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# Do Omega-6 and *Trans* Fatty Acids Play a Role in Complex Regional Pain Syndrome? A Pilot Study

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## Abstract

**Objectives.—**The study aims to compare the omega-6 (n−6) and omega-3 (n−3) highly unsaturated fatty acids (HUFA), and *trans* fatty acid (*trans* FA) status of Complex Regional Pain Syndrome (CRPS) patients to pain-free controls.

**Design.—**Case control study.

**Setting.—**The setting was at a multidisciplinary rehabilitation center.

**Patients.—**Twenty patients that met the Budapest research diagnostic criteria for CRPS and 15 pain-free control subjects were included in this study.

**Outcome Measures.—**Fasting plasma fatty acids were collected from all participants. In CRPS patients, pain was assessed using the McGill Pain Questionnaire—Short Form.In addition, results from the perceived disability (Pain Disability Index), pain-related anxiety (Pain Anxiety Symptom Scale Short Form), depression (Center for Epidemiologic Studies Depression Scale Short Form), and quality of life (Short Form-36 [SF-36]) were evaluated.

**Results.—**Compared with controls, CRPS patients demonstrated elevated concentrations of n−6 HUFA and *trans* FA. No differences in n−3 HUFA concentrations were observed. Plasma concentrations of the n−6 HUFA docosatetraenoic acid were inversely correlated with the "vitality" section of the SF-36. *Trans* FA concentrations positively correlated with pain-related disability and anxiety.

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Disclosures

Robert David, PhD, and J. Alexander Bralley, PhD, are full-time employees of Metametrix Clinical Laboratory (Metametrix), which provided blood fatty analysis for this project. Christopher Ramsden, MD, has previously served as a consultant for Metametrix. No other authors report any disclosures.

**Conclusion.—**These pilot data suggest that elevated n−6 HUFA and *trans* FA may play a role in CRPS pathogenesis. These findings should be replicated, and more research is needed to explore the clinical significance of low n−6 and *trans* FA diets with or without concurrent n−3 HUFA supplementation, for the management of CRPS.

### Keywords

CRPS; Omega-6; Omega-3; Trans Fatty Acids; Arachidonic Acid; Chronic Pain

## Introduction

Complex Regional Pain Syndrome (CRPS) is a disabling neurological disorder that follows injury to peripheral nerves or their soft tissue innervations [1]. The most prominent feature of CRPS is refractory persistent pain, usually in a distal limb. Pain is typically accompanied by vasomotor and sudomotor changes, edema, trophic changes, and impaired motor function [1]. While the underlying biologic mechanisms are not fully known, accumulating evidence suggests that sustained immune activation may participate in the development and perpetuation of CRPS [2–4]. Further evidence indicates that CRPS is characterized by major changes in the structure and function of the central nervous system [5,6]. These derangements may distort pain processing in a manner that is manifest as chronic hyperalgesia and allodynia [5,6]. Despite advances in our understanding of CRPS pathophysiology, patients often do not obtain satisfactory or lasting relief from conventional therapies, which rely heavily on pharmacologic agents. The interdisciplinary standard of care is often unavailable to patients for a variety of reasons, prominently funding or access [7]. Thus, lack of effective or accessible treatment options makes CRPS a challenging condition for patients and clinicians; novel prevention and treatment strategies are urgently needed.

Recently, dietary and supplemental fatty acids have received considerable attention as risk modifiers for a wide range of chronic medical conditions, including immune [8] and neuropsychiatric disorders [9,10]. Because these bioactive acids influence several of the putative mechanisms involved in pain processing, dietary choices may play a role in CRPS prevention and management.

### Omega-6 and Omega-3 Fatty Acids and Pain Processing

Omega-6 (n−6) and omega-3 (n−3) 20− and 22− carbon highly unsaturated fatty acids (HUFA) with three or more double bonds are fundamental structural components of neuronal, glial, myelin, and immune cell membrane phospholipids [11,12]. Here, they influence a host of biochemical processes that are involved in chronic pain, including: 1) ion channel activity and neuronal membrane excitability [13,14]; 2) monoamine neurotransmission [15], and 3) immune/inflammatory responses [12].

Because humans lack the enzymatic machinery to synthesize n−6 or n−3 acids de novo, the n−6 and n−3 HUFA composition of blood and tissue membranes are largely determined by dietary supplies of n−6 and n−3 HUFA and their respective 18-carbon n−6 and n−3 precursors [16]. The n−6 and n−3 HUFA have different, and sometimes opposite, impacts

on key biochemical processes involved in pain processing. In general, n−6 HUFA and their oxidized metabolites promote [17,18], and n−3 HUFA antagonize (or minimally influence) [19,20], metabolic processes that facilitate hyperalgesia. Thus, n−6 and n−3 fatty acids may play conflicting roles in the development or maintenance of CRPS and other pathological pain states.

Previous reports have indicated that supplemental doses of the two principle n−3 HUFA eicosapentaenoic acid (EPA; 20:5 n−3) and docosahexaenoic acid (DHA; 22:6 n−3), have moderate analgesic or nonsteroidal anti-inflammatory drug (NSAID)-sparing effects in inflammatory arthritis [8], dysmenorrhea [21], and chronic musculoskeletal pain [22,23]. Beneficial effects of n−3 HUFA were generally attributed to competition with the n−6 HUFA arachidonic acid (AA; 20:4 n−6), and ensuing reduction of hyperalgesic AA-derived eicosanoids. However, n−6 and n−3 HUFA are pleiotropic molecules that may also influence pain signaling by modulating the functions of synaptic and axonal ion channels [13], serving as substrates for mediators actively involved in inflammatory resolution [24], and by acting as potent ligands for nuclear receptors that modulate gene expression [25].

## Trans *Fatty Acids*

Like n−6 and n−3 HUFA, *trans* fatty acids (*trans* FA) produced by industrial hydrogenation [26], deodorization [27], and/or frying [28] of vegetable oils, can alter nervous tissue and immune tissue structure and function. For example, moderate quantities of dietary *trans* FA increased nervous tissue accretion of n−6 HUFA [29], and altered brain monoamine neurotransmitter concentrations in rats [29] and pigs [30]. In humans, *trans* FA intake is associated with elevated circulating pro-inflammatory cytokines [31], which have previously been implicated in peripheral and central pain sensitization [32,33]. Thus, plausible biologic mechanisms exist whereby *trans* FA may alter the development and maintenance of pathological pain, as well as common pain-related comorbidities such as depression [34], anxiety [35], and catastrophizing [36]. To our knowledge, however, the relationship between *trans* FA and chronic pain has not been previously investigated.

Because n−6, n−3 HUFA, and *trans* FA are readily modifiable through dietary changes, and high n−6 and *trans* FA, and/or low n−3 HUFA may be risk factors for the development of chronic pain, a more thorough understanding of the roles of dietary fatty acids in chronic pain may lead to new treatments for these conditions. The demonstration of baseline differences in the n−6 HUFA, n−3 HUFA, and/or *trans* FA status between chronic pain patients and controls may have important implications for future therapeutic intervention trials.

## Objectives

The major objective of this pilot study was to investigate the potential relationships between plasma concentrations of n−6 HUFA, n−3 HUFA, and *trans* FA and persistent pain, with CRPS selected as a paradigm of chronic pain. Our principal hypothesis was that, compared with those without pain, CRPS patients would have lower concentrations of fatty acids with purported analgesic properties (n−3 HUFA), and higher concentrations of fatty acids with possible hyperalgesic properties (n−6 HUFA and *trans* FA). A secondary hypothesis was that

n−6 HUFA and *trans* FA would be positively correlated, and n−3 HUFA would be inversely correlated, with self-reported measures of pain severity, disability, anxiety and depressive symptoms in CRPS patients.

## Materials and Methods

### Patients and Controls

Patients with chronic CRPS were recruited from an outpatient chronic pain center, inpatient hospital, and other outpatient clinics affiliated with an urban academic rehabilitation hospital. Individuals at least 18 years of age who satisfied the Budapest research diagnostic criteria for CRPS [1] were invited to participate in the study. Controls were recruited via advertising in the same outpatient and inpatient settings. Individuals at least 18 years of age without active pain were invited to participate in the study. Pregnant women and those regularly consuming fatty acid supplements were excluded from both groups. The Institutional Review Board approved the study protocol, and all subjects provided written consent prior to the study.

### Assessments

Potential participants were evaluated during a single morning visit that included a review of eligibility and exclusion criteria. CRPS patients who met the eligibility criteria were enrolled in the study, underwent a focused history and physical exam, provided a fasting blood sample, and completed a self-report measures questionnaire battery that included: the McGill Pain Questionnaire Short Form (MPQ-SF) [37], the Pain Disability Index (PDI) [38], the Pain Anxiety Symptom Scale Short Form (PASS-20) [39], the Center for Epidemiologic Studies Depression Scale Short Form (CESD-10) [40], and the Short Form-36 Health Survey (SF-36) [41]. Control subjects completed a visual analog scale (VAS) to confirm lack of pain, which was defined as <5 mm on the 100-mm scale. Those who met all eligibility criteria provided a fasting blood sample. All study visits took place in the outpatient clinics.

### Blood Collection and Analytic Methods

Fasting whole blood samples were collected into lavender-top EDTA glass tubes. Samples were centrifuged immediately, and plasma was pipetted into a transfer tube and stored in a −70°C freezer until ready for analysis. Plasma fatty acids were determined using gas chromatography-mass spectrometry GC/MS in SIM mode (Metametrix Clinical Laboratory). Total fatty acids were esterified using direct transesterification with an acetyl chloride methanol : iso-octane mixture. The fatty acid methyl esters (FAME) were then separated by GC using an HP-23 *Cis/Trans* FAME capillary column. The sample fatty acids were identified and quantified against a standard mixture of known fatty acids using an HP 5793 MS [42]. Plasma fatty acid measurements were reported in micromolar (umol/L) concentrations, and also were converted to percent of total fatty acids by weight (%TFA) for quantitative and qualitative analysis, respectively.

### Data Analysis

Individual fatty acids of interest were measured. These included the n−3 HUFA EPA (20:5n−3), docosapentaenoic acid (DPA; 22:5n−3), and DHA (22:6n−3), and the n−6 HUFA

dihomo-gamma-linolenic acid (DGLA; 20:3n−6), AA (20:4n−6), and docosatetraenoic acid (DTA; 22:4n−6), as well as total 18-carbon *trans* FA. Ratios and percentages of interest were also calculated. These included the ratio of n−6 AA divided by n−3 EPA, and the percentage of n−6 HUFA in total HUFA (*%n6 in HUFA*). HUFAs were considered to be fatty acids if they were at least 20 carbons in length with three or more double bonds. The equation for calculation of *%n6 in HUFA* was: (20:3n−6 + 20:4n−6 + 22:4n−6)/(20:5n−3 + 22:5n−3 + 22:6n−3 + 20:3n−6 + 20:4n−6 + 22:4n−6) × 100. Because of our small sample size and the non-normal distributions for some fatty acid data, we used the Wilcoxon rank sum test, a test of medians, to compare the individual fatty acids by case status (CRPS vs control). Spearman's rank correlation coefficients were used to examine the associations of the individual fatty acids with scores obtained via self-reported outcome measures (MPQ-SF, PDI, PASS-20, CES-D-10, SF-36). A student's *t*-test was used to examine the comparability of demographic data for the two groups. All significance levels were set at .05 with no correction for multiple comparisons. All statistics were completed with Stata statistical software, release 11 (College Station, TX, USA).

## Results

### Demographics

Thirty-five participants, 20 with CRPS and 15 controls were enrolled in the study (Table 1). Of those with CRPS, 80% were female. Their ages ranged from 23 to 65 with an average age of 44 (standard deviation [SD] = 13). The duration of CRPS ranged from 7 to 479, with an average of 96 months (SD = 113). Eighty-seven percent of controls were female. Their ages ranged from 24 to 67, with an average age of 36 (SD = 13) (Table 1). There were no significant differences in gender, age, or ethnicity between groups (all *P*'s > 0.05).

### Comparison of Fatty Acid Data by Group

The median concentration of total n−6 HUFA was significantly higher in CRPS patients than controls (698.2 vs 602.5 umol/L; $P < 0.01$, Table 2). Median concentrations of individual n−6 HUFA were also higher in CRPS patients than controls, as follows: DGLA (157.5 vs 107.0, $P < 0.01$); AA (536.8 vs 478.7, $P = 0.10$); DTA (26.6 vs 19.7, $P < 0.01$). There were no significant differences in median concentrations of total n−3 HUFA, EPA, DPA, or DHA between CRPS patients and controls (all *P*'s > 0.05).

The median concentration of total 18-carbon *trans* FA was also significantly higher in CRPS patients vs controls (67.8 vs 48.5; $P < 0.01$). The median total fatty acid concentration was significantly higher in CRPS patients than controls (11262.3 vs 9335.9; $P \leq 0.01$). Plasma triglyceride concentrations were not measured directly, but all four major components of triglycerides (saturated fatty acids, 4554.3 vs 3707.3, $P < 0.01$; monounsaturated fatty acids, 2781.3 vs 1860.8, $P < 0.01$; n−6 linoleic acid, 2038.5 vs 1739.1, $P = 0.07$; and n−3 alpha-linolenic acid, 54.4 vs 35.1, $P = 0.01$), were higher in CRPS patients than controls (Table 2, and Appendix 1). When fatty acids were expressed qualitatively as a %TFA (Table 3), median concentrations of total n−3 HUFA were significantly lower in CRPS patients vs controls (3.55 vs 4.42; $P = 0.03$). There were no statistically significant differences in n−6 HUFA or *trans* FA between patients and controls (all *P*'s > 0.05).

### Ratios and Percentages of Interest

The mean %*n−6 in HUFA* was 72.2% in the CRPS patients vs 69.2% in controls ($P = 0.11$, Table 3). No significant differences were seen for AA to EPA ratios (16.4 vs 14.7, $P = 0.42$).

### Relationships among Fatty Acids and Outcome Data in CRPS Patients

On Spearman correlation analysis, CRPS subjects with higher n−6 DTA tended to have lower vitality scores on the SF-36 ($r = -0.50$, $P = 0.03$). There were no other significant correlations between other n−6 HUFA, n−3 HUFA, or total HUFA and measures of pain severity, depressive symptoms, anxiety, or general health (all $P$'s > 0.05). CRPS subjects with higher total 18-carbon *trans* FA tended to have higher pain-related anxiety (PASS-20; $r = 0.56$; $P = 0.03$) and pain-related disability (PDI; $r = 0.63$; $P = 0.02$). No other significant correlations between *trans* FA and the other measures were present (all $P$'s > 0.05).

## Discussion

This study showed that plasma concentrations of both n−6 HUFA and *trans* FA are significantly higher in CRPS patients than in pain-free controls (Table 2). To our knowledge, this is the first demonstration of elevated n−6 HUFA or *trans* FA in CRPS. Contrary to our expectations, elevated n−6 HUFA concentrations in CRPS patients were not accompanied by predicted deficits in n−3 HUFA concentrations.

Median plasma concentrations of total n−6 HUFA, DGLA, and DTA, were significantly higher in CRPS patients than controls (Table 2). Median n−6 AA concentrations were also higher in CRPS patients, but the difference did not reach statistical significance ($P = 0.10$). Interestingly, the maximum value observed for AA in the 15 control participants was <550 umol/L, while 9 of 20 CRPS patients (45%) had AA concentrations above 550 umol/L.

Several plausible biologic mechanisms exist whereby the overabundance of n−6 HUFA observed in our study could predispose to both hyperalgesia and common pain-related psychological comorbidities. First, n−6 AA is the precursor to 2-series prostanoids, 4-series leukotrienes, and other potent mediators of pain and inflammation [17,18]. As part of the inflammatory milieu produced by activated immune cells and glial cells, these AA-derived eicosanoids amplify and perpetuate the inflammatory response by recruiting and activating other immune cells [43], sensitizing nerve endings, and lowering pain thresholds [17,18]. Recently, peripheral AA-derived prostanoids have been shown to relay inflammatory signals and to induce long-term synaptic plasticity throughout the neural axis [44–46]. Hyperalgesia in response to peripheral inflammation is in part dependent upon supraspinal AA signaling [47,48]. Second, as a major component of excitable membranes, AA modulates virtually all known ion channels, blocking some and activating others [13,49]. Animal evidence suggests that AA interacts with and augments glutamate-induced N-methyl-D-aspartate receptor activation [50], a key metabolic component of central sensitization [51]. Moreover, researchers have uncovered biochemical cross-talk between glutamate-induced excitotoxicity and neuroinflammation involving AA signaling [52]. Finally, accumulating evidence indicates that HUFA influence monoamine neurotransmission [15], perhaps via altering membrane function and scaffolding for

monoamine neurotransmitter receptors or transporters [53–55]. Indeed, high blood and tissue levels of n−6 HUFA, high n−6 HUFA to n−3 HUFA ratios, and elevated n−6 AA metabolism have been linked to major depressive disorder [56], refractory depression [57], and neuroticism [58], three conditions characterized by dysfunctional monoaminergic neurotransmission [59]. Thus, three neurobiological derangements observed in central pain sensitization (neuronal hyperexcitability, dysfunctional monoamine neurotransmission, and neuroinflammation) converge at the level of supraspinal AA metabolism.

The presence of higher n−6 DTA in CRPS patients than controls may also have important implications. Like AA, DTA is enriched in peripheral and central neural tissues, and is the third most plentiful polyunsaturated fat in the brain (after AA and DHA) [11,60]. DTA is especially abundant in myelin lipids [11], which have recently been implicated in the perpetuation of pathological pain [32]. Like AA, which is converted to eicosanoids, DTA can be converted to hormone-like mediators known as dihomoeicosanoids, with unknown metabolic roles [61]. Additionally, DTA can be swiftly retro-converted back to AA (far more efficiently than corresponding n−3 fatty acids) [62]. In this respect, DTA may serve as a reservoir to maintain high tissue AA levels, even in the context of elevated AA metabolism. High DTA concentrations may also be an indirect indicator of DHA deficiency [63]. Indeed, with n−3 deficiency, human tissues increase conversion of AA (20:4n−6) to DTA (22:4n−6) and n−6 DPA (22:5n−6), which partially replace the more elastic DHA (22:6n−3) in synaptic phospholipids [64]. We did not measure n−6 DPA; elevated levels would support a possible role for tissue DHA deficiency, and should be examined in future studies. Given the many plausible mechanisms in which overabundance of n−6 HUFA could predispose to pain, it is not clear why neither total n−6 HUFA, DGLA, AA, nor DTA were significantly associated with pain characteristics or pain intensity.

Contrary to our expectations, plasma concentrations of EPA, DHA, and total n−3 HUFA were not different in CRPS patients and controls. This was somewhat surprising considering previous reports of moderate analgesic and/or NSAID-sparing effects of n−3 HUFA supplements [8,21–23] and a wide array of potentially beneficial mechanisms of action of n−3 HUFA [24,25,65]. Although there were no differences in median n−3 HUFA plasma concentrations, CRPS patients had significantly lower n−3 HUFA than control subjects when expressed as %TFA. However, this finding appears to be skewed by the presence of elevated triglycerides in the CRPS group, as discussed next.

Beneficial effects of n−3 HUFA supplements are often attributed to partial substitution of n−3 HUFA for n−6 AA, and ensuing reduction of AA-derived eicosanoids with hyperalgesic properties [17,18]. However, the addition of even very high doses of n−3 HUFA has a limited effect on reducing tissue concentrations of n−6 AA when its precursor, linoleic acid (18:2 n−6), is consumed at the very high levels that are uniformly present in modern Western diets [66]. For example, Canadian women receiving 4.0 g per day of supplemental n−3 HUFA exhibited profound increases in tissue concentrations of EPA and DHA, but only slightly reduced AA concentrations by 16% [67]. After 4 weeks of high-dose supplementation, AA concentrations remained 62% higher than a nearby Canadian Inuit population consuming a high n−3 and low n−6 diet. Hence, low dietary n−6 fatty acids may

be required for major reductions of AA and other n−6 HUFA, and to maximize analgesic benefits of adding n−3 HUFA.

### %n−6 in HUFA as a Biomarker of n−6 and n−3 HUFA status

The biomarkers of %*n−6 in HUFA* and the closely related %*n−3 in HUFA* were designed by Lands et al. [16] to provide a broad assessment of HUFA status by expressing n−6 or n−3 HUFA as a percentage *of total* HUFA. By emphasizing the competitive interactions of n−3 and n−6 HUFA, these biomarkers provide a snapshot of HUFA status of various tissues where they have critical physiological consequences. In a recent study, the *%n−6 in HUFA* measured in whole blood correlated closely with liver, heart, and brain HUFA status in autopsied rats and pigs [67]. If this relationship holds true for humans, %*n−6 in HUFA* (measured in blood or plasma) may be a useful indicator of the n−6 and n−3 HUFA status of tissues involved in pain processing.

The mean %*n−6 in HUFA* in tissue phospholipids are known to vary widely, from less than 25% to more than 85%, in worldwide populations consuming dissimilar diets [16,68]. Comparison of mean population values for %*n−6 in HUFA* in rural Japan (34%), urban Japan (47%), with Japanese Americans (70%) [69] indicate that environment (presumably diet), rather than genetics, is the major determinant of HUFA status. We found only a nonsignificant trend toward a higher %*n−6 in HUFA* in CRPS patients compared with pain-free controls (72.2% vs 69.1%; $P = 0.11$, Table 4). However, %*n−6 in HUFA* was very high in both groups, when judged by global and historical standards, as was expected in this population consuming a modern American, high n−6 plus low n−3 diet [68]. The finding of high %*n−6 in HUFA* in both groups leads us to speculate that individuals consuming a typical American diet, including individuals who are currently pain-free, may be metabolically predisposed to develop chronic pain after a sufficient triggering stimulus.

### Trans *FA*

Eighteen-carbon *trans* FA (primarily elaidic acid) were significantly higher in CRPS patients than controls. Like n−6 HUFA, several plausible biologic mechanisms exist whereby *trans* FA could promote both hyperalgesia and exacerbate common pain-related psychological comorbidities. First, *trans* FA consumption is associated with elevated activity of pro-inflammatory cytokines [31], which are capable of inducing hyperalgesia and anhedonia [33,70,71], and have previously been linked to CRPS [2,3]. Moreover, dietary *trans* FA have been shown to disturb the release of monoamine neurotransmitters in the brains of rats [29] and pigs [30]. Resulting dysfunctional neurotransmission would be expected to reduce the activities of descending tracts that provide inhibitory input at the level of the dorsal horn, and therefore to exacerbate pain. Dysfunctional neurotransmission might also be expected to facilitate pain-related depression and anxiety [72,73]. Thus, our findings of positive correlations between *trans* FA and pain-related anxiety (PASS-20) and disability (PDI), warrant further investigation. Interestingly, *trans* FA are known to elevate blood triglycerides (TG) [74]. Thus, high dietary *trans* FA intake may be partly responsible for the apparent presence of elevated TG in our CRPS patients.

## Elevated Triglycerides in CRPS

Recently, hypertriglyceridemia (HTG) has been reported in fibromyalgia [75], which like CRPS, is an idiopathic pain condition characterized by central sensitization. Although we did not directly measure plasma TG, our CRPS patients had higher concentrations of total fatty acids and all four major components of TG than control participants (Table 2; see also Table 5). The apparent elevation of TG has important implications for interpretation of our results. HUFA account for only for 1% to 5% of total acids in TG vs 18% to 25% in phospholipids (PL) [16,76]. Hence, the apparent TG elevations in our CRPS group are expected to have only a minor impact on plasma HUFA concentrations, which are determined primarily by PL. However, the increased plasma concentrations of the many non-HUFA acids that are present in high quantities in TG (see Table 5) will reduce the values of HUFA when expressed qualitatively as %TFA. This appears to be the case with our sample; median values for total HUFA were 11.9% TFA in CRPS patients vs 13.4%TFA in the control group ($P = 0.10$). Thus, %TFA values are difficult to interpret in our study. Given the competitive nature of n−6 and n−3 HUFA, the finding that higher n−6 HUFA concentrations in CRPS were not accompanied by elevated n−3 HUFA has important implications for the interpretation of our results. Plasma concentrations, which provide a quantitative indication of n−6 and n−3 HUFA available for various metabolic processes (e.g., eicosanoid synthesis), appear to be the most informative way to express our data in this pilot study. An interesting question is whether the HTG observed in fibromyalgia and the apparent HTG in our CRPS sample is a feature of other chronic pain syndromes, and whether elevated TG are a consequence of dietary habits, metabolic phenomena, or other factors.

## Limitations

Several limitations of this pilot study merit discussion. First, because the CRPS population consisted of prevalent cases, it is not possible to assess whether the observed differences in fatty acids were a cause or consequence of having CRPS. For example, functional limitations or financial hardship resulting from CRPS could alter dietary habits in a manner to increase n−6 and *trans* fatty acids. Because dietary characteristics were not assessed, it is not possible to conclude whether metabolic differences, or different diets, accounted for the observed differences in plasma fatty acids. Another limitation is the lack of adjustments for potential confounding variables. Next, the small sample size may have resulted in large confidence intervals and lower statistical power for detecting differences between groups. We cannot rule out the possibility that differences in variables, including those that approached statistical significance such as n−6 AA and %*n6 in HUFA,* would become significant with the additional power afforded by larger sample sizes. Another limitation was the relative homogeneity of our study population, which consumed modern U.S. diets that are uniformly high in n−6 fatty acids. Lack of n−6 variability may have obscured differences in variables of interest and their correlations with pain characteristics, which would become apparent with more heterogeneity. Furthermore, we did not measure n−6 DPA (a numerator variable in %*n6 in HUFA*), and therefore may have underestimated %*n−6 in HUFA.* Future studies may benefit by measuring n−6 DPA. Future studies may also benefit by isolating and measuring the various lipid fractions, such as TG and PL. This would allow for more useful

information to be gleaned from the %TFA measurement, even if TG concentrations differ markedly between groups.

## Conclusion

The pilot data presented here, in conjunction with plausible biologic mechanisms, suggest that elevated n−6 HUFA and *trans* FA may play a role in CRPS pathogenesis. These findings should be replicated, and more research is needed to explore the clinical significance of low n−6 and *trans* FA diets, with or without concurrent n−3 HUFA supplementation, for the prevention or management of CRPS.

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## References

1. Harden RN, Bruehl S, Stanton-Hicks M, Wilson PR. Proposed new diagnostic criteria for complex regional pain syndrome. Pain Med 2007;8(4):326–31. [PubMed: 17610454]
2. Alexander GM, Perreault MJ, Reichenberger ER, Schwartzman RJ. Changes in immune and glial markers in the CSF of patients with Complex Regional Pain Syndrome. Brain Behav Immun 2007;21(5):668–76. [PubMed: 17129705]
3. Uceyler N, Eberle T, Rolke R, Birklein F, Sommer C. Differential expression patterns of cytokines in complex regional pain syndrome. Pain 2007;132(1–2):195–205. [PubMed: 17890011]
4. Schinkel C, Kirschner MH. Status of immune mediators in complex regional pain syndrome type I. Curr Pain Headache Rep 2008;12(3):182–5. [PubMed: 18796267]
5. Geha PY, Baliki MN, Harden RN, et al. The brain in chronic CRPS pain: Abnormal gray-white matter interactions in emotional and autonomic regions. Neuron 2008;60(4):570–81. [PubMed: 19038215]
6. Del Valle L, Schwartzman RJ, Alexander G. Spinal cord histopathological alterations in a patient with longstanding complex regional pain syndrome. Brain Behav Immun 2009;23(1):85–91. [PubMed: 18786633]
7. Harden RN, Swan M, King A, Costa B, Barthel J. Treatment of complex regional pain syndrome: Functional restoration. Clin J Pain 2006;22(5):420–4. [PubMed: 16772795]
8. Goldberg RJ, Katz J. A meta-analysis of the analgesic effects of omega-3 polyunsaturated fatty acid supplementation for inflammatory joint pain. Pain 2007; 129(1–2):210–23. [PubMed: 17335973]
9. Freeman MP, Hibbeln JR, Wisner KL, et al. Omega-3 fatty acids: Evidence basis for treatment and future research in psychiatry. J Clin Psychiatry 2006;67(12):1954–67. [PubMed: 17194275]
10. Hibbeln JR, Davis JM. Considerations regarding neuropsychiatric nutritional requirements for intakes of omega-3 highly unsaturated fatty acids. Prostaglandins Leukot Essent Fatty Acids 2009;81(2–3):179–86. [PubMed: 19619995]
11. Sastry PS. Lipids of nervous tissue: Composition and metabolism. Prog Lipid Res 1985;24(2):69–176. [PubMed: 3916238]
12. Calder PC. The relationship between the fatty acid composition of immune cells and their function. Prostaglandins Leukot Essent Fatty Acids 2008;79(3–5):101–8. [PubMed: 18951005]
13. Meves H Arachidonic acid and ion channels: An update. Br J Pharmacol 2008;155(1):4–16. [PubMed: 18552881]
14. Young C, Gean PW, Chiou LC, Shen YZ. Docosahexaenoic acid inhibits synaptic transmission and epileptiform activity in the rat hippocampus. Synapse 2000;37(2):90–4. [PubMed: 10881029]

15. Hibbeln JR, Linnoila M, Umhau JC, et al. Essential fatty acids predict metabolites of serotonin and dopamine in cerebrospinal fluid among healthy control subjects, and early- and late-onset alcoholics. Biol Psychiatry 1998;44(4):235–42. [PubMed: 9715354]
16. Lands WE, Libelt B, Morris A, et al. Maintenance of lower proportions of (n−6) eicosanoid precursors in phospholipids of human plasma in response to added dietary (n−3) fatty acids. Biochim Biophys Acta 1992;1180(2):147–62. [PubMed: 1463766]
17. Hedenberg-Magnusson B, Ernberg M, Alstergren P, Kopp S. Pain mediation by prostaglandin E2 and leukotriene B4 in the human masseter muscle. Acta Odontol Scand 2001;59(6):348–55. [PubMed: 11831483]
18. Martin HA, Basbaum AI, Goetzl EJ, Levine JD. Leukotriene B4 decreases the mechanical and thermal thresholds of C-fiber nociceptors in the hairy skin of the rat. J Neurophysiol 1988;60(2):438–45. [PubMed: 2845013]
19. Wada M, DeLong CJ, Hong YH, et al. Enzymes and receptors of prostaglandin pathways with arachidonic acid-derived versus eicosapentaenoic acid-derived substrates and products. J Biol Chem 2007;282(31):22254–66. [PubMed: 17519235]
20. Serhan CN. Systems approach with inflammatory exudates uncovers novel anti-inflammatory and pro-resolving mediators. Prostaglandins Leukot Essent Fatty Acids 2008;79(3–5):157–63. [PubMed: 19008087]
21. Harel Z, Biro FM, Kottenhahn RK, Rosenthal SL. Supplementation with omega-3 polyunsaturated fatty acids in the management of dysmenorrhea in adolescents. Am J Obstet Gynecol 1996;174(4):1335–8. [PubMed: 8623866]
22. Eriksen W, Sandvik L, Bruusgaard D. Does dietary supplementation of cod liver oil mitigate musculoskeletal pain? Eur J Clin Nutr 1996;50(10):689–93. [PubMed: 8909937]
23. Maroon JC, Bost JW. Omega-3 fatty acids (fish oil) as an anti-inflammatory: An alternative to nonsteroidal anti-inflammatory drugs for discogenic pain. Surg Neurol 2006;65(4):326–31. [PubMed: 16531187]
24. Serhan CN. Novel omega-3-derived local mediators in anti-inflammation and resolution. Pharmacol Ther 2005;105(1):7–21. [PubMed: 15626453]
25. Jump DB, Clarke SD. Regulation of gene expression by dietary fat. Annu Rev Nutr 1999;19:63–90. [PubMed: 10448517]
26. Beare-Rogers JL, Gray LM, Hollywood R. The linoleic acid and trans fatty acids of margarines. Am J Clin Nutr 1979;32(9):1805–9. [PubMed: 112850]
27. Ackman RG, Hooper SN. Linolenic acid artifacts from the deodorization of oil. J Am Oil Chemist Soc 1974;51:42–9.
28. Chardigny JM, Sebedio JL, Grandgirard A, et al. Identification of novel trans isomers of 20:5n−3 in liver lipids of rats fed a heated oil. Lipids 1996;31(2):165–8. [PubMed: 8835404]
29. Acar N, Chardigny JM, Darbois M, Pasquis B, Sebedio JL. Modification of the dopaminergic neurotransmitters in striatum, frontal cortex and hippocampus of rats fed for 21 months with trans isomers of alpha-linolenic acid. Neurosci Res 2003;45(4):375–82. [PubMed: 12657450]
30. Acar N, Chardigny JM, Berdeaux O, Almanza S, Sebedio JL. Modification of the monoaminergic neurotransmitters in frontal cortex and hippocampus by dietary trans alpha-linolenic acid in piglets. Neurosci Lett 2002;331(3):198–202. [PubMed: 12383930]
31. Lopez-Garcia E, Schulze MB, Meigs JB, et al. Consumption of trans fatty acids is related to plasma biomarkers of inflammation and endothelial dysfunction. J Nutr 2005;135(3):562–6. [PubMed: 15735094]
32. Thacker MA, Clark AK, Marchand F, McMahon SB. Pathophysiology of peripheral neuropathic pain: Immune cells and molecules. Anesth Analg 2007;105(3):838–47. [PubMed: 17717248]
33. Kawasaki Y, Zhang L, Cheng JK, Ji RR. Cytokine mechanisms of central sensitization: Distinct and overlapping role of interleukin-1beta, interleukin-6, and tumor necrosis factor-alpha in regulating synaptic and neuronal activity in the superficial spinal cord. J Neurosci 2008;28(20):5189–94. [PubMed: 18480275]
34. Dantzer R, O'Connor JC, Freund GG, Johnson RW, Kelley KW. From inflammation to sickness and depression: When the immune system subjugates the brain. Nat Rev Neurosci 2008;9(1):46–56. [PubMed: 18073775]

35. Koo JW, Duman RS. Interleukin-1 receptor null mutant mice show decreased anxiety-like behavior and enhanced fear memory. Neurosci Lett 2009;456(1):39–43. [PubMed: 19429130]
36. Edwards RR, Kronfli T, Haythornthwaite JA, et al. Association of catastrophizing with interleukin-6 responses to acute pain. Pain 2008;140(1):135–44. [PubMed: 18778895]
37. Melzack R The short-form McGill Pain Questionnaire. Pain 1987;30(2):191–7. [PubMed: 3670870]
38. Pollard CA. Preliminary validity study of the Pain Disability Index. Percept Mot Skills 1984;59(3):974. [PubMed: 6240632]
39. McCracken LM, Dhingra L. A short version of the Pain Anxiety Symptoms Scale (PASS-20): Preliminary development and validity. Pain Res Manag 2002;7(1):45–50. [PubMed: 16231066]
40. Andresen EM, Malmgren JA, Carter WB, Patrick DL. Screening for depression in well older adults: Evaluation of a short form of the CES-D (Center for Epidemiologic Studies Depression Scale). Am J Prev Med 1994;10(2):77–84. [PubMed: 8037935]
41. Ware JE, Kosinski M, Keller SD. SF-36 Physical and Mental Health Summary Scales: A User's Manual. Boston: The Health Institute; 1994.
42. Lepage G, Levy E, Ronco N, et al. Direct transesterification of plasma fatty acids for the diagnosis of essential fatty acid deficiency in cystic fibrosis. J Lipid Res 1989;30(10):1483–90. [PubMed: 2614252]
43. Funk CD. Prostaglandins and leukotrienes: Advances in eicosanoid biology. Science 2001;294(5548):1871–5. [PubMed: 11729303]
44. Smith VA, Beyer CE, Brandt MR. Neurochemical changes in the RVM associated with peripheral inflammatory pain stimuli. Brain Res 2006;1095(1):65–72. [PubMed: 16730668]
45. Vasquez E, Bar KJ, Ebersberger A, et al. Spinal prostaglandins are involved in the development but not the maintenance of inflammation-induced spinal hyperexcitability. J Neurosci 2001;21(22):9001–8. [PubMed: 11698610]
46. Yang H, Chen C. Cyclooxygenase-2 in synaptic signaling. Curr Pharm Des 2008;14(14):1443–51. [PubMed: 18537667]
47. Coderre TJ, Yashpal K. Intracellular messengers contributing to persistent nociception and hyperalgesia induced by L-glutamate and substance P in the rat formalin pain model. Eur J Neurosci 1994;6(8):1328–34. [PubMed: 7526941]
48. Bianchi M, Martucci C, Ferrario P, Franchi S, Sacerdote P. Increased tumor necrosis factor-alpha and prostaglandin E2 concentrations in the cerebrospinal fluid of rats with inflammatory hyperalgesia: The effects of analgesic drugs. Anesth Analg 2007;104(4):949–54. [PubMed: 17377112]
49. Meves H Modulation of ion channels by arachidonic acid. Prog Neurobiol 1994;43(2):175–86. [PubMed: 7526418]
50. Miller B, Sarantis M, Traynelis SF, Attwell D. Potentiation of NMDA receptor currents by arachidonic acid. Nature 1992;355(6362):722–5. [PubMed: 1371330]
51. Woolf CJ, Thompson SW. The induction and maintenance of central sensitization is dependent on N-methyl-D-aspartic acid receptor activation; implications for the treatment of post-injury pain hypersensitivity states. Pain 1991;44(3):293–9. [PubMed: 1828878]
52. Chang YC, Kim HW, Rapoport SI, Rao JS. Chronic NMDA administration increases neuroinflammatory markers in rat frontal cortex: Cross-talk between excitotoxicity and neuroinflammation. Neurochem Res 2008;33(11):2318–23. [PubMed: 18500552]
53. Hibbeln JR, Umhau JC, George DT, et al. Plasma total cholesterol concentrations do not predict cerebrospinal fluid neurotransmitter metabolites: Implications for the biophysical role of highly unsaturated fatty acids. Am J Clin Nutr 2000;71(suppl 2):331S–8S. [PubMed: 10617992]
54. Chalon S, Vancassel S, Zimmer L, Guilloteau D, Durand G. Polyunsaturated fatty acids and cerebral function: Focus on monoaminergic neurotransmission. Lipids 2001;36(9):937–44. [PubMed: 11724466]
55. Chapkin RS, McMurray DN, Davidson LA, et al. Bioactive dietary long-chain fatty acids: Emerging mechanisms of action. Br J Nutr 2008;100(6):1152–7. [PubMed: 18492298]

56. Adams PB, Lawson S, Sanigorski A, Sinclair AJ. Arachidonic acid to eicosapentaenoic acid ratio in blood correlates positively with clinical symptoms of depression. Lipids 1996;31(Suppl):S157–61. [PubMed: 8729112]
57. Dinan T, Siggins L, Scully P, et al. Investigating the inflammatory phenotype of major depression: Focus on cytokines and polyunsaturated fatty acids. J Psychiatr Res 2009;43(4):471–6. [PubMed: 18640689]
58. Conklin SM, Manuck SB, Yao JK, et al. High omega-6 and low omega-3 fatty acids are associated with depressive symptoms and neuroticism. Psychosom Med 2007;69(9):932–4. [PubMed: 17991818]
59. Sublette ME, Russ MJ, Smith GS. Evidence for a role of the arachidonic acid cascade in affective disorders: A review. Bipolar Disord 2004;6(2):95–105. [PubMed: 15005747]
60. Philbrick DJ, Mahadevappa VG, Ackman RG, Holub BJ. Ingestion of fish oil or a derived n−3 fatty acid concentrate containing eicosapentaenoic acid (EPA) affects fatty acid compositions of individual phospholipids of rat brain, sciatic nerve and retina. J Nutr 1987;117(10):1663–70. [PubMed: 2822876]
61. Harkewicz R, Fahy E, Andreyev A, Dennis EA. Arachidonate-derived dihomoprostaglandin production observed in endotoxin-stimulated macrophage-like cells. J Biol Chem 2007;282(5):2899–910. [PubMed: 17135246]
62. Rosenthal MD, Garcia MC, Jones MR, Sprecher H. Retroconversion and delta 4 desaturation of docosatetraenoate (22:4(n−6)) and docosapentaenoate (22:5(n−3)) by human cells in culture. Biochim Biophys Acta 1991;1083(1):29–36. [PubMed: 2031936]
63. Innis SM, Friesen RW. Essential n−3 fatty acids in pregnant women and early visual acuity maturation in term infants. Am J Clin Nutr 2008;87(3):548–57. [PubMed: 18326591]
64. Greiner RS, Catalan JN, Moriguchi T, Salem N Jr. Docosapentaenoic acid does not completely replace DHA in n−3 FA-deficient rats during early development. Lipids 2003;38(4):431–5. [PubMed: 12848290]
65. Ozyurt B, Sarsilmaz M, Akpolat N, et al. The protective effects of omega-3 fatty acids against MK-801-induced neurotoxicity in prefrontal cortex of rat. Neurochem Int 2007;50(1):196–202. [PubMed: 16971021]
66. Ramsden CE, Faurot KR, Carrera-Bastos P, et al. Dietary fat quality and coronary heart disease prevention: A unified theory based on evolutionary, historical, global, and modern perspectives. Curr Treat Options Cardiovasc Med 2009;11(4):289–301. [PubMed: 19627662]
67. Stark KD, Mulvad G, Pedersen HS, et al. Fatty acid compositions of serum phospholipids of postmenopausal women: A comparison between Greenland Inuit and Canadians before and after supplementation with fish oil. Nutrition 2002;18(7–8):627–30. [PubMed: 12093443]
68. Hibbeln JR, Nieminen LR, Blasbalg TL, Riggs JA, Lands WE. Healthy intakes of n−3 and n−6 fatty acids: Estimations considering worldwide diversity. Am J Clin Nutr 2006;83(6 Suppl):1483S–93S. [PubMed: 16841858]
69. Iso H, Sato S, Folsom AR, et al. Serum fatty acids and fish intake in rural Japanese, urban Japanese, Japanese American and Caucasian American men. Int J Epidemiol 1989;18(2):374–81. [PubMed: 2767851]
70. Watkins LR, Maier SF, Goehler LE. Immune activation: The role of pro-inflammatory cytokines in inflammation, illness responses and pathological pain states. Pain 1995;63(3):289–302. [PubMed: 8719529]
71. Samad TA, Moore KA, Sapirstein A, et al. Interleukin-1beta-mediated induction of cox-2 in the CNS contributes to inflammatory pain hypersensitivity. Nature 2001;410(6827):471–5. [PubMed: 11260714]
72. Poole H, White S, Blake C, Murphy P, Bramwell R. Depression in chronic pain patients: Prevalence and measurement. Pain Pract 2009;9(3):173–80. [PubMed: 19298363]
73. Dickenson AH, Ghandehari J. Anti-convulsants and anti-depressants. Handb Exp Pharmacol 2007;177:145–77.
74. Cassagno N, Palos-Pinto A, Costet P, et al. Low amounts of trans 18:1 fatty acids elevate plasma triacylglycerols but not cholesterol and alter the cellular defence to oxidative stress in mice. Br J Nutr 2005;94(3):346–52. [PubMed: 16176604]

75. Loevinger BL, Muller D, Alonso C, Coe CL. Metabolic syndrome in women with chronic pain. Metabolism 2007;56(1):87–93. [PubMed: 17161230]

76. Lands WE. Biosynthesis of prostaglandins. Annu Rev Nutr 1991;11:41–60. [PubMed: 1892707]

**Table 1**

Characteristics of the study population, Complex Regional Pain Syndrome (CRPS) patients and healthy controls, Chicago, 2007–2008

| Characteristic | CRPS (N = 20) Mean (SD) | Non-CRPS (N = 15) Mean (SD) |
|---|---|---|
| Age in years | 44 (13) | 36 (13) |
| Duration of CRPS in months | 96.1 (113.0) | Not applicable |
| Gender | | |
| Male | 4 (20) | 2 (13) |
| Female | 16 (80) | 13 (87) |
| Ethnicity | | |
| Caucasian, non-Hispanic | 17 (85.0) | 12 (80.0) |
| Non-White | 2 (10.0) | 3 (20) |
| Missing | 1 | 0 |

**Table 2**

Median fatty acid concentrations in CRPS patients vs pain-free controls, Chicago, 2007–2008

| | CRPS (N = 20) | | Control (N = 15) | | Difference of medians* | | |
|---|---|---|---|---|---|---|---|
| | **Median (umol/L)** | **95% CI** | **Median (umol/L)** | **95% CI** | **Diff.** | **95% CI** | ***P* value**† |
| Omega-6 HUFA | | | | | | | |
| 20:3n−6 (DGLA) | 157.5 | 121.6, 183.6 | 107.0 | 95.6, 136.1 | 40.4 | 14.1, 73.8 | <0.01 |
| 20:4n−6 (AA) | 536.8 | 458.3, 612.4 | 478.7 | 424.2. 527.7 | 72.3 | −7.0, 153.3 | 0.10 |
| 22:4n−6 (DTA) | 26.6 | 24.0, 34.3 | 19.7 | 14.8, 24.4 | 8.7 | 3.8, 14.4 | <0.01 |
| Total n6 HUFA | 698.2 | 632.9, 824.3 | 602.5 | 554.8, 665.9 | 116.6 | 32.5, 217.3 | <0.01 |
| Omega-3 HUFA | | | | | | | |
| 20:5n−3 (EPA) | 36.5 | 27.5, 43.6 | 32.5 | 24.8, 48.5 | 1.5 | −11.0, 11.4 | 0.82 |
| 22:5n−3 (DPA) | 55.4 | 39.2, 67.1 | 53.5 | 47.8, 61.9 | −0.1 | −0.3, 0.1 | 0.95 |
| 22:6n−3 (DHA) | 184.1 | 151.9, 208.6 | 172.8 | 141.0, 213.0 | 11.5 | −21.9, 47.2 | 0.55 |
| Total n3 HUFA | 281.8 | 243.8, 318.4 | 259.4 | 227.2, 331.1 | 9.1 | −36.8, 54.2 | 0.71 |
| Total HUFA | 994.6 | 890.2, 1097.2 | 913.95 | 811.0, 938.2 | 125.0 | 19.7, 246.2 | 0.02 |
| HUFA Precursors | | | | | | | |
| 18:2n−6 (LA) | 2,038.5 | 1,913.9, 2,367.6 | 1,739.1 | 1,484.0, 2,114.2 | 257.0 | −28.0, 565.5 | 0.07 |
| 18:3n−6 (GLA) | 26.0 | 20.3, 33.4 | 16.2 | 10.3, 17.8 | 11.7 | 4.6, 19.1 | <0.01 |
| 18:3n−3 (ALA) | 54.4 | 37.9, 65.5 | 35.1 | 27.7, 48.9 | 15.3 | 2.4, 28.5 | 0.01 |
| Total MUFA | 2,781.3 | 2,283.9, 3,446.4 | 1,860.8 | 1,623.6, 2,311.7 | 853.6 | 435.8, 1,339.3 | <0.01 |
| Total SFA | 4,554.3 | 3,836.9, 5,239.8 | 3,707.3 | 3,261.7, 4,165.5 | 844.2 | 321.1, 1,538.9 | <0.01 |
| 18C trans FA | 67.8 | 54.7, 96.8 | 48.5 | 39.0, 54.3 | 20.7 | 7.2, 43.1 | <0.01 |
| Total Fatty Acids | 11,262.3 | 10,428.0, 13,047.6 | 9,335.9 | 8,166.8, 10,334.8 | 2,224.0 | 1,005.5, 3,655.6 | <0.01 |

*The Hodges–Lehmann test was used to provide the difference between the medians with confidence intervals.

†*P* values are based on the Wilcoxon rank-sum test.

HUFA = highly unsaturated fatty acid; DGLA = dihomo-gamma-linolenic acid; AA = arachidonic acid; DTA = docosatetraenoic acid, EPA = eicosapentaenoic acid; DPA = docosapentaenoic acid; DHA = docosahexaenoic acid; LA = linoleic acid; GLA = gamma-linolenic acid; ALA = alpha-linolenic acid; MUFA = mono-unsaturated fatty acids; SFA = saturated fatty acids.

**Table 3**

Median Weight Percentages in CRPS patients vs pain-free Controls, Chicago, 2007–08

| | CRPS (N = 20) | | Control (N = 15) | | Difference of medians* | | |
|---|---|---|---|---|---|---|---|
| | Median (%TFA) | 95% CI | Median (%TFA) | 95% CI | Diff. | 95% CI | *P* value† |
| Omega-6 HUFA | | | | | | | |
| 20:3n−6 (DGLA) | 1.83 | 1.64, 1.96 | 1.59 | 1.48, 1.96 | 0.15 | −0.17, 0.40 | 0.40 |
| 20:4n−6 (AA) | 6.21 | 5.69, 7.17 | 7.17 | 5.98, 7.90 | −0.64 | −1.55, 0.41 | 0.18 |
| 22:4n−6 (DTA) | 0.37 | 0.34, 0.41 | 0.33 | 0.25, 0.40 | 0.05 | −0.02, 0.12 | 0.17 |
| Total n6 HUFA | 8.47 | 7.70, 9.33 | 9.04 | 7.70, 10.51 | −0.43 | −1.61, 0.69 | 0.47 |
| Omega-3 HUFA | | | | | | | |
| 20:5n−3 (EPA) | 0.42 | 0.34, 0.50 | 0.46 | 0.37, 0.78 | −0.09 | −0.30, 0.06 | 0.24 |
| 22:5n−3 (DPA) | 0.73 | 0.60, 0.93 | 0.97 | 0.68, 1.12 | −0.20 | −0.40, −.02 | 0.03 |
| 22:6n−3 (DHA) | 2.56 | 2.11, 2.71 | 2.71 | 2.47, 3.18 | 11.45 | −21.87, 47.15 | 0.13 |
| Total n3 HUFA | 3.55 | 3.16, 3.94 | 4.42 | 3.59, 4.96 | −0.84 | −1.47, 0.04 | 0.03 |
| HUFA Precursors | | | | | | | |
| 18:2n−6 (LA) | 23.20 | 19.51, 24.59 | 23.27 | 22.82, 25.54 | −1.99 | −4.39, 0.35 | 0.16 |
| 18:3n−6 (GLA) | 0.28 | 0.22, 0.40 | 0.20 | 0.16, 0.27 | 0.08 | 0.01, 0.19 | 0.04 |
| 18:3n−3 (ALA) | 0.53 | 0.46, 0.57 | 0.46 | 0.38, 0.65 | 0.03 | −0.09, 0.15 | 0.63 |
| Total MUFA | 23.56 | 22.58, 25.62 | 21.97 | 20.28, 22.68 | 2.40 | 0.75, 3.93 | <0.01 |
| Total SFA | 38.13 | 37.46, 39.64 | 38.75 | 37.87, 39.37 | −0.20 | −1.43, 1.47 | 0.69 |
| 18C trans FA | 0.76 | 0.67, 0.95 | 0.64 | 0.50, 0.82 | 0.13 | −0.07, 0.35 | 0.22 |
| Total HUFA | 11.90 | 10.87, 13.91 | 13.39 | 11.95, 15.34 | −1.15 | −2.71, 0.21 | 0.10 |

*The Hodges–Lehmann test was used to provide the difference between the medians with confidence intervals.

†*P* values are based on the Wilcoxon rank-sum test.

HUFA = highly unsaturated fatty acid; DGLA = dihomo-gamma-linolenic acid; AA = arachidonic acid; DTA = docosatetraenoic acid; EPA = eicosapentaenoic acid; DPA = docosapentaenoic acid; DHA = docosahexaenoic acid; LA = linoleic acid; GLA = gamma-linolenic acid; ALA = alpha-linolenic acid; MUFA = mono-unsaturated fatty acids; SFA = saturated fatty acids.

**Table 4**

Ratios and percentages in CRPS patients vs pain-free controls, Chicago, 2007–2008

| | CRPS | | Control | | |
|---|---|---|---|---|---|
| | **Mean (SD)** | **95% CI** | **Mean (SD)** | **95% CI** | ***P* value*** |
| AA to EPA ratio | 16.4 (5.3) | 13.9, 18.9 | 14.7 (6.9) | 10.9, 18.5 | 0.42 |
| %n6 in HUFA | 72.2 (4.7) | 70.0, 74.4 | 69.1 (6.1) | 65.8, 72.5 | 0.11 |
| %n3 in HUFA | 27.8 (4.7) | 25.6, 30.0 | 30.0 (6.1) | 27.5, 34.2 | 0.11 |

AA = arachidonic acid; %n6 in HUFA = percentage of omega-6 HUFA in total HUFA; HUFA = highly unsaturated fatty acid.

**Table 5**

Typical fatty acid content of phospholipids and triglycerides

| | Phospholipids (%) | Triglycerides (%) |
|---|---|---|
| Total SFA | 40–50 | 30–40 |
| Total MUFA | 10–15 | 35–45 |
| LA | 20–25 | 15–25 |
| ALA | <0.5 | 0.8–1.5 |
| HUFA | 18–25 | 1–5 |

SFA = saturated fatty acid; MUFA = monounsaturated fatty acid; LA = linoleic acid; ALA = alpha linolenic acid; HUFA = highly unsaturated fatty acid.