouraged the use of the late-stage/early-stage ratios as the treatment predictors.

Finally, these findings are limited to the CAD population and may not be generalizable to other populations with depression. Depressive symptom severity in this sample was mild and uncomplicated by psychiatric-comorbidities. Whether the late-stage/early-stage ratios pertain to n-3 PUFA treatment success in more severely depressed samples should be investigated in future studies.

5. Conclusions

Greater oxidative stress prior to n-3 PUFA antidepressant treatment was associated with greater depressive symptom improvement over 12 weeks. These findings support oxidative stress as a potential biomarker that may clarify the variability in n-3 PUFA antidepressant efficacy observed in previous trials.

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