Peritraumatic Plasma Omega-3 Fatty Acid Concentration Predicts Chronic Pain Severity Following Thermal Burn Injury

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Chronic pain is a significant comorbidity of burn injury affecting up to 60% of survivors. Currently, no treatments are available to prevent chronic pain after burn injury. Accumulating evidence suggests that omega-3 fatty acids (O3FAs) improve symptoms across a range of painful conditions. In this study, we evaluated whether low peritraumatic levels of O3FA predict greater pain severity during the year after burn injury. Burn survivors undergoing skin autograft were recruited from three participating burn centers. Plasma O3FA (n = 77) levels were assessed in the early aftermath of burn injury using liquid chromatography/mass spectrometry, and pain severity was assessed via the 0 to 10 numeric rating scale for 1 year following burn injury. Repeated-measures linear regression analyses were used to evaluate the association between peritraumatic O3FA concentrations and pain severity during the year following burn injury. Peritraumatic O3FA concentration and chronic pain severity were inversely related; lower levels of peritraumatic O3FAs predicted worse pain outcomes (β = −0.002, P = .020). Future studies are needed to evaluate biological mechanisms mediating this association and to assess the ability of O3FAs to prevent chronic pain following burn injury.

Pain is a common morbidity of major burn injury. Acute pain universally affects burn survivors,[1–3] and chronic pain affects up to 60% of survivors and causes substantial interference in life function.[1,4–7] Despite this high prevalence and morbidity, mechanisms of chronic pain pathogenesis after burn injury remain poorly understood. This lack of understanding continues to limit the development of effective secondary preventive interventions.

Omega-3 fatty acids (O3FAs) are dietary lipids with anti-inflammatory,[8,9] neuroprotective[10] effects that have been found to be beneficial across a range of health conditions.[11–14] O3FAs are derived exclusively from dietary sources,[15,16] and the great majority of Americans have low consumption of O3FAs,[16–18] thus O3FA levels in the U.S. population are generally low. Low O3FA levels have been associated with increased pain across a range of other painful disorders including migraine headache,[19] rheumatoid arthritis,[20,21] and inflammatory arthritis.[22] Low O3FA levels may be particularly deleterious after burn injury, as the postburn metabolic state is characterized by increased free (plasma) fatty acids availability, potentiating the beneficial effect of any O3FA present.[23] In burn survivors, low O3FA levels have been associated with increased infection and mortality.[23]

Low levels of O3FAs may also contribute to worse pain outcomes after burn injury. O3FAs and their pro-resolving lipid mediators have been shown to reduce pain in preclinical[24,25] and clinical models,[19,26] and O3FA supplementation has improved pain and related outcomes in a range of neuro/inflammatory disorders.[19,20,27,28] The anti-inflammatory[8,9] and neuroprotective[10,29] properties of O3FA in the immediate aftermath of burn injury may be beneficial in preventing chronic pain development.[19,26,30]

In this analysis, we evaluated peritraumatic O3FA levels in plasma samples obtained during a longitudinal, multicenter, observational study of hospitalized burn survivors. We hypothesized that peritraumatic O3FAs would predict improved pain outcome trajectories after burn. Specifically, we evaluated whether plasma O3FA levels, obtained in the early aftermath of burn, would be associated with pain severity during the year following burn.

METHODS

Design, Setting, Participant Eligibility Criteria

Patients undergoing tissue autograft after burn between February 2012 and June 2015 at one of the three burn

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centers in the Southeast were enrolled in this observation study as previously described.[1,31,32] All patients who had plasma samples available for analysis were included (Figure 1, STROBE diagram). Exclusion reasons, as reported previously, are described in Figure 1.

Study Procedures

Study procedures have been previously reported.[1] In brief, the institutional review board at each burn center approved the study protocol, and each participant provided written informed consent. Study flow chart is shown in Figure 1. Structured, in-person interviews were conducted by research assistants at the time of enrollment. Follow-up telephone interviews were conducted at subsequent major timepoints. Data regarding burn injury characteristics, including estimated burn total body surface area (TBSA) and mechanism, were extracted from the medical record following enrollment.

Pain Assessments

Verbal, numeric rating scales (NRS) are strongly correlated with visual analog scales[33–35] and are ideal for burn survivors who may have injury-related impairment in dexterity. A 0 to 10 verbal NRS score was used to evaluate burn-site/graft-site pain severity at the time of enrollment and at each subsequent major timepoint reported here (week 6, month 3, month 6, and 1 year following burn injury). Based on estimates in musculoskeletal pain, the minimal clinically important difference is 1 on the 0 to 10 NRS.[36]

Pain Interference

Pain interference was assessed at 6 months following burn injury using the Brief Pain Inventory (BPI).[37] The BPI is a validated scale that uses a 0 to 10 rating scale to evaluate pain interference across domains important for life function.[37] For analyses, scores across domains were summed to yield an

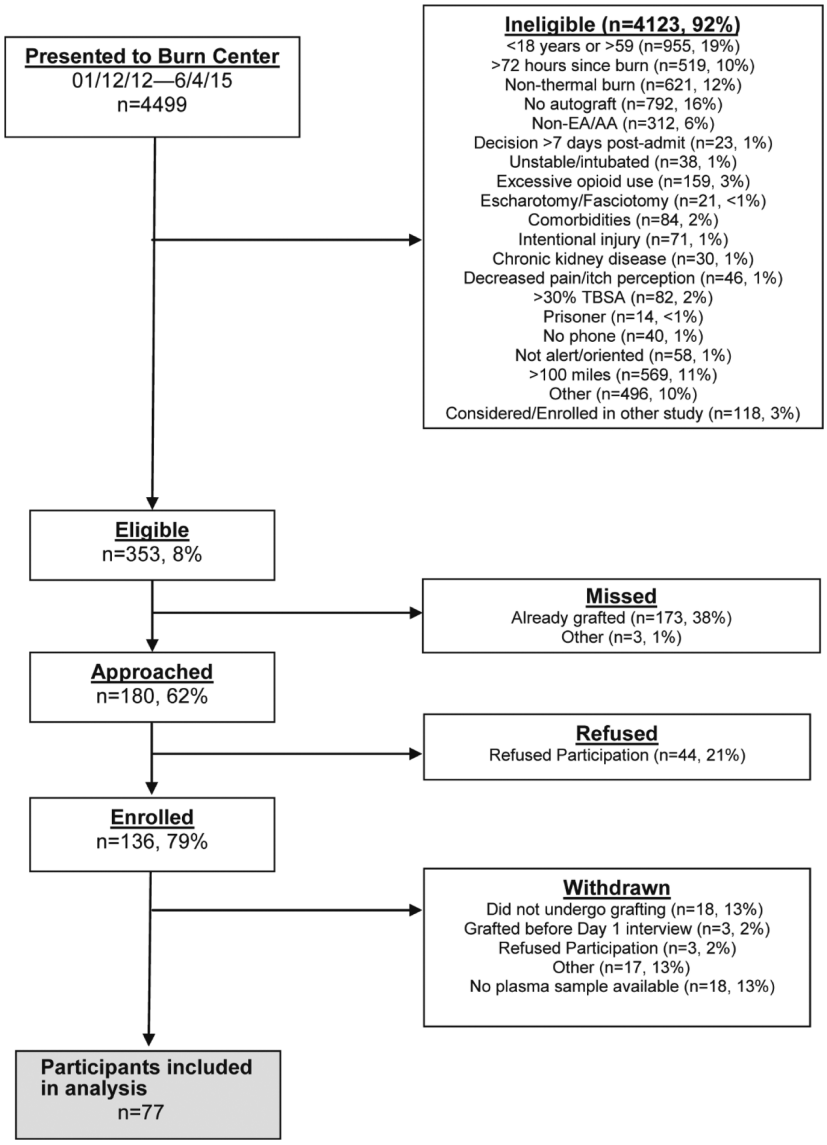

Figure 1. STROBE (Strengthening the Reporting of Observational Studies in Epidemiology) flow diagram. Participants included in the analysis were those who had available peritraumatic plasma samples for omega-3 fatty acid analysis.

overall, 0 to 70, pain interference score. The minimal clinically important difference for each subscale is approximately 2.[38,39]

Determination of Plasma Fatty Acid Concentration in the Immediate Aftermath of Burn Injury

Plasma was collected from study participants (n = 77) using a previously described, standardized protocol[40] at the time of study enrollment (within 72 hours of burn). Plasma samples were stored at –80°C and thawed immediately before analysis. Plasma samples were prepared on a 96-well plate and analyzed using Ultraperformance Liquid Chromatography (UPLC)/Electrospray Ionization Mass Spectrometry (UPLC/ESI/MS/MS; Duke Proteomics and Metabolomics Core Facility, Durham, NC). About 10 µL injections were used and UPLC separation of hydroxycholesterols was performed on a Waters Acquity UPLC (Milford, MA) using a Waters Acquity 2.1 mm × 10 mm 1.7 µm CSH C18 column. Mobile phase A was 10 mM ammonium formate and 0.1% formic acid in 40/60 v/v water/MeCN. Mobile phase B was 0.1% formic acid in 10/90 v/v MeCN/2-propanol. Injections were performed at a starting rate of 0.6 ml/min and 40% mobile phase B. Gradient continued with the same flow rate with linear steps of the following conditions: 43% at 1.3 minutes, 50% at 1.4 minutes, 52% at 4.7 minutes, 99% at 5 minutes, 99% at 5.2 minutes, 40% at 5.3 minutes, and hold at 40% to re-equilibrate for a total time of 7 minutes. Flow from the LC separation was introduced via negative mode electrospray ionization (ESI+) into a Q-ToF G2 mass spectrometer (Waters, Milford, MA). Electrospray voltage was 2.0 kV negative, 30 V cone, source temp of 110°C, desolvation temperature of 500°C, desolvation gas flow of 700 liter/h N_2, and a cone gas flow of 150 liter/h N_2. The mass analyzer used a resolution of approximately 12,000 over a scan range from 50 to 1300 m/z. The 554.2615 m/z ion (Leu-Enk (M-H)) was used as lockmass ion. Quantification of each fatty acid was performed using peak integration (Skyline Software, Seattle, WA). Total micromolar O3FA concentration was calculated by adding the concentration values for docosahexaenoic acid (DHA), eicosapentaenoic acid (EPA), docosapentaenoic acid (DPA), and alpha-Linolenic acid (ALA).

Statistical Analysis

Patient characteristics and outcomes were summarized using standard descriptive statistics (SPSS Statistics version 23; IBM Corporation, Armonk, NY). Peritraumatic O3FA concentrations were compared to a previously published normative population and plotted in Figure 2 (GraphPad Software, San Diego, CA).[41] Individuals were divided into tertiles based on their peritraumatic O3FA concentration, and mean pain severity was plotted over time in Figure 3 (GraphPad Software). Two-tailed non-paired *t* tests were used to evaluate for significant differences between the burn and normative population. Repeated-measures linear regression models were generated to evaluate the association between peritraumatic plasma concentration of O3FAs and pain severity over the 1 year following injury. These linear repeated-measures models reported in Table 2 were adjusted for age, sex, race, income, education, days since injury, and were clustered by participant (Stata 14, College Station, TX). Linear regression models reported in Table 3 were also used to evaluate the relationship between plasma fatty acid concentration and pain interference 6 months following burn injury (Stata 14). Beta coefficients (β) or slopes of the linear regression models are reported in each table which indicate the direction (sign) and magnitude of change in pain/interference for each unit increase in O3FA concentration. A *P* value less than .05 is considered statistically significant.

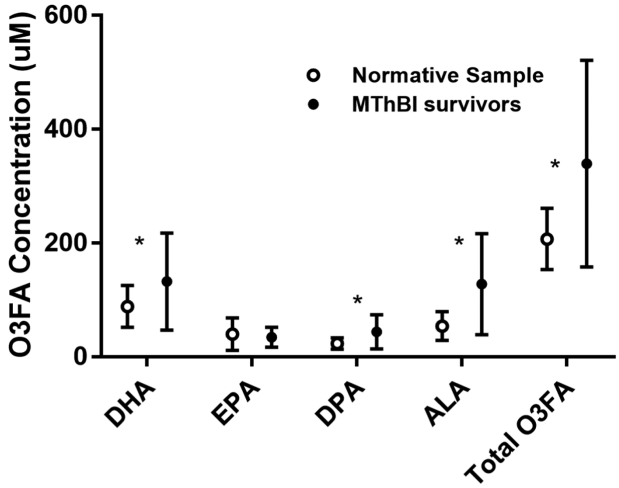

Figure 2. Peritraumatic, plasma omega-3 fatty acid (O3FA) concentration (µM) compared to previously published normative population.[41] Total O3FA and component fatty acids (decosahexaenoic acid [DHA], eicosapentaenoic acid [EPA], docosapentaenoic acid [DPA], and alpha-Linolenic acid [ALA]) are shown. Open circles indicate previously published mean concentrations from a normative sample, and closed circles represent mean concentrations from burn survivors in the immediate aftermath of the injury. Error bars show the standard deviation. Statistically significant differences are indicated with an asterisk (*) which indicates $P < .05$ on an unpaired *t* test.

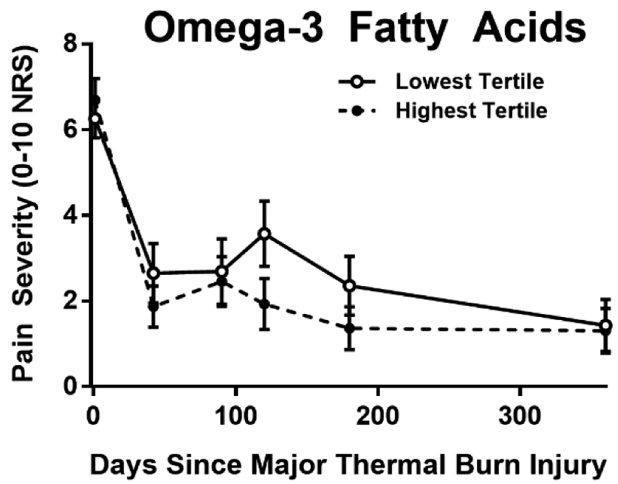

Figure 3. Influence of peritraumatic, plasma O3FA concentration on pain severity over 1 year following major thermal burn injury. Pain severity was measured with a 0 to 10 Numeric Rating Scale (NRS). Mean pain severity over time is plotted among individuals in the highest tertile (dotted line, closed circles) vs those in the lowest tertile (solid line, closed circles).

RESULTS

Demographic Characteristics of the Sample

The majority of burn survivors enrolled were White American males younger than the age of 50 (Table 1). Most had some education beyond high school and earned less than $60,000 a year. The average hospital length of stay was 10 ± 3 days.

Sample Burn Injury Characteristics

The majority of participants sustained a burn injury that was less than 10% of their TBSA, averaging 5 ± 3%. The most common mechanisms of thermal burn injury were scald (34/77, 44%) and flame (35/77, 45%). Thermal burns involving the upper extremity were most common (60/77, 78%,), followed by those involving the lower extremity (26/77, 34%). It is known that one patient in the cohort had a blood transfusion.

O3FA Concentrations in the Immediate Aftermath of Burn Injury

The mean peritraumatic plasma O3FA concentration was 339.66 ± 181 µM. Although cutoff values defining O3FA deficiency have not been established, the sample mean concentration of EPA (35 ± 18) was within 1 standard deviation of previously reported normative population values.[41] In contrast, sample mean DHA, DPA, and ALA were significantly higher than normative population values[41] (133 ± 85, 44 ± 30, and 128 ± 89 µM, respectively, Figure 2).

Table 1. Patient characteristics (n = 77)

Characteristic	n (%)
Age	
18–32	33 (43)
33–49	26 (34)
50–65	18 (23)
Gender	
Male	58 (75)
Female	29 (25)
Race	
White American	39 (51)
Black American	38 (49)
Education	
8–11 years	8 (10)
High school	28 (36)
Post high school	41 (53)
Income	
$0–$19,999	11 (14)
$20,000–$39,999	20 (26)
$40,000–$59,999	15 (20)
$60,000–$79,999	7 (9)
$80,000+	12 (16)
Do not know	11 (14)
Refused to answer	1 (1)
Percent TBSA	
Mean (*SD*)*	5 (3)

n, number; *TBSA*, total body surface area; *SD*, standard deviation.
*TBSA was estimated for 76 of 77 patients.

Table 2. O3FAs predict pain severity over the year following major thermal burn injury

Dependent: Pain	β	*P* Value	95% CI
O3FA total (µM)	−0.002	.020*	−0.0038 to −0.0034
Race (Ref = White)	0.585	.198	−0.3120 to 1.4823
Sex (Ref = Male)	2.056	.001	0.8541 to 3.2587
Age	0.015	.340	−0.0168 to 0.0480
Education	−0.216	.265	−0.5988 to 0.1672
Income	0.047	.610	−0.1357 to 0.2297
%TBSA	0.050	.420	−0.0731 to 0.1734
Days since injury	2.031	.070	−0.1696 to 4.2322

%TBSA, percent total body surface area burned; *O3FAs*, omega-3 fatty acids.
Repeated-measures linear regression models for O3FA adjusted for time, race, sex, income, education, and days since injury were performed. This analysis included 76 patients. One patient was not included because there was no TBSA reported.
*Indicates significance after correction for multiple comparisons ($P < .025$).

Table 3. Association between biomarkers and domains of brief pain inventory 6 months after burn

	O3FA	
Domains of Brief Pain Inventory	β	*P* Value
General activity	−0.003*	.029
Mood	−0.003	.177
Walking ability	−0.001	.364
Normal work	−0.004*	.042
Relationships	−0.005*	.001
Sleep	−0.005*	.013
Enjoyment	−0.003	.137
Overall	−0.024*	.021

O3FA, omega-3 fatty acid.
Linear regression models were adjusted for age, sex, and race. 66 patients were included in this analysis, given response rate at 6 months.
*Indicates significance $P < .05$.

O3FA Levels Predict Pain Severity Following Burn Injury

In the year following burn injury, participants in the lowest tertile of peritraumatic O3FA levels experienced greater pain severity at each timepoint than those in the highest tertile (Figure 3). In repeated-measures linear regression including all participants adjusted for time, race, sex, income, education, and days since injury, for every 100 µM increase in total O3FA, average pain severity after burn injury was reduced by 0.2 (95% CI: −0.0038 to −0.0034; 0–10 NRS) (Table 2). In this model, a clinically meaningful 1 point reduction in the NRS would correspond to a 500 µM increase in total O3FA concentration. In addition to predicting pain severity over time, lower peritraumatic O3FA level also predicted greater pain interference across domains important to life function (Table 3). Lower peritraumatic O3FA level predicted greater overall pain interference 6 months following burn, as well as greater pain interference with general activity, normal work, relationships, and sleep (Table 3). For example, adjusted linear regression analyses describing the relationship between general life function and total O3FA concentration indicate for every 100 µM increase in total O3FA, average interference

with general function 6 months after burn was reduced by 0.3. This regression model indicates that an increase of 666 µM in total O3FA would correspond to a clinically meaningful reduction of 2 points on the general life function.

DISCUSSION

In this multicenter cohort study, hospitalized burn survivors with low peritraumatic plasma levels of O3FA had more severe pain during the year after burn injury and greater inference with life function. To the best of our knowledge, this study is the first to demonstrate an association between peritraumatic O3FA levels following burn injury and pain outcomes. The association between low levels of O3FA and worse pain outcomes is consistent with findings in other settings[19,20,22] and with the documented anti-inflammatory,[8,9] antidepressive,[28,42] and neuroprotective[10] effects of O3FAs.

There are no widely accepted clinical cutoffs defining plasma O3FA deficiency. In comparison to a previous normative study measuring circulating plasma O3FA levels in healthy individuals, burn survivors in our cohort had significantly higher total O3FA, DHA, DPA, and ALA concentrations. These data are consistent with a recent prospective cohort study that demonstrated a marked increase in free fatty acids following burn injury compared to controls[23] and with postburn physiology that has shifted to increased lipid metabolism in the aftermath of burn.[43]

In a recent randomized controlled trial of O3FA supplementation in burn survivors, those receiving O3FA had lower rates of infectious complications.[44] The beneficial effects of O3FA on both pain and infectious outcomes may be related to the ability of O3FA to generate pro-resolving lipid mediators,[45,46] reduce TLR4 signaling,[47–49] attenuate innate immunity,[50] and modulate T-cell responses.[45,46] Further mechanistic work is needed to determine whether O3FA supplementation following burn affects these immune pathways and, most importantly, improves pain outcomes. O3FAs are safe, well-tolerated, widely available treatment, and because of their anti-inflammatory, neuroprotective effects are an ideal non-opioid preventative therapeutic.[8–10,26,51,52]

Limitations

There are a number of limitations that should be considered when interpreting study results. First, our sample size of 77 participants is small. However, despite the small sample size, a statistically significant effect of O3FA on pain and pain interference was identified. Second, due to our observational design, it cannot be determined whether low O3FA concentrations were causal or were associated with other causal factors. Causal relationships are best assessed in the context of intervention trials. Third, our study measured plasma concentration of O3FA rather than erythrocyte concentration, which may introduce variation based on the participant's most recent meal.[53,54] This method was performed, as erythrocyte samples from this cohort were not available for analysis. Furthermore, there was no interrogation of inflammatory markers, which might help to evaluate for evidence that O3FAs influence pain outcomes via modulation of inflammatory mechanisms. Finally, our study did not fully assess whether blood transfusions influence peritraumatic O3FA concentration; however, future studies should examine this problem. Performing analyses excluding the patient with known blood transfusion did not alter our results.

CONCLUSIONS

In this longitudinal, multicenter, observational cohort study, low peritraumatic circulating O3FA concentrations predicted greater pain severity and greater pain interference following burn injury. These findings are important because if O3FA supplementation improves pain outcomes after burn injury, then it would be a safe, low-cost, non-opioid alternative for burn survivors. A small randomized clinical trial is underway to determine the feasibility of O3FA supplementation and to assess for preliminary evidence for potential efficacy. Future interventional studies are needed, which evaluate the ability of O3FA supplementation after burn injury to improve pain outcomes and which assess potential therapeutic mechanisms.

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