Supplementation with Specialized Pro-resolving Mediators Reduces Inflammatory Biomarkers and Improves Reported Clinical Symptomology in Subjects with Chronic Inflammatory Conditions

Results from a Multi-Center Open-Case Series

OVERVIEW

- Inflammation has 2 phases: initiation and resolution. Many chronic health issues are linked to unresolved inflammation
- Specialized pro-resolving mediators are endogenous molecules essential for resolution of inflammation but may not be produced in required levels in certain condition
- Multi-center case study assessed effects of a proprietary specialized pro-resolving mediator supplement (LM-O3) on inflammatory biomarkers in 34 men and women (21-75 y/o) with conditions indicating raised inflammatory tone
- Results showed a 43% reduction in high-sensitivity C-reactive protein (hs-CRP) at 4 weeks with concurrent reduction in prostaglandin E_2 (PGE_2)
- At 8 weeks, hs-CRP remained reduced, and PGE_2 was reduced to within normal range
- Functional measurements including reported measures of pain as well as quality of life indicated continued improvement at 4 and 8 weeks
- Adverse events were minimal and managed without incident

BACKGROUND

The inflammatory response has two phases – an initiation phase and a resolution phase. Ideally, inflammation is a self-limited process, leading to complete resolution that enables tissue healing and a return to previous normal condition.[1] However, if the inflammatory response is left unresolved, the surrounding tissues can be negatively impacted over time. Many chronic diseases such as cardiovascular disease, arthritis, diabetes, metabolic syndrome, inflammatory bowel disease, periodontal disease, asthma, and age-related macular degeneration, as well as some neurological disorders, have been linked to chronic inflammation.[2-7]

During the resolution phase, specialized pro-resolving mediators are produced at the affected tissue site, orchestrating the resolution-related activities and facilitating the return to homeostasis.[8] 18-hydroxyeicosapentaenoic acid (**18-HEPE**) and 17-hydroxydocosahexaenoic acid (**17-HDHA**) are two important specialized pro-resolving mediators derived from the omega-3 fatty acids eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA), respectively, via enzymatic pathways.[1] 18-HEPE and 17-HDHA are rapidly taken up by the activated immune cells and converted into other specialized pro-resolving mediators including resolvins, protectins and maresins.[9] Each Specialized pro-resolving mediator plays a distinct role in resolving inflammation, and through their combined actions the return to homeostasis is achieved.[1]

Some individuals may not produce desirable levels of specialized pro-resolving mediators – due to lifestyle behaviors, dietary choices, age, or health status – in response to an immune challenge. As a result, the resolution of their inflammation can be impacted.[8,10] Since specialized pro-resolving mediators are essential for the resolution, supplementation of specialized pro-resolving mediators may represent a nutritional approach to support the resolution of inflammation.[8]

Objective

The objective of this study was to observe the effect of a supplement containing **fractionated lipid concentrate standardized to 18-HEPE and 17-HDHA (LM-O3; Table 1)** on select circulating inflammatory biomarkers and on overall well-being assessed by multiple questionnaires in a group of volunteers recruited from 6 clinic sites.

METHODS/DESIGN

Participants

Participants were recruited from the patient base at the study clinical sites. Eligible participants were men and women age 21 – 75 y/o with chronic inflammatory conditions. Inclusion and exclusion criteria can be found in the **Appendix** section. The study was carried out in compliance with the Helsinki Declaration of 1975, and was approved by the Western Independent Review Board (Seattle, WA). Informed written consent was obtained from all participants prior to enrollment.

Study design

This 8-week, open-label, case observation study was conducted at 6 clinic sites in the U.S. including 4 MDs, 1 DO and 1 ND. After baseline assessment (Visit 1), participants began to consume 6 softgels once daily of the LM-O3 supplement taken together and were instructed to consume with a lipid-containing meal. After Week 4 assessment (Visit 2), participants began to consume 8 softgels once daily of the LM-O3 supplement (**Table 1**). The effect of this increased dose was evaluated at Week 8 (Visit 3). Participants returned to the clinic at Week 4 (Visit 2) and Week 8 (Visit 3) for clinical evaluation and assessment for compliance and adverse events. An overview of clinical visits is summarized in the Appendix section.

Table 1. Nutritional profile summary of the supplement LM-O3.

	6 softgels	8 softgels
Energy (kcal)	15	20
Total fat (g)	1.5	2.0
Fractionated lipid concentrate (mg)†	750	1000

Ingredients: concentrated fish oil (anchovy and sardine oil, and mixed tocopherols), softgel shell (gelatin, glycerin, water, pectin, and sorbitol), and lemon oil.
†Specialized pro-resolving mediators content standardized to 18-HEPE and 17-HDHA.

Laboratory analysis

Fasting blood samples obtained at each clinic visit were analyzed within the typical diagnostic laboratories at each study site for biochemical markers including hs-CRP, PGE_2, erythrocyte sedimentation rate (ESR), fibrinogen, B-type natriuretic peptide (BNP), serum ferritin, and the pro-inflammatory cytokines tumor necrosis factor alpha (TNF-α), and interleukin-6 (IL-6).

Statistical analyses

Data collected from all 6 sites were analyzed as one cohort. Those who completed all 8 weeks were included in the final analyses. Changes from baseline to 4 weeks and 8 weeks were analyzed separately using two-sided paired t-test. Missing values were not imputed for these analyses. Data are reported as mean ± SD. A value of $P<0.05$ was considered statistically significant. Spearman correlation coefficient was used to explore relationships between variables.

RESULTS

Participant characteristics

Fifty-two participants (all Caucasian) were enrolled from the 6 study clinics and 34 (28 women and 6 men) completed the study. Reasons for dropout included requirement to start study prohibited medications, loss to follow up (unable to attend clinic within specified study time-frame), participant preference to reduce overall medications/supplements taken, participant preference not to have further blood draws, unanticipated effects of the study product (including asthma symptoms and gastrointestinal disturbances).

The average age of those who completed the study was 49.3 ± 10.8 years old, and their BMI was 29.4 ± 8.2 kg/m^2. Among the 34 participants, 14 subjects had arthritis (rheumatoid arthritis or osteoarthritis), 6 subjects had fibromyalgia, and 15 subjects had chronic pain (including 1 subject who had both chronic pain and fibromyalgia). Additionally, most subjects experienced other co-morbidities, including insomnia, reflux, fatigue, constipation, hypothyroidism, metabolic syndrome, hyperlipidemia, hypertension, migraine, Sjogren's syndrome, Hashimoto's, and Lyme disease.

Clinical biomarkers of inflammation were significantly reduced at 4 and 8 weeks

Concentrations of hs-CRP, an acute phase reactant reflective of overall inflammatory environment were above normal reference range at baseline. hsCRP was reduced from 9.2 ±15.8 mg/L at baseline to 5.2 ± 9.5 mg/L at 4 weeks (43% reduction; p=0.031) and to 6.3 ± 10.6 mg/L at 8 weeks (32% reduction; p=0.007). The difference between 4 and 8 weeks was not statistically significant (**Table 2**). Concentrations of PGE_2, a lipid molecule active during inflammation initiation and a driver of pain, edema and fever, were also elevated in this cohort at baseline. PGE_2 concentrations showed a trend toward decrease from 590.6 ± 802.0 pg/mL at baseline to 486.5 ± 400.4 pg/mL at 4 weeks (p=0.30), and was significantly reduced to 350.6 ± 334.3 pg/mL at 8 weeks compared with baseline (p = 0.039). By 8 weeks the group average was within the normal range of 200-400 pg/mL (Table 2).

Table 2. Inflammatory markers at baseline, 4 weeks and 8 weeks significantly reduced among participants who completed the 8-week study.

Biomarker	Level	p value	Reference range
hs-CRP (mg/L)	Baseline: 9.2 ± 15.8 4 weeks: 5.2 ± 9.5 8 weeks: 6.3 ± 10.6	 **0.031*** **0.007***	0-3
PGE_2 (pg/mL)	Baseline: 590.6 ± 802.0 4 weeks: 486.5 ± 400.4 8 weeks: 350.6 ± 334.3	0.30 **0.039***	200-400
Fibrinogen (mg/dL)	Baseline: 343.9 ± 93.3 4 weeks: 324.6 ± 114.0 8 weeks: 315.0 ± 74.2	 0.11 **0.007***	193-504

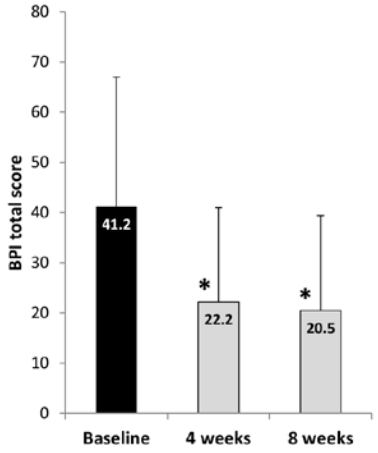
Data are expressed as mean ± SD.*statistically significant from baseline as assessed by paired t-tests between time points. Sample size for each factor may vary due to missing data. Missing values were not imputed for paired t-tests analyses

Other biomarkers reflective of acute phase response and ongoing inflammation (ESR, ferritin, BNP, IL-6, TNF- α) were within normal limits at baseline and did not significant change throughout the study period. ESR levels at baseline were 12.5± 13.4 mmHr (normal reference range 0-32). At 4 and 8 weeks ESR levels were 13.1 ± 13.9 and 14.2 ± 13.8 respectively (p-value 0.52 and 0.82 compared to baseline, NS). Ferritin concentrations at baseline were 93.5 ± 99.5 (normal reference range 15-150). At 4 and 8 weeks, ferritin concentrations were 83.3 ± 90.2 and 102.9 ± 96.8 (p-value 0.25 and 0.70 compared to baseline, NS). At baseline, BNP levels were 27.5 ± 23.6 (normal reference range 0-100). These were no significantly changed at 4 weeks (28.0 ± 21.9, p-value 0.87) or 8-weeks (24.0 ± 25.4, p-value 0.27) compared to baseline. At baseline, IL-6 levels were 5.4 ± 9.6 (normal reference range 0-15.3). Although these were reduced at 4-weeks (3.9 ± 5.5) and 8 weeks (3.1 ± 3.0), this difference was not significant (p-value 0.52 and 0.54 for 4 and 8 weeks compared to baseline). A second inflammatory cytokine TNF-α was within normal limits at baseline (7.6 ± 26.9; normal reference range 0 – 8.1), and did not change significantly at 4 or 8 weeks (4.6 ± 11.4 and 4.6 ± 11.4respectively; p-value 0.32 and 0.33 for 4 and 8 weeks compared to baseline).

Functional symptoms of inflammation and pain were reduced at 4 and 8 weeks

Total scores on the Brief Pain Inventory (BPI) – a tool used to assess the severity of pain and the impact of pain on daily functions in patients with pain from chronic diseases or conditions such osteoarthritis and low back pain, or with pain from acute conditions[11] – were significantly reduced at 4 and 8 weeks compared with baseline (**Figure 1**). No statistically significant difference was seen between 4 and 8 weeks.

Figure 1: BPI total scores from baseline to 8 weeks *statistically significant from baseline (p<0.001).



The reduction in scores was related to the baseline score (baseline and 4-week change; rho = -0.644, p < 0.001) (baseline and 8-week change; rho = -0.706, p<0.001). Additionally, the magnitude of pain was reduced in the total group (**Table 3**), and the reported interference of pain on activities and daily functions was also significantly reduced at 4 and 8 weeks of supplementation (Table 3).

Table 3. Brief Pain Inventory: Score on individual domains.*

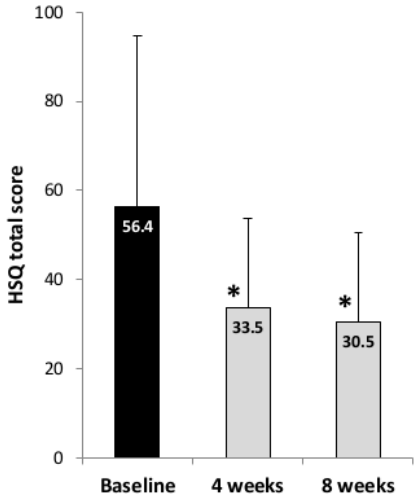
Item	Score	p (vs. baseline)
Pain at its worst in the last 24 hr	Baseline: 5.0 ± 2.4	
	4 weeks: 3.6 ± 2.4	**0.036**
	8 weeks: 3.4 ± 2.1	**0.004**
Pain at its least in the last 24 hr	Baseline: 2.2 ± 1.9	
	4 weeks: 1.2 ± 1.3	**0.025**
	8 weeks: 1.1 ± 1.4	**0.004**
Pain on average	Baseline: 4.2 ± 1.7	
	4 weeks: 3.0 ± 1.5	**0.005**
	8 weeks: 2.7 ± 1.4	**<0.001**
Pain level right now	Baseline: 3.6 ± 2.4	
	4 weeks: 2.2 ± 1.8	**0.007**
	8 weeks: 2.0 ± 1.9	**<0.001**
During the past 24 hr, pain has interfered with your:		
General activity	Baseline:4.0 ± 3.2	
	4 weeks: 1.6 ± 2.2	**<0.001**
	8 weeks: 1.6 ± 2.4	**<0.001**
Mood	Baseline: 3.9 ± 3.1	
	4 weeks: 1.8 ± 2.2	**<0.001**
	8 weeks: 1.7 ± 2.5	**<0.001**
Walking ability	Baseline: 4.0 ± 3.5	
	4 weeks: 1.7 ± 2.4	**0.002**
	8 weeks: 1.7 ± 2.7	**0.001**
Normal work	Baseline: 4.2 ± 3.3	
	4 weeks: 1.6 ± 2.4	**<0.001**
	8 weeks: 1.7 ± 2.7	**0.002**
Relations with others	Baseline: 3.2 ± 3.0	
	4 weeks: 1.2 ± 1.9	**<0.001**
	8 weeks: 1.4 ± 2.1	**<0.001**
Sleep	Baseline: 3.8 ± 3.6	
	4 weeks: 2.2 ± 2.7	**0.024**
	8 weeks: 1.8 ± 2.6	**0.007**
Enjoyment of life	Baseline: 5.1 ± 3.2	
	4 weeks: 2.0 ± 2.4	**<0.001**
	8 weeks: 2.3 ± 2.6	**<0.001**

*Score interpretation can be found in the Appendix section

Improvements in health domains reflective of subject clinical condition

Health Symptoms Questionnaire (HSQ[12]) total scores were reduced from 56.4 ± 38.2 at baseline to 33.5 ± 20.1 at 4 weeks (p<0.001) and to 30.5 ± 20.0 at 8 weeks (p<0.001; **Figure 2**). The difference between 4 and 8 weeks was not significant. Individual MSQ domains – including joints/muscle subscale – reflective of the overall patient population clinical diagnoses were improved.

Figure 2: HSQ total scores from baseline to 8 weeks. *statistically significant from baseline (p<0.001).



Significant improvements reported in health-related quality of life across the study

SF-12 was not significantly different and reported overall good quality of life in the participants, however, more clinically focused instruments such as the American Chronic Pain Association Quality of Life (ACPA QOL) Scale highlighted improvements in quality of life linked with specific clinical improvements in this patient group, which included subjects with chronic pain, or clinical conditions related to inflammation and chronic pain (**Table 4**).

Table 4. SF-12 and ACPA QOL questionnaires at baseline, 4 weeks and 8 weeks.*

Questionnaire	Score	p (vs. baseline)
SF-12	Baseline: 34.0 ± 3.2	
	4 weeks: 34.6 ± 2.7	0.29
	8 weeks: 33.6 ± 3.4	0.56
ACPA QOL Scale	Baseline: 7.8 ± 2.0	
	4 weeks: 8.8 ± 1.3	**0.025**
	8 weeks: 8.5 ± 1.4	**0.042**

*The scale interpretation can be found in Appendix.

Adverse events

Throughout the 8 weeks, adverse events were recorded in adverse events forms, patient discontinuation forms, and study progress notes. These included gastrointestinal disturbances, exacerbation of asthma symptoms, occasional fishy burps, and constipation (**Table 5**). However, none were considered serious adverse events.

Table 5. Frequency of reported adverse events at 4 weeks and 8 weeks.

Event	4 weeks (6 softgels)	8 weeks (8 softgels)
Loose stools, nausea or abdominal discomfort	3	3
Asthma symptoms exacerbation	0	2
Fishy burps	0	1
Constipation	1	0

INDIVIDUAL CASE MANAGEMENT

From the 34 participants who completed the 8-week study, 2 selected cases are described in detail.

Case 1

Background

The first case was a 50 y/o Caucasian man who had had osteoarthritis for 4 years and hypothyroidism and hypertension for 2 years. He was also obese (weight 244 lbs and BMI 34.0 kg/m^2). Family history included father with diabetes and chronic obstructive pulmonary disease (COPD) and mother with Celiac disease, lupus, hypothyroidism, osteoarthritis, fibrocystic lung disease, and hypertension. Medications he was taking at study outset included desiccated thyroid (81.25 mg/d) and zolpidem (Ambien, 10 mg) nightly for insomnia. He also took dietary supplements daily, including diindolylmethane (DIM; 300 mg/d), vitamin D_3 (5000 IU/d) and fish oil (1 capsule day providing 330mg total omega-3 fatty acids). He had been taking fish oil for 4 years.

Baseline presentation

At baseline, patient reported daily lower back pain (7/10) and sharp, shooting pain in left shoulder (4/10 but could increase to 10/10 if moved in certain positions). Patient also reported daily right knee pain (4/10 which could increase with certain movements). Daily right great toe pain (5/10) with swelling was also reported. Baseline MSQ total score was 38, with joint/muscle subscale (score = 15) the predominant domain affected. In terms of quality of life, the ACPA QOL scale of 8 indicated the patient's ability to work and volunteer for a few hours daily, and to be active for at least five hours each day. Baseline biomarkers of inflammation (**Table 6)** indicate elevated hs-CRP and PGE_2 concentrations.

Nutritional management

This patient commenced 6 softgels/day of LM-O3 for the first 4 weeks and increased to 8 softgels/day of LM-O3 for the subsequent 4 weeks.

Progress

At 4 weeks, hs-CRP was reduced to within normal range. PGE_2 remained elevated (Table 6). Daily pain was similar to baseline (lower back 7/10; left shoulder 4/10 up to 10/10 with certain movements; right knee 4/10 with increase with certain movements, pain and swelling in right great toe 5/10). Patient reported taking 4 instead of 6 LM-O3 softgels/day by mistake during the first 4 weeks of the study. During this phase, he reported no change to medications or treatments other than LM-O3 supplementation. No adverse events occurred.

At 8 weeks, both hs-CRP and PGE_2 were reduced to within normal range (Table 6). Reductions in pain were reported; daily lower back pain was reduced to severity of 3-4/10, though it could be worse on some days. Daily left shoulder pain was reduced to 2/10, although certain movements increased pain score. Daily right knee pain was reduced to 3/10. Right great toe has improved the most; only 'very little' pain and swelling was reported. Overall, nagging pain is better; pain with certain movements still sharp and 10/10. During the second phase, he was 100% compliant, taking 8 softgels/day. No issues or negative effects were reported.

Table 6. Inflammatory markers at baseline, 4 weeks and 8 weeks in Case 1.

Biomarker	Level	Reference range
hs-CRP (mg/L)	Baseline: 8.32 4 weeks: 0.86 8 weeks: 0.74	0-3
PGE_2 (pg/mL)	Baseline: 794 4 weeks: 847 8 weeks: 182	200-400
ESR (mm/Hr)	Baseline: 5 4 weeks: 2 8 weeks: 2	0-32
Ferritin (ng/dL)	Baseline: 57 4 weeks: 42 8 weeks: 82	15-150
Fibrinogen (mg/dL)	Baseline: 396 4 weeks: 223 8 weeks: 226	193-504
BNP (pg/mL)	Baseline: <2.5 4 weeks: <2.5 8 weeks: 24.4	0-100
IL-6 (pg/mL)	Baseline: 4.8 4 weeks: <0.7 8 weeks: 1.8	0-15.3
TNF (pg/mL)	Baseline: 1.3 4 weeks: 1.0 8 weeks: 2.2	0-8.1

At 4 and 8 weeks, HSQ total scores had reduced to 23 and 19, respectively. HSQ muscle/joint subscale experienced the most pronounced reduction (to 10 and 7, respectively). BPI total scores were reduced modestly at 4 weeks but then notably at 8 weeks (55 and 20, respectively). At 8 weeks, patient reports reduction in all BPI individual scores. The score interpretation can be found in Appendix.

In terms of quality of life questionnaires, improvements were seen with SF-12 which increased to 34 at both 4 and 8 weeks. ACPA QOL scale moved from 7 at baseline to 8 at both 4 and 8 weeks, suggesting that the patient felt ability to work and volunteer for at least six hours daily, and had energy to make plans for one evening social activity during the week and be active on weekends.

Case 2

Background

The second case was a 62 y/o Caucasian woman diagnosed with osteoarthritis a year ago, who had had fibromyalgia for 10 years, Sjogren's syndrome for 4 years, Hashimoto's thyroiditis for 9 years, and chronic fatigue syndrome for 15 years. The patient was overweight at baseline (168.4 lbs; BMI 26.4 kg/m^2). Family history included mother with hypothyroidism and rheumatoid arthritis, father with squamous cell carcinoma (throat), sister with Hashimoto's thyroiditis, paranoid schizophrenia, and suicide (at age 40), and maternal grandfather with CVD and stroke. At study outset she was taking both Gabapentin (400 mg nightly) and clonazapin (1-3 mg nightly) for sleep, and levothyroxine (125 mg) each morning for hypothyroidism.

Baseline Presentation

At baseline, patient reported daily pain in right and left legs (7/10), knees (6/10), ankles (6/10), calves (6/10), feet (6/10), shoulders (6/10), lower back (7/10), and neck (5/10 with limited range of motion). She also reported TMJ headaches twice weekly. Pain was interfering with overall quality of life, as indicated by a score of 6 on the ACPA QOL scale. Clinical presentation and diagnoses were reflected in the HSQ total score of 62, with joints/muscle being the predominant domain contributing to this score (19), with digestive tract (6), head (6) and mind (6) also contributing strongly. BPI total score of 49 indicated high levels of pain in the past 24 hours, and interference in activities of daily living. At baseline, the inflammatory biomarker PGE_2 was elevated (**Table 7**).

Table 7. Inflammatory markers at baseline, 4 weeks and 8 weeks in Case 2.

Biomarker	Level	Reference range
hs-CRP (mg/L)	Baseline: 1.12 4 weeks: 1.04 8 weeks: 1.24	0-3
PGE_2 (pg/mL)	Baseline: 1052 4 weeks: 1510 8 weeks: 346	200-400
ESR (mm/Hr)	Baseline: 22 4 weeks: 34 8 weeks: 21	0-32
Ferritin (ng/dL)	Baseline: 10 4 weeks: 7 8 weeks: 177	15-150
Fibrinogen (mg/dL)	Baseline: 316 4 weeks: 354 8 weeks: 340	193-504
BNP (pg/mL)	Baseline: 18.2 4 weeks: not collected 8 weeks: 6	0-100
IL-6 (pg/mL)	Baseline: 2.7 4 weeks: 2.3 8 weeks: 2.4	0-15.3
TNF (pg/mL)	Baseline: 5.0 4 weeks: not collected 8 weeks: 3.5	0-8.1

Nutritional management

This patient commenced 6 softgels/day of LM-O3 for the first 4 weeks and increased to 8 softgels/day of LM-O3 for the subsequent 4 weeks.

Progress

At 4 weeks, severity of pain was reduced in legs (2/10), knees (3/10), ankles (1/10), calves (1/10), and feet (3/10). No pain was now reported in left shoulder, with right shoulder pain reduced (2/10). Overall pain and range of motion in the neck was improved (3/10). Pain in hands, wrists, elbows, and triceps (1/10), and lower back pain (4/10) was also reduced. Patient was amazed that instead of being in constant pain, she now could engage in pretty much most activities, including attending exercise class that she normally would not have allowed herself to do. Patient was compliant with the LM-O3 supplementation protocol, and reported no adverse events.

At 8 weeks, the elevated PGE_2 level was decreased to within normal range (Table 7). Pain in legs, knees or ankles was gone. Pain in right shoulder was gone and left shoulder pain reduced to 1/10. There was no neck pain, and range of motion in the neck was good. Lower back pain decreased to 1-2/10. She reported no TMJ headaches. She expressed feeling better when going up to 8 softgels/ day versus 6 softgels/day.

As the pain subsided, her overall quality of life improved, as indicated by a score of 8 on the ACPA QOL scale at 4 weeks and to a score of 9 at 8 weeks. MSQ total scores had reduced to 43 at 4 weeks and to 12 at 8 weeks. MSQ muscle/joint subscale experienced the most pronounced score reduction with further reductions seen in energy, mind and head domains. BPI total scores were notably reduced at 4 weeks and at 8 weeks (22 and 11, respectively). The reduction was seen in every BPI individual score.

SUMMARY

This 8-week multi-center open-case series demonstrated that LM-O3, a Specialized pro-resolving mediator supplement containing fractionated lipid concentrate standardized to 18-HEPE and 17-HDHA, exerted beneficial effects on biomarkers of inflammation (e.g., hs-CRP and PGE_2) in subjects with health conditions associated with chronic unresolved inflammation. Functional symptoms associated with inflammation, as assessed by various health status questionnaires and quality-of-life questionnaires, were also improved after consumption of LM-O3.

Not unexpectedly, results from questionnaires that assessed the severity of pain and the impact of pain on daily functions indicated the potential benefits of LM-O3 in the resolution of pain. Pain is one of the cardinal signs of inflammation, and PGE_2 is the best known eicosanoid that causes inflammatory pain.[13] In this study, the reduction in PGE_2 levels after LM-O3 treatment may have contributed to the improvement in pain. Mechanistically, specialized pro-resolving mediators decrease production of pro-inflammatory mediators and thus reduce swelling and pain. Specialized pro-resolving mediators may also resolve neuroinflammation that is linked to chronic pain.[14] Recent research also suggests that Specialized pro-resolving mediators may directly regulate the function of the sensory neural circuit and produce analgesic effect.[14]

This open-label case series suggests that supplementation of specialized pro-resolving mediators can positively impact inflammatory markers and subject quality of life measurements. This is the first study to demonstrate these effects in humans, future placebo-controlled randomized study with a larger sample size will be needed to address the limitations inherent in this observational study design.

Inflammation complicates the management of many conditions such as obesity, metabolic syndrome, cardiovascular disease and diabetes. The inability to resolve both acute and chronic inflammation leads to progression and often complications of the disease state later on. Thus, improved management of an elevated inflammatory response is an important objective in patient care. This single-arm, practice-based observation study provides preliminary evidence that direct treatment with specialized pro-resolving mediators represents a potential novel approach in promoting inflammation resolution.

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APPENDIX

Main study inclusion criteria:

- Individuals with chronic pain lasting 3 months or longer
- Individuals with arthritis or other joint-related conditions
- Individuals with vascular disease
- Obese individuals (BMI > 30 kg/m^2) with elevated high-sensitivity C-reactive protein (hs-CRP > 4 mg/L)
- Diabetic individuals with elevated hs-CRP (> 4 mg/L)
- Individuals with auto-immune conditions
- Individuals with fibromyalgia

Main study exclusion criteria:

- Initiation of or changes in use of fish oil, krill oil, or omega-3 supplements and omega-3-based drugs within the past 3 months
- Initiation of or changes in pain medications and anti-inflammatory medications (e.g., NSAIDs, COX-2 inhibitors, and corticosteroids)
- Daily aspirin use > 325 mg/day
- Use of lipid-lowering drugs or anticoagulant medications within 4 weeks prior to the study
- History of renal, hepatic, and autoimmune disease
- History of cancer, AIDS, deep vein thrombosis or pulmonary embolus
- Pregnancy or breastfeeding
- Use of alcohol within 24 hours of the evaluation visits

Clinical visit overview

Visit 1 (Wk 0)	• Obtain informed consent • Fasting blood collection, physical measurements, and clinical examination • Education on study protocol • Provide study product • Assess baseline diet and lifestyle via a questionnaire • Participants complete health status questionnaires Brief Pain Inventory (BPI) and Health Symptoms Questionnaire (HSQ) and quality-of-life questionnaires [SF-12 and American Chronic Pain Association Quality of Life (ACPA QOL) Scale]
Visit 2 (Wk 4)	• Fasting blood collection, physical measurements, and clinical examination • Refresh education on study protocol • Provide study product • Assess diet and lifestyle via a questionnaire • Participants complete BPI, HSQ, SF-12, and ACPA QOL Scale • Physician summary of reported outcomes • Record adverse events through adverse event forms, patient discontinuation forms and study progress notes
Visit 3 (Wk 8)	• Fasting blood collection, physical measurements, and clinical examination • Assess diet and lifestyle via a questionnaire • Participants complete BPI, HSQ, SF-12, and ACPA QOL Scale • Physician summary of reported outcomes • Record adverse events through adverse event forms, patient discontinuation forms and study progress notes

Interpretations of questionnaire scales used in the study

Brief Pain Inventory (BPI):

- A reduction in score indicates improvement
- Each individual scale ranges from 0 (no pain or pain does not interfere with activity in question) to 10 (pain as bad as you can imagine or pain completely interferes with activity in question)

Health Symptoms Questionnaire (HSQ), previously known as Medical Symptoms Questionnaire (MSQ):

- A reduction in score indicates improvement
- Each individual domain ranges from 0 (never or almost never have the symptom) to 4 (frequently have it, effect is severe)

SF-12:

A detailed interpretation of each question can be downloaded at:

http://www.health.utah.gov/opha/publications/2001hss/sf12/SF12_Interpreting.pdf

American Chronic Pain Association Quality of Life (ACPA QOL) Scale:

- Scale ranges from 0 to 10 with the following definition:

0	Stay in bed all day Feel hopeless and helpless about life
1	Stay in bed at least half the day Have no contact with outside world
2	Get out of bed but don't get dressed Stay at home
3	Get dressed in the morning Minimal activities at home Contact with friends via phone, email
4	Do simple chores in the morning Minimal activities at home two days a week
5	Struggle but fulfill daily home responsibilities No outside activity Not able to work or volunteer
6	Work/volunteer limited hours Take part in limited social activities on weekends
7	Work/volunteer for a few hours daily Can be active at least five hours a day Can make plans to do simple activities on weekends
8	Work/volunteer for at least six hours daily Have energy to make plans for one evening social activity during the week Active on weekends
9	Work/volunteer/be active eight hours daily Take part in family life Outside social activities limited
10	Go to work/volunteer each day Normal daily activities each day Have a social life outside of work Take an active part in family life