

Can Diet Modification Be an Effective Treatment in Aspirin-Exacerbated Respiratory Disease?



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Individuals with aspirin-exacerbated respiratory disease (AERD), as is the case with most immune-mediated disease, often ask care providers whether diet changes or adding supplements could improve their condition. AERD, a condition without a cure and often difficult to treat, leads patients to explore this issue on their own, often experimenting with a variety of diets, supplements, and vitamins.

Although the effect of diet on asthma has been studied numerous times, results are conflicting, likely due, in part, to the challenges of performing such studies. It is unknown whether to expect dietary changes to affect lung function, exacerbation rates, or quality of life, leaving researchers uncertain regarding what respiratory outcomes should be measured. Blinding dietary changes for a sustained period would be difficult. Separation of nutritional influences from other indirect effects of dietary changes, such as weight loss, complicates interpretation of any study.

In spite of these issues, a dietary strategy to treat AERD, which offers a chance at a simple, economically inexpensive solution without risk of drug side effects, warrants further exploration. In this issue of *JACI: In Practice*, Schneider et al¹ provide new evidence that a tip in the dietary balance from proinflammatory omega-6 to anti-inflammatory omega-3 may reduce inflammation in AERD. The authors chose to study AERD, which typically presents in adulthood without a strong association with other atopic disease. AERD is known to have type 2 inflammation in both upper and lower airways; thus, the homogeneous and inflammatory nature of AERD suggests that it would be more amendable to such treatment. Studying the AERD population controls for inherent differences between asthmatic populations, such as type 2 high, type 2 low, and other subphenotypes that could potentially respond differently to a dietary intervention. In a novel methodology, the authors used lipidomics to verify adherence, and more importantly, to show that dietary-induced changes in lipid metabolism would be anticipated to have therapeutic benefit.

Dietary intervention studies in asthma fall into 2 general categories: broad dietary changes, such as the “Mediterranean diet,” which may have several beneficial effects not necessarily limited to asthma, and a targeted diet approach where a limited number of nutritional components are isolated and studied, often with the goal of inflammatory pathway modulation.

A systematic analysis of studies using a Mediterranean diet to treat pediatric asthma concluded that adherence to a Mediterranean diet and asthma symptoms had an inverse relationship.² In a pilot trial of DASH (Dietary Approaches to Stop Hypertension), a diet rich in vegetables, fruits, and low-fat dairy foods with moderate amounts of whole grains, fish, poultry, and nuts resulted in an improvement in quality of life among uncontrolled asthmatics.³ As weight loss plus exercise has been shown to result in a similar quality of life benefit in obese asthmatics,⁴ one must take into consideration the likelihood that an attempt to “get healthy” can have a salutary effect on asthma.

In a targeted dietary approach, omega-3 fatty acid supplementation has been shown in a few studies to inhibit exercise or eucapnic voluntary hyperventilation-induced bronchospasm.⁵⁻⁷ In contrast and more recently, Brannan et al⁸ showed that fish oil supplementation had no effect on bronchial hyper-reactivity to mannitol and did not change markers of type 2 inflammation such as sputum eosinophil counts and urinary mast cell mediator measurements. Similar conflicting reports exist for vitamin C, vitamin A, and vitamin E supplementation, and complicate any recommendations that these supplements may improve asthma. Dietary differences, dose effects, and asthma heterogeneity likely influence conflicting findings, as animal models have consistently suggested dietary changes matter.

Yet, in the last decade, the landscape of asthma has changed. Understanding asthma as a heterogeneous syndrome made of distinct inflammatory phenotypes has become imperative in the application of novel therapies. And there is no reason that this should not be true with dietary modification. Perhaps a specific dietary treatment should be applied to a distinct inflammatory asthmatic pattern.

As a specific endotype of asthma, AERD could benefit from a targeted dietary approach. The first such studies in AERD, performed by Sommer et al,^{9,10} evaluated a low salicylate diet in AERD under the assumption that a high salicylate diet could decrease COX2 expression and patients would presumably be more likely to react to dietary salicylates. This is a tenuous supposition without any evidence that salicylates in general or dietary salicylates specifically can cause either acute or chronic worsening in AERD. These studies showed improvement in both subjective and objective (Lund-Kennedy endoscopic score) measures, but in a study design where blinding was impossible to the patient, the results need to be interpreted cautiously. The authors did not report any biochemical measures to evaluate an immunomodulatory effect of a low salicylate diet.^{9,10} Although

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both of these studies are positive, dietary recommendations cannot be made without confirmatory studies or a mechanistic understanding of how these interventions could be effective.

Schneider et al¹ devised a dietary strategy unique to AERD. Although prior dietary studies featured omega-3 supplementation, this is the first to “starve” the inflammatory lipid mediator pathway by simultaneously decreasing omega-6 intake. Decreasing omega-6 while increasing omega-3 results in a reduction of arachidonic acid precursors, and a concurrent increase in eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) formed via an omega-3 pathway. EPA and DHA precursors form the anti-inflammatory resolvins, protectins, and maresins that modulate prostaglandin, thromboxanes, and leukotrienes. In contrast, a modern western diet, with an elevated omega-6 to omega-3 ratio, leaves cell membranes deficient in EPA and DHA, shifting the balance away from the less inflammatory 5 series leukotrienes (LTB₅ and PGE₃) to the more potent 4 series (LTC₄, LTD₄, LTE₄). In a disease inherently skewed toward inflammatory lipid mediator production, substantial alterations in the omega-6:omega-3 ratio might be necessary to achieve clinical benefit.

The diet in this study was effective in accomplishing lipid mediator shifts in the urine as anticipated by their hypothesis. Early symptomatic and objective improvements in disease measures were observed. Although potentially difficult to adhere to as a long-term treatment strategy, this pilot study demonstrates a clear mechanistic underpinning for future diet approaches to AERD treatment.

Schneider et al¹ address the financial cost of their diet recommendation as being a possible limitation. This should be balanced with the knowledge that most patients with AERD are on multiple medications to control their airway disease, usually using a combination of an asthma controller, aspirin desensitization, an antileukotriene drug, nasal corticosteroids, and nasal rinses. Some patients continue to require repeated sinus surgery and biologic therapy. In comparison with these, the costs of a targeted diet, while expensive, would still pale in comparison with costs to the patient and third-party payers.

The result of this study opens the door to several important follow-up questions. Is it possible that failure to show benefit of other omega-3 supplementation trials in asthma was because

depletion of omega-6 was overlooked? Second, although the diet of the current study might not be feasible for long-term use, can a less aggressive diet strategy be equally effective and improve adherence? A third question is whether a dietary intervention in combination with a 5-lipoxygenase inhibitor could augment and achieve a superior clinical effect. This successful pilot study paves the way for larger well-designed trials with the intention of providing specific diet recommendations. This study should also lead us to rethink our evaluation of the successes and failures of dietary intervention studies in asthma.

REFERENCES

- Schneider TR, Johns CB, Palumbo ML, Murphy KC, Cahill KN, Laidlaw TM. Dietary fatty acid modification for the treatment of aspirin-exacerbated respiratory disease: a prospective pilot trial. *J Allergy Clin Immunol Pract* 2018;6:825-31.
- Papamichael MM, Itsiopoulos C, Susanto NH, Erbas B. Does adherence to the Mediterranean dietary pattern reduce asthma symptoms in children? A systematic review of observational studies. *Public Health Nutr* 2017;20:2722-34.
- Ma J, Strub P, Lv N, Xiao L, Camargo CA, Buist AS, et al. Pilot randomised trial of a healthy eating behavioural intervention in uncontrolled asthma. *Eur Respir J* 2016;47:122-32.
- Freitas PD, Ferreira PG, Silva AG, Stelmach R, Carvalho-Pinto RM, Fernandes FL, et al. The role of exercise in a weight-loss program on clinical control in obese adults with asthma. A randomized controlled trial. *Am J Respir Crit Care Med* 2017;195:32-42.
- Mickleborough TD, Murray RL, Ionescu AA, Lindley MR. Fish oil supplementation reduces severity of exercise-induced bronchoconstriction in elite athletes. *Am J Respir Crit Care Med* 2003;168:1181-9.
- Mickleborough TD, Lindley MR, Ionescu AA, Fly AD. Protective effect of fish oil supplementation on exercise-induced bronchoconstriction in asthma. *Chest* 2006;129:39-49.
- Tecklenburg-Lund S, Mickleborough TD, Turner LA, Fly AD, Stager JM, Montgomery GS. Randomized controlled trial of fish oil and montelukast and their combination on airway inflammation and hyperpnea-induced bronchoconstriction. *PLoS One* 2010;5:e13487.
- Brannan JD, Bood J, Alkhabaz A, Balgoma D, Otis J, Delin I, et al. The effect of omega-3 fatty acids on bronchial hyperresponsiveness, sputum eosinophilia, and mast cell mediators in asthma. *Chest* 2015;147:397-405.
- Sommer DD, Rotenberg BW, Sowerby LJ, Lee JM, Janjua A, Witterick IJ, et al. A novel treatment adjunct for aspirin exacerbated respiratory disease: the low-salicylate diet: a multicenter randomized control crossover trial. *Int Forum Allergy Rhinol* 2016;6:385-91.
- Sommer DD, Hoffbauer S, Au M, Sowerby LJ, Gupta MK, Nayan S. Treatment of aspirin exacerbated respiratory disease with a low salicylate diet: a pilot crossover study. *Otolaryngol Head Neck Surg* 2015;152:42-7.