Original Article

Dietary Fatty Acid Modification for the Treatment of Aspirin-Exacerbated Respiratory Disease: A Prospective Pilot Trial

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What is already known about this topic? It is known that patients with aspirin-exacerbated respiratory disease (AERD) overproduce the proinflammatory lipids, leukotriene E_4 and prostaglandin D_2, and that these lipids are derived from the metabolism of dietary sources of omega-6 fatty acids.

What does this article add to our knowledge? This study demonstrates that in patients with AERD, dietary modifications to increase omega-3 and decrease omega-6 fatty acid consumption can decrease their systemic production of leukotriene E_4 and prostaglandin D_2, and can lead to improved respiratory symptom control.

How does this study impact current management guidelines? Our results suggest that a diet high in omega-3 and low in omega-6 fatty acids may be a viable nonpharmaceutical adjunct for patients with AERD.

BACKGROUND: The high levels of eicosanoid production and the clinical efficacy of leukotriene-modifying pharmacotherapies for patients with aspirin-exacerbated respiratory disease (AERD) suggest that other interventions targeting arachidonic acid dysregulation may also improve disease control.

OBJECTIVE: To assess the utility of a high omega-3/low omega-6 diet for the treatment of AERD.

METHODS: Prospective, nonblinded dietary intervention in 10 adult patients with AERD at Brigham and Women's Hospital in Boston, MA. The primary objective was for subjects to reduce dietary omega-6 fatty acid consumption to less than 4 g/d and increase omega-3 intake to more than 3 g/d. The primary outcome was change in urinary leukotriene E_4, with changes in other eicosanoids, platelet activation, lung function, and patient-reported questionnaires also assessed.

RESULTS: Of the 10 subjects who screened for the study, all 10 completed the dietary intervention. Urinary leukotriene E_4 decreased by 0.17 ng/mg (95% CI, −0.29 to −0.04; $P = .02$) and tetranor prostaglandin D-M decreased by 0.66 ng/mg creatinine (95% CI, −1.21 to −0.11; $P = .02$). There was a 15.1-point reduction in the 22-item Sino-Nasal Outcome Test score (95% CI, −24.3 to −6.0; $P = .01$), a 0.27-point reduction in the 7-item Asthma Control Questionnaire score (95% CI, −0.52 to −0.03; $P = .03$), and no change in FEV_1 % predicted ($P = .92$) or forced vital capacity % predicted ($P = .74$). All patients lost some weight over the 2-week intervention period, and there were no diet-associated adverse events.

CONCLUSIONS: A high omega-3/low omega-6 diet may be an appropriate adjunct treatment option for patients with AERD. **(J Allergy Clin Immunol Pract 2018;6:825-31)**

Key words: *Aspirin-exacerbated respiratory disease; AERD; Samter's Triad; Diet; Asthma; Nasal polyps; Aspirin; NSAIDs; Fatty acids; Omega-3; Omega-6; LTE_4*

Aspirin-exacerbated respiratory disease (AERD), also known as Samter's Triad, is characterized by adult-onset asthma, chronic rhinosinusitis with nasal polyps, and clinical reactions to aspirin and other nonsteroidal anti-inflammatory drugs (NSAIDs). Dysregulation of arachidonic acid metabolism plays an integral role in the pathogenesis of AERD; excessive production of cysteinyl leukotrienes and other inflammatory lipid mediators, including prostaglandin D_2, are responsible for the hallmark respiratory and sinonasal symptoms at baseline and during aspirin-induced reactions.[1] Dietary fatty acids (FAs) are requisite precursors in the generation of arachidonic acid, and thus dietary modifications may provide therapeutic relief for patients with AERD. Leukotrienes and prostaglandins are generated by

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Abbreviations used
ACQ-7- 7-item Asthma Control Questionnaire
AERD- Aspirin-exacerbated respiratory disease
FA- Fatty acid
LTE_4- Leukotriene E_4
PGD-M- Tetranor prostaglandin D-M
SNOT-22- 22-item Sino-Nasal Outcome Test

the metabolism of arachidonic acid (20:4n-6), a polyunsaturated omega-6 FA, through the enzymatic activity of 5-lipoxygenase and cyclooxygenase, respectively. The amount of arachidonic acid in inflammatory cells is directly correlated to the dietary intake of arachidonic acid and of its precursor linoleic acid (18:2n-6), also an omega-6 FA,[2,3] and increased consumption of polyunsaturated long-chain omega-3 FAs, such as eicosapentaenoic acid (20:5n-3) and docosahexaenoic acid (22:6n-3) present largely in fish oil, increases the proportions of omega-3 FAs in inflammatory cells. Because this reduces the amount of arachidonic acid substrate available for the synthesis of the leukotrienes, supplementation of the diet with omega-3 FAs has been shown to result in decreased generation of inflammatory leukotrienes.[4,5]

In the United States, a 1000-fold increase in the prevalence of corn and soybean oil over the past century has led to a sizable shift in the ratio of omega-6 to omega-3 FA consumption. Although in the early 20th century it was estimated that humans generally consumed food sources with roughly equivalent omega-6 and omega-3 FA content, the ratio in modern Western diets is now estimated to be as high as 30:1. This change has been mirrored by a reduction in the proportion of omega-3 FAs present in tissue phospholipids.[6] A robust body of evidence suggests that omega-3 FAs aid in the prevention and management of several diseases, and the disequilibrium of dietary FA consumption may be detrimental to human health.[7] Although many studies have examined the effect of omega-3 FA supplementation on various disease states, the role of reducing dietary omega-6 FA consumption remains poorly understood and is worthy of further consideration.

In this trial, we sought to decrease the availability of arachidonic acid, and therefore the generation of downstream lipid mediators, through a 2-week dietary intervention aimed at restoring a more balanced omega-6 to omega-3 FA ratio. The clinical efficacy of zileuton, a medication that blocks 5-lipoxygenase enzymatic activity and inhibits leukotriene biosynthesis, supports this approach.[8,9] Zileuton has been shown to decrease urinary leukotriene E_4 (LTE_4) by up to 36%, and in one study of aspirin-intolerant patients with asthma, a 2-week course of zileuton increased lung function by an average of 9% compared with placebo and provided improvements in sense of smell and rhinorrhea.[9] These data suggest that other leukotriene-modifying interventions may also provide clinical benefit to patients with AERD.

We hypothesized that strict adherence to a diet rich in omega-3 FAs and deficient in omega-6 FAs could diminish the downstream production of both cysteinyl leukotrienes and prostaglandin D_2, and thereby improve upper and lower airway symptoms in patients with AERD. To test this hypothesis, we designed a prospective pilot trial and assessed the feasibility of a dietary intervention aimed at markedly decreasing the ratio of omega-6 to omega-3 FA consumption.

TABLE I. Summary of dietary recommendations

Recommended
Wild-caught, cold-water, oily fish (salmon, sardines, mackerel, herring, anchovies, tuna)
Fat-free dairy products
Egg whites
Dark leafy green vegetables (Brussels sprouts, kale, spinach, broccoli, salad greens)
Other vegetables (cabbage, turnips, green beans, carrots, sweet potatoes, squash)
Raw fruits
Ground flaxseeds or flaxseed oil
Wild-caught fish oils
Suggested in limited quantities
Kidney beans, mung beans, black beans, pinto beans
Other beans (cowpeas, navy beans, lentils, lima beans, split peas)
Potatoes
White rice and grains (barley)
Olive oil
Butter from grass-fed cows
Discouraged
Meat
Poultry
Fat-containing dairy products (regular milk, cheese, and yogurt)
Egg yolks
Peanuts and peanut butter
Tree nuts (almond, cashew, pistachio)
Avocados
Fried food
High-fat sweets and desserts
Margarine and vegetable oils, including corn oil, grape seed oil, soybean oil, safflower oil, sunflower oil, and cottonseed oil

METHODS

Study design

In this prospective trial, 10 subjects were recruited to complete 3 in-person visits over a 4-week study period. Following a screening visit to confirm study eligibility and obtain written informed consent, subjects began phase I, a 2-week period during which they were instructed to maintain their "normal" diet without alteration. The inclusion of phase I allowed for standardized collection of baseline nutrition data. In phase II, the 2-week treatment period, subjects were asked to (1) increase their daily omega-3 FA intake above 3 g/d (either through the frequent addition of wild-caught fish to their diet, or through fish oil supplementation) and (2) decrease their omega-6 FA consumption below 4 g/d. At the start of phase II, subjects were counseled by the study team and provided with educational materials on how to achieve these objectives. A summary of dietary recommendations appears in Table I. Subjects maintained a daily food and drink diary for the duration of the trial, and entries were reviewed in detail during weekly telephone consultations with a registered dietitian at the Center for Clinical Investigation Nutrition Core at Brigham and Women's Hospital. Each subject received a total of $150 in compensation to help offset study-related costs, including fish oil supplements and other food items. This trial was approved by the Partners Human Research Committee (Protocol 2013P002683) and is registered with ClinicalTrials.gov (Identifier NCT02064738).

TABLE II. Baseline demographic and clinical characteristics of the study population

Subject	Age (y)	Sex	Race	BMI	Montelukast (Y/N)	Lifetime polypectomies (no.)	ICS Use (mg/d)*
01	31	F	White	19.46	N	3	0
02	33	F	White	19.79	N	1	0
03	44	F	White	29.42	Y	7	1760
04	57	M	White	26.23	Y	2	0
05	55	F	Black	33.47	Y	1	940
06	65	F	Black	22.36	Y	2	1240
07	46	F	White	20.48	N	1	
08	59	F	White	23.93	Y	1	220
09	63	F	White	30.95	N		200
10	54	F	White	23.68	Y	2	320
Median	54.5	—	—	23.81	—		

BMI, Body mass index; *ICS*, inhaled corticosteroid; *M*, male; *N*, no; *F*, female; *Y*, yes.
*ICS use is calculated as fluticasone equivalent dose.

Participant selection and eligibility

This study was conducted between April 2014 and April 2017 at the Brigham and Women's Hospital in Boston, MA. Inclusion criteria specified that eligible participants were between the ages of 18 and 70 years with a physician diagnosis of AERD, defined as a current history of asthma, nasal polyposis, and at least 1 physician-observed reaction to oral aspirin or other nonselective cyclooxygenase inhibitor with features of lower and/or upper airway involvement. Subjects were excluded if they were current tobacco smokers, were pregnant or breast-feeding, had a body mass index of less than 18.5, had fish allergy or were unwilling to eat fish during the treatment period, had an implanted defibrillator, used zileuton or oral steroids within the 2 weeks before screening, or anticipated the use of any cyclooxygenase inhibitors during the study.

Interventions and measurements

The 7-item Asthma Control Questionnaire (ACQ-7) and the 22-item Sino-Nasal Outcome Test (SNOT-22) are validated questionnaires that were administered at each study visit to assess the severity of respiratory and sinonasal symptoms, respectively. The published minimally important difference for ACQ-7 is 0.5 points[10] and for SNOT-22 is 8.9 points[11]; these thresholds were used to provide clinical context to our findings. Vital signs, including height and weight, were collected at each visit. Pulmonary function tests were performed at all 3 visits with a CareFusion Micro I spirometer to measure FEV_1 and forced vital capacity. Blood samples were collected at visit 2 (baseline) and visit 3 (posttreatment) to quantify plasma lipid levels, blood eosinophil counts, and platelet activation. Similarly, urine samples were collected pretreatment and posttreatment to measure urinary LTE_4, tetranor prostaglandin D-M (PGD-M), an endogenous metabolite of prostaglandin D_2, and tetranor prostaglandin E-M, an endogenous metabolite of prostaglandin E_2. Participants were encouraged to maintain their usual medications throughout the trial, and they were interrogated at each visit about the occurrence of any potential adverse events.

Plasma samples were analyzed at the University of California, San Diego Lipidomics Core by ultra-performance liquid chromatography-tandem mass spectrometry as previously described.[12] Urinary samples for LTE_4, PGD-M, and tetranor prostaglandin E-M were analyzed by mass spectrometric assay at the Vanderbilt University Eicosanoid Core Laboratory as previously described.[13] Complete blood cell counts with differentials were performed by LabCorp (Raritan, NJ).

To monitor platelet activation (surface expression of CD62P on free platelets), peripheral blood was drawn into heparinized tubes, kept at room temperature, and assayed within 1 hour of collection. Platelet-rich plasma was obtained from the top layer of blood samples after a 20-minute centrifuge at 200*g*. We incubated 10 μL of platelet-rich plasma with directly conjugated antibodies specific for CD61 and CD62P, or appropriate isotype controls (BD Biosciences, San Jose, Calif) for 20 minutes, then fixed the cells in 1% paraformaldehyde. At least 50,000 platelets were recorded for each sample in a FACSAria flow cytometer (BD Biosciences).

End points

The primary end points were changes in urinary LTE_4 and plasma leukotriene B_4. Secondary end points were changes in patient-reported questionnaire (ACQ-7 and SNOT-22) scores and pulmonary function (FEV_1 and forced vital capacity). Exploratory end points included changes in urinary prostaglandin metabolites, blood eosinophil count, and platelet activation. All end points were prespecified and calculated as the change between visit 2 (baseline) and visit 3 (posttreatment).

Statistical analysis

Study data were collected and managed using Research Electronic Data Capture tools hosted at Brigham and Women's Hospital. Research Electronic Data Capture is a secure, Web-based application designed to support data capture for research studies.[14] Quantitative differences between treatment phases were analyzed using the paired Student *t* test ($\alpha = 0.05$), and all data were analyzed in GraphPad Prism version 7.03 for Windows (GraphPad Software, La Jolla, Calif). Data are represented as the mean and 95% CI unless stated otherwise. Treatment assignments and secondary clinical outcomes were not blinded to the subject or study team; however, biomarkers for the primary and exploratory end points including urinary and plasma lipid levels and platelet activation were analyzed without knowledge of the corresponding subject ID or collection time point.

RESULTS

Baseline characteristics of the study population

Baseline characteristics are summarized in Table II. All 10 study subjects lost body weight during the 2-week intervention phase, with an average loss of 3.25 lb (95% CI, −4.94 to −1.57; $P = .002$). Likewise, average body mass index also significantly decreased by 0.58 (95% CI, −0.99 to −0.06, $P = .03$). Nine of 10 subjects were females. Although female participants were overrepresented in our pilot trial, AERD is known to be more

TABLE III. Nutrient intake pretreatment vs posttreatment

Nutrient	Phase I (normal diet)	Phase II (treatment diet)	*P* Value
Carbohydrates (g/d)	200.0 ± 54.4	199.0 ± 70.9	.97
% of energy	45.2 ± 7.1	57.1 ± 10.6	—
Protein (g/d)	77.6 ± 12.3	71.1 ± 15.0	.08
% of energy	17.4 ± 2.2	20.4 ± 4.3	—
Total fat (g/d)	73.4 ± 16.1	32.9 ± 18.5	**<.001**
% of energy	37.3 ± 6.6	21.2 ± 8.1	—
Saturated fat (g/d)	23.4 ± 8.1	9.4 ± 7.0	**.001**
MUFA (g/d)	27.3 ± 6.0	9.1 ± 6.2	**<.001**
PUFA (g/d)	16.7 ± 4.5	8.9 ± 6.1	**<.001**
Total omega-3	2.0 ± 0.6	5.5 ± 4.0	**.01**
From food sources	2.0	3.8	—
From supplements	0.0	1.7	—
Total omega-6	14.5 ± 4.2	3.8 ± 2.6	**<.001**
From food sources	14.5	3.8	—
From supplements	0	0	—
Total energy (kcal/d)	1,787.8 ± 333.3	1,393.5 ± 463.8	**<.001**

MUFA, monounsaturated fatty acid; PUFA, polyunsaturated fatty acid.
Data are presented as mean ± SD. Bold indicates statistical significance ($P < .05$).

prevalent in women than in men. In our AERD patient registry with 546 patients, 344 (63.0%) are females.

Compliance with the dietary intervention

All 10 subjects who were screened for the study met eligibility criteria and completed enrollment. Participants demonstrated greater than 95% compliance with recording their daily food and drink diary, defined as the percentage of days with complete records. Nutrient intake data were calculated from the subject diaries by a registered dietitian and are summarized in Table III. Overall, participants achieved their goal of increasing omega-3 FA intake to greater than 3 g/d while decreasing omega-6 FA intake below 4 g/d. Dietary omega-3 was increased by an average of 3.5 g/d (95% CI, 0.9-6.1; $P = .01$) from phase I to phase II, whereas dietary omega-6 was simultaneously reduced by 10.7 g/d (95% CI, −12.9 to −8.6; $P < .001$) over the same time interval (Figure 1). Accordingly, the omega-6:omega-3 ratio decreased 10-fold (from 7.3 to 0.7) in phase II compared with phase I. Daily total energy consumed decreased by an average of 385.7 kcal/d (95% CI, −526.8 to −244.5; $P = .001$) during the study intervention. Although study subjects consumed similar quantities of protein ($P = .08$) and carbohydrates ($P = .97$) in both phases, overall fat intake was substantially reduced in phase II ($P < .001$).

Laboratory end points

Urinary LTE_4 decreased by 0.17 ng/mg creatinine after the 2-week dietary intervention period compared with baseline (95% CI, −0.29 to −0.04; $P = .02$), and there was a notable decrease of 0.66 ng/mg creatinine (95% CI, −1.21 to −0.11; $P = .02$) in the production of tetranor PGD-M (Figure 2 and Table IV); there was no change in the production of tetranor prostaglandin E-M (data not shown). Plasma leukotriene B_4 was undetectable in 75% of the samples tested, and therefore could not be analyzed. Plasma levels of the free omega-3 FAs eicosapentaenoic acid and docosahexaenoic acid increased significantly by 4-fold ($P = .016$) and 2-fold ($P = .015$), respectively. In addition, the combined plasma levels of detectable eicosapentaenoic acid–derived lipid metabolites (5-HEPE, 15-HEPE, 12-HEPE, 14(15)-EpETE) increased by 2-fold ($P = .041$), as did the plasma levels of docosahexaenoic acid–derived metabolites (Resolvin D1, 7,17-dHDPA, 19(20)-EpDPE, 19,20-DiHDPA) ($P < .001$).

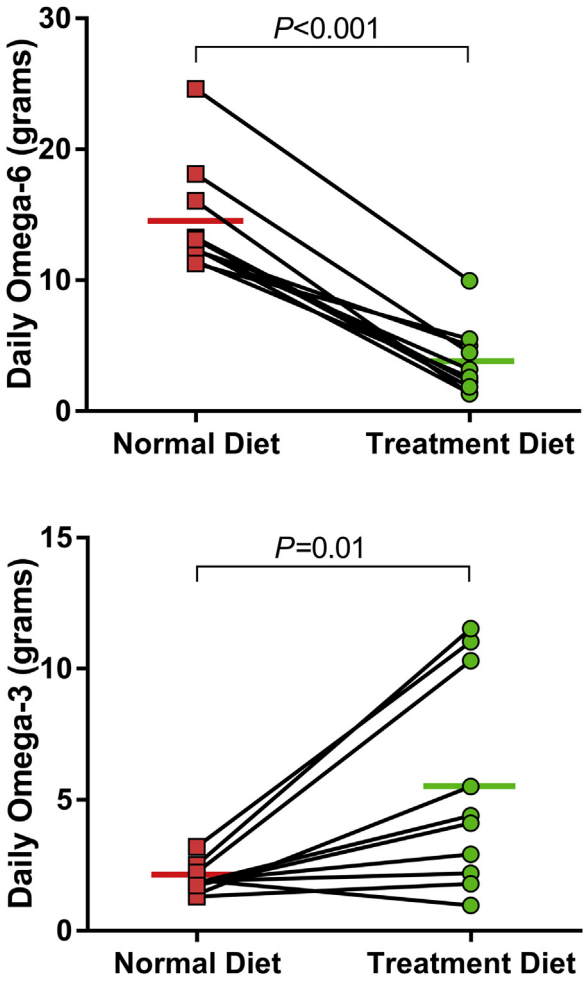

FIGURE 1. Omega-3 and omega-6 FA intake during 2-week dietary intervention. Changes in average daily nutritional intake of omega-6 (top) and omega-3 (bottom) FAs are shown. Individual data points are shown with means for each phase.

Absolute blood eosinophil count remained unchanged after the treatment diet, with a baseline average of 540 eosinophils/μL and a posttreatment diet average of 510 eosinophils/μL (mean of differences = −0.03; 95% CI, −0.16 to 0.10; $P = .60$). Platelet activation levels of free plasma platelets were also unchanged on the treatment diet, with a baseline average of 29.9% $CD62P^+$ platelets and a posttreatment diet average of 31.8% $CD62P^+$ platelets (mean of differences = 1.9; 95% CI, −5.0 to 8.8; $P = .55$).

Clinical end points

For patient-reported outcomes, the SNOT-22 score decreased by 15.1 points (95% CI, −24.3 to −6.0; $P = .01$) and the ACQ-7 score decreased by 0.27 points (95% CI, −0.52 to −0.03; $P = .03$) (Figure 3 and Table IV). The decrease in the SNOT-22 score is clinically significant; the improvement in the ACQ-7 score, although statistically significant, does not meet the

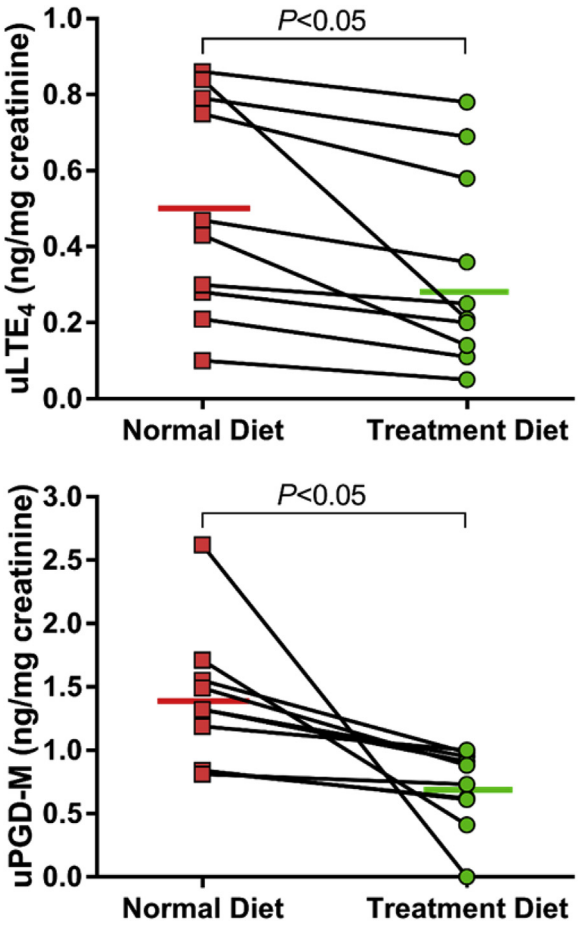

FIGURE 2. Urinary LTE_4 and PGD-M levels during 2-week dietary intervention. Changes in $uLTE_4$ (top) and uPGD-M (bottom) levels are shown. Individual data points are shown with means for each phase.

published threshold for clinical significance.[10,11] There were no significant correlations between clinical symptom improvement and total change in urinary LTE_4, urinary PGD-M, or quantified FA consumption. No differences were observed with respect to the pulmonary function tests (FEV_1 % predicted: mean of differences = −0.1%; 95% CI, −3.3 to 3.0; $P = .92$; forced vital capacity % predicted: mean of differences = 0.5%; 95% CI, −2.9 to 3.9; $P = 0.74$). No adverse events were reported in either the pretreatment phase or the posttreatment phase.

DISCUSSION

In the 2-week intervention period, we found that a diet high in omega-3 FAs and low in omega-6 FAs was generally safe and well-tolerated, improved AERD-associated symptoms, and decreased levels of proinflammatory biomarkers. We were able to demonstrate that the dietary intervention changed cellular FA composition sufficiently to provide for a measurable reduction in both LTE_4 and PGD-M, 2 arachidonic acid–derived inflammatory lipids relevant in AERD,[13,15] while maintaining unchanged levels of the metabolite of prostaglandin E_2, which may be protective in the disease.[16,17] Furthermore, we found evidence that the dietary intervention also increased the production of omega-3 FA-derived lipid metabolites, including Resolvin D1, which may promote the resolution of chronic airway inflammation.[18] This combination of biochemical changes allowed for the improved symptomatic control reported by the patients in this study.

TABLE IV. Study outcomes

End point	Visit 2 (baseline)	Visit 3 (posttreatment)	*P* Value
Laboratory end points			
Urinary LTE_4 (ng/mg creatinine)	0.50 ± 0.39	0.34 ± 0.26	**.02**
Urinary prostaglandin D_2 (ng/mg creatinine)	1.37 ± 0.54	0.71 ± 0.32	**.03**
Blood eosinophils (absolute)	0.54 ± 0.29	0.51 ± 0.27	.60
Platelet activation (%$CD62P^+$)	29.9 ± 9.6	31.8 ± 13.8	.55
Clinical end points			
ACQ score	0.83 ± 0.55	0.56 ± 0.40	**.03**
SNOT-22 score	30.0 ± 15.2	14.9 ± 6.6	**.02**
FEV_1 (L)	2.36 ± 0.42	2.37 ± 0.45	.70
FEV_1 (% predicted)	85.0 ± 11.6	84.9 ± 11.4	.92
FVC (L)	3.11 ± 0.45	3.16 ± 0.51	.37
FVC (% predicted)	90.7 ± 12.7	91.2 ± 11.6	.74

FVC, Forced vital capacity.
Data are presented as mean ± SD. Bold indicates statistical significance ($P < .05$).

Previous literature has remained inconclusive about the protective role of omega-3 supplementation in asthma control and pulmonary function. Our subjects failed to show improvement in their pulmonary function tests after the 2-week treatment period. This result is consistent with a study by Brannan et al[19] that showed that fish oil supplementation in a population of patients with asthma did not produce a change in FEV_1 percent predicted compared with placebo after 3 weeks of supplementation.[19] However, 2 studies by Mickleborough et al[20,21] demonstrated a protective effect of fish oil supplementation on exercise-induced bronchoconstriction in adults with asthma and in a cohort of elite athletes. The discrepancy in our results may be attributed to the differences in subject phenotypes as well as the heterogeneic nature of asthma. Also, our patients had generally normal FEV_1 values, and reversibility of bronchoconstriction was not an inclusion criterion, so large changes in FEV_1 were not necessarily expected.

To date, only 2 AERD-specific diet trials have been published, both by Sommer et al,[22,23] for the evaluation of a low-salicylate diet. In the larger of their 2 studies, a total of 30 patients were randomly assigned to either maintain their regular diet or start on a low-salicylate diet for 6 weeks, after which they crossed over into the opposite treatment arm an additional 6 weeks. Compared with the regular diet arm, patients randomized to the low-salicylate diet did demonstrate improvement with respect to several subjective and objective measurements.[23] The biological rationale for a low-salicylate diet in the treatment of AERD, however, is unclear. Aspirin (acetylsalicylic acid)-induced respiratory reactions are triggered by irreversible inhibition of cyclooxygenase-1 activity; acetylation of serine 530 creates a steric hindrance that blocks the entry of arachidonic acid into the enzyme's active site.[24] The generation of salicylic acid occurs downstream of cyclooxygenase-1 inhibition and is therefore unlikely to contribute to AERD-related symptoms. There is no known mechanism by which dietary salicylates would perturb the biological pathways implicated in the pathogenesis of AERD.

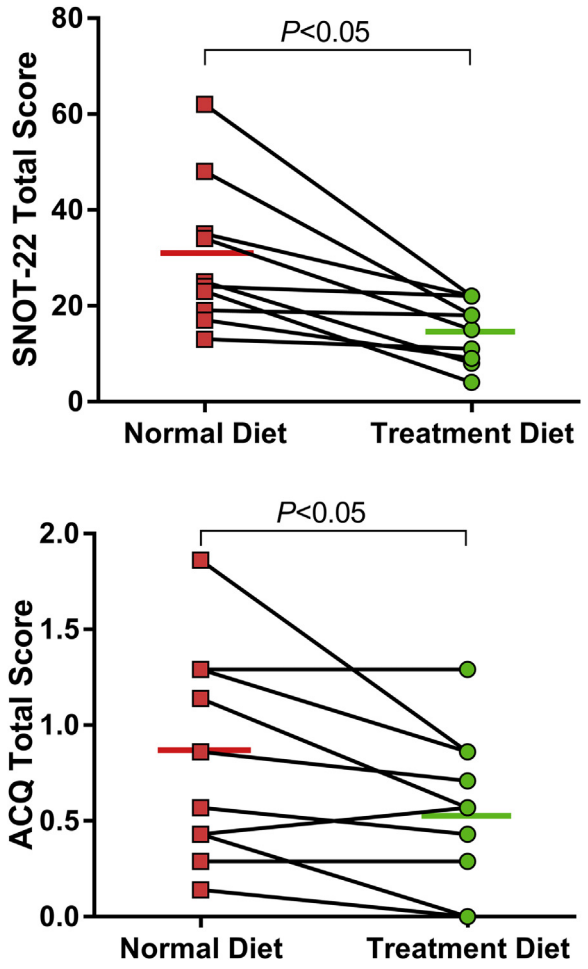

FIGURE 3. SNOT-22 and ACQ scores during 2-week dietary intervention. Changes in patient-reported SNOT-22 (top) and ACQ (bottom) scores are shown. Individual data points are shown with means for each phase.

The current study does have several limitations. First, the intervention period was just 2 weeks in length, in part because we were uncertain about the long-term feasibility of adhering to the study diet. The observed weight loss would likely be unsustainable if the diet were followed for an indefinite period. Future studies should introduce additional measures to ensure that participants consume enough protein and carbohydrates to balance the net reduction in dietary fats and thus maintain adequate total caloric intake. Second, because the study diet required substantial dietary modifications, it was not practical to blind the participants or the study staff to the intervention. Third, the small sample size and predominantly female study population may limit the generalizability of the results. Fourth, disparities in access to healthy food options may hinder widespread implementation of this diet, and the cost of fish oil supplements and other recommended foods such as wild-caught fish or animal products from grass-fed sources may be prohibitive for some patients.

Strengths of this study include meticulous documentation and accounting of nutrient intake as well as excellent subject adherence to the target omega-3 and omega-6 FA objectives. Although there exists a large body of research examining the health effects of omega-3 supplementation, information about the role of dietary omega-6 reduction remains scarce. Our study is novel because it emphasized the importance of reducing omega-6 consumption in conjunction with omega-3 supplementation to maintain a more historically natural balance between them.

The treatment options for AERD remain limited. Current management includes nasal polypectomy, aspirin desensitization, nasal and oral corticosteroids, leukotriene-modifying agents, monoclonal asthma medications such as omalizumab and mepolizumab, and inhaled corticosteroids.[25] Our study takes an important step toward expanding the arsenal of treatment options available to patients and clinicians. Specifically, with the decrease in both urinary LTE_4 and PGD-M, combined with the increase in proresolving lipid metabolites, this dietary approach has several biochemical advantages over the existing antileukotriene medications. Our results generally support the hypothesis that a diet high in omega-3 FAs and low in omega-6 FAs may be a viable nonpharmaceutical option for patients looking to augment their standard treatment plan. Additional studies are warranted to more precisely determine the effect size of our findings and to assess the long-term feasibility of a low omega-6/high omega-3 diet.

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