CASE STUDY

Antioxidants and Asthma
A Case Report and Review of the Evidence

Christine Karpinski, MA, RD, LDN, CSSD;
Riva Touger-Decker, PhD, RD, FADA

Asthma is a chronic, nonspecific lung disease that affects 15.7 million adults in the United States. Treatment typically focuses on removing potential allergens and prescription medications. Given the potential adverse effects of many medications, some patients explore the use of alternative treatments such as antioxidants. Research exploring the role of antioxidants in the prevention and management of chronic disease has dramatically increased in 30 years. Because asthma is an inflammatory disease that has been associated with oxidative stress, it is plausible to consider the role of antioxidant supplementation as an alternative treatment of asthma. This article addresses the case of an adult woman who tried antioxidants as adjunct therapy in the management of her asthma. The scientific relevance regarding antioxidant supplement use in asthma in adults is presented using an evidence-based approach. Key words: antioxidants, asthma, diet, disease management, oxidative stress

The following case is that of a 62-year-old female (N.H.) with asthma who tried antioxidant supplementation as an alternative to her current medication protocol. Antioxidant supplementation is not currently prescribed as part of the standard clinical practice guidelines established by the National Asthma Education and Prevention Program (NAEPP) coordinated by the National Heart, Lung, and Blood Institute. 

This case study will provide an overview of asthma, the current clinical practice guidelines for management of asthma, and the existing evidence of the relationship between antioxidants and asthma. It will follow the specific case of NH and her use of antioxidant supplementation as adjunctive therapy in the management of asthma.

Asthma etiology and symptoms

Asthma is a nonspecific, chronic lung disease that involves the inflammation of the airways due to allergic and nonallergic causes. It is generated by immunologic responses; mast cells, eosinophils, and T lymphocytes play an important role. Asthma is characterized by recurrent attacks of labored breathing, wheezing, a sense of chest constriction, and coughing. During an attack, the lining of the bronchial tubes swells, which shrinks the diameter of the airways and reduces the flow of air into and out of the lungs. There is a strong genetic component that is not fully understood, as well as developmental and environmental factors. Asthma can be successfully managed with effective treatment.

Asthma can be triggered by a number of factors that can be determined by symptoms, such as coughing, wheezing, chest tightness,
shortness of breath, and loud breathing. Skin allergy tests and blood tests, such as a radioallergosorbent testing or an immunoassay capture test, can be performed, as well as a spirometer test to confirm the diagnosis. Finally, other tests might be given to rule out other possible diagnoses, including a chest x-ray and electrocardiogram. Common allergens include the following: animal dander; house dust mites; cockroaches; pollen and outdoor and indoor molds; and work environment chemicals. Tobacco smoke is a major irritant whether it is inhaled through smoking cigarettes or through secondhand smoke. Some other common irritants are as follows: burning wood, unvented stoves or heaters, perfumes, cleaning agents, sprays, dust, and vapors.

Asthma has been associated with increased morbidity and mortality, including lack of sleep, fatigue, missed school or work, and overall decreased quality of life. In 2000, asthma was estimated to directly and indirectly cost $18.3 billion. Asthma continues to burden the US healthcare system, with a reported 14.7 million outpatient asthma visits to physician offices and hospital outpatient departments or 508 per 10 000 people; 1.8 million visits to emergency departments for asthma in 2004 or 64 per 10 000 people; and 497 000 asthma hospitalizations in 2004 or 17 per 10 000 people in 2004. In 2003, 4055 people died from asthma or 1.4 per 100 000 people.

According to the 2005 National Health Interview Survey, 15.7 million adults in the United States had asthma and 23 million adults had ever been diagnosed with asthma during their lifetime. According to the World Health Organization, asthma is underdiagnosed and often goes untreated, worldwide.

PREVENTION AND TREATMENT OF ASTHMA

The NAEPP published the third Expert Panel Report (EPR-3) in 2007 that established 4 components of asthma-related care and a stepwise approach for managing asthma that is integral to quality asthma care. This document explains the 4 essential components of asthma management: assessment and monitoring; education for partnership in care; control of environmental factors and comorbid conditions; and medications. There are no diet-related interventions cited; however, there is a recommendation to advise overweight and obese patients that weight loss may improve their asthma control.

There is an abundance of current literature that has inferred an association between obesity and asthma prevalence, although most are animal studies or epidemiological studies, and the exact cause of this relationship remains unclear. There is a paucity of research that looks at the management of those previously diagnosed with asthma, which would be more relevant for this case study. Rodrigo et al conducted a prospective cohort study and found that overweight/obese patients (body mass index >25 kg/m^2) with asthma were admitted to the hospital more frequently (13.7% vs 6.8%; P = .02), had a higher rate of steroid usage in the past 7 days, and experienced more wheezing than under- or normal-weight patients.

There is limited published research on the relationship between diet and asthma management. Other studies have looked at the prevention of asthma and its association with dietary intake, serum and cellular levels, and related pulmonary diseases. Several studies have documented lower serum and cellular levels of selenium, vitamin C, and vitamin E in adults with asthma. The results of epidemiologic and observational studies have revealed that lower intakes of vitamins C and E are associated with lung function and asthma. Devereux and Seaton cited several epidemiological studies that found associations between asthma onset and both dietary antioxidants and lipid intake but found trials with supplementation studies to have weak associations. Two 2004 systematic reviews concluded that there is insufficient evidence to assess the usefulness of vitamin C or selenium supplementation in the prevention of
Other studies have hypothesized that decreasing antioxidant intake (fruit and vegetables), increasing n-6 polyunsaturated fatty acid (PUFA) (margarine, vegetable oil), and decreasing n-3 PUFA (oily fish) intakes have contributed to the recent increases in asthma prevalence.27,28 Although not a focus of this case study, the anti-inflammatory action of essential fatty acids may also be of interest. After reviewing PUFA, inflammation, and inflammatory diseases, Calder30 concluded that evidence of the therapeutic potential of long-chain n-3 PUFAs in asthma is lacking and that more well-designed and larger trials are required. Lastly, Ziboh et al31 investigated whether dietary γ-linolenic acid in borage oil would attenuate asthma symptoms.31 Although the results were not statistically significant, a trend in the suppression of the asthma scores was observed.

**CASE HISTORY**

N.H. is a generally healthy 62-year-old, postmenopausal woman who exercises regularly and follows a diet consistent with the 2005 Dietary Guidelines for Americans.32 She has a history of asthma, allergies, and glaucoma. Her average blood pressure is 128/70 mm Hg; pulse is 61 beats per minute. NH weighs 133 lb (60.5 kg) and is 63 inches (160 cm) tall; her body mass index is 24 kg/m². Tables 1 and 2 list NH’s prescription medications and dietary supplements.

N.H. was diagnosed with asthma in 1995 and subsequently referred to a pulmonologist/allergist in 1997. She has been seen by her current specialist for routine follow-up visits every 4 to 6 months over the past 10 years, unless otherwise necessary. According to established clinical indicators,33,34 NH’s asthma was classified in the moderate-persistent severity category. N.H. is susceptible to upper respiratory tract infections, as evidenced by bouts of bronchitis in February in 2005 and 2006 that were successfully treated with antibiotics. She has had overall good control of her asthma for several years as a result of successful medication protocols and lifestyle management. Cutaneous and intradermal skin tests in 1997 and again in 2005 revealed allergies to Virginia live oak, water oak and Australian pine pollen, dust mites, cats, and dogs. These allergies have the potential to trigger an asthma attack. NH receives allergy immunotherapy injections every 2 to 4 weeks, unless she is immunocompromised (sinusitis, bronchitis, etc). N.H. has minimized the environmental triggers of asthma.

N.H.’s desire to decrease and/or stop some or all of her medications led her to an Internet search for alternative therapies. After reading about the potential benefits of antioxidants, she started taking a variety of products.

**Table 1. Prescription medications of 62-year-old woman**

<table>
<thead>
<tr>
<th>Medication</th>
<th>Dosage</th>
<th>Year when started</th>
</tr>
</thead>
<tbody>
<tr>
<td>Budesonide inhalation (Pulmicort, corticosteroid)</td>
<td>1 click, bid</td>
<td>1995</td>
</tr>
<tr>
<td>Albuterol (adrenergic bronchodilator)</td>
<td>prn</td>
<td>1995</td>
</tr>
<tr>
<td>Mometasone nasal (Nasonex, corticosteroid)</td>
<td>1 spray daily</td>
<td>1995</td>
</tr>
<tr>
<td>Fexofenadine hydrochloride and pseudoephedrine</td>
<td>prn</td>
<td>1995</td>
</tr>
<tr>
<td>hydrochloride (Allegra)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Latanoprost ophthalmic (Xalantan, glaucoma)</td>
<td>1 drop/eye/d (2.5 mg at</td>
<td>1996</td>
</tr>
<tr>
<td></td>
<td>0.005%)</td>
<td></td>
</tr>
<tr>
<td>Conjugated estrogens, oral (Premarin, hormone</td>
<td>0.625 mg/d</td>
<td>1992</td>
</tr>
<tr>
<td>replacement therapy)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Table 2. Dietary supplements of 62-year-old woman

<table>
<thead>
<tr>
<th>Dietary supplementation</th>
<th>Dosage</th>
<th>Year when started</th>
</tr>
</thead>
<tbody>
<tr>
<td>Calcium complex: (Member's Mark “Calcium plus minerals with vitamin D”; 1 tablet contains: 600-mg calcium carbonate, 200 IU vitamin D, 40-mg magnesium, 7.5-mg zinc, 1.8-mg manganese, and 250-μg boron)</td>
<td>1 tablet, bid</td>
<td>1991</td>
</tr>
<tr>
<td>Multivitamin (Member’s Mark “Mature Multi”)</td>
<td>2 tablets/d</td>
<td>1991</td>
</tr>
<tr>
<td>Isotonix OPC-3 (market America; 1 capful contains: 25-mg grape seed extract, 25-mg red wine extract, 25-mg pycnogenol, 25-mg bilberry extract, 25-mg citrus extract, and 93-mg potassium bicarbonate)</td>
<td>1 capful bid</td>
<td>2004</td>
</tr>
<tr>
<td>Fish oil (Solgar Max EPA; 2 capsules contain: 2000-mg fish oil concentrate—360-mg eicosapentaenoic acid and 240-mg docosahexaenoic acid)</td>
<td>1 capsule bid</td>
<td>2004</td>
</tr>
<tr>
<td>Antioxidant complex (Vitamin Shoppe “Super Antioxidant”; 2 capsules contain: 1000 IU beta carotene, 60-mg vitamin C, 200 IU vitamin E, 25-mg thiamin, 25-mg riboflavin, 25-mg niacin, 25-mg vitamin B₆, 250-μg vitamin B₁₂, 25-mg pantothenic acid, 15-mg zinc, 75-μg selenium, 15-mg manganese, 50-mg N-acetyl cysteine, 50-mg l-glutathione, 25-mg green tea, 10-mg coenzyme Q10, 10-mg alpha-lipoic acid, 100-mg garlic, and 10-mg grape seed extract.</td>
<td>2 capsules/d</td>
<td>2005</td>
</tr>
</tbody>
</table>

containing antioxidant ingredients. For the past 3 and 4 years, respectively, NH has been taking a broad-spectrum antioxidant complex and a product containing oligomeric proanthocyanidins (see Table 2). When asked about her asthma symptoms in September 2006, N.H. reported that she has noticed significant improvement in her asthma control. She discontinued her mometasone nasal (Nasonex) and uses her exofenadine (Allegra) rarely. She reported that she has not used her albuterol since June 2006, 18 months after starting to take her first antioxidant supplement. She has been able to regularly take only 1 puff per d of her budesonide inhalation (Pulmicort), which was a treatment goal set by the doctor at her last visit. In October 2006, N.H. was told that her allergy immunotherapy shots were going to be discontinued indefinitely. All medications were prescribed as needed (prn), except 1 puff per day of budesonide inhalation. No pulmonary function test was performed because of her level of control and lack of symptoms. N.H. continued to note significant improvement in her asthma control and as of April 2007, N.H. had achieved her personal goal of discontinuing all medications. This was approximately 3 years following initiation of her antioxidant supplementation.

**DISCUSSION**

An evidence-based approach was taken to explore the relationship between NH’s treatment and the most recent evidence to support it. The Cochrane Database of Systematic Reviews, ClinicalResource®Ovid (included Cochrane, CINAHL, and MEDLINE) and PubMed search engines were used with keywords “antioxidants” and “asthma” and a date range of 2003 to 2007. Inclusion criteria included reviews, systematic reviews, and primary research (epidemiological,
cross-sectional, case control, cohort, or controlled clinical trials) and adults (18- to 75-year-old). Exclusion criteria included children (<18-year-old) and animal studies. All abstracts were reviewed and those that did not have clinical relevance or did not include dietary or supplemental antioxidants were excluded. The literature search started with approximately 100 studies and concluded with 7 studies (6 primary studies and 9 reviews) that were critically appraised. The primary articles were categorized as either being a “diet” or “supplement” study. Summaries of the primary studies35–41 listed in chronological order by category are in the next section, followed by a summary of the 3 reviews.23,42,43

SUPPLEMENTATION STUDIES

Shaheen et al35 conducted a randomized, double-blind, placebo-controlled study on 197 adults with asthma to assess differences in asthma symptoms of those who received selenium supplementation (100 μg/d) from those who did not. After 24 weeks, there were no significant differences in quality of life between those subjects receiving selenium and controls. There were several considerations that may have led to the negative results, including lack of a causal link between selenium and asthma; intake during childhood may have a significant effect on adult asthma; selenium may benefit severe asthma, but not moderate asthma; the study population might have had adequate baseline serum selenium levels; and most participants were using steroid inhalers. Despite the negative results, this study was rated as good.

Fogarty36 conducted a parallel-group randomized, placebo-controlled study to assess the a priori hypothesis that regular supplementation with vitamin C and magnesium permits a reduction in the corticosteroid dose required to maintain asthma control in adults. When looking at corticosteroid reduction, the unadjusted difference between the vitamin C and placebo groups was significant (P = .04), although the adjusted difference was not statistically significant (P = .06). There was no difference in corticosteroid reduction between the magnesium and placebo groups. The authors concluded that oral magnesium supplementation for 26 weeks had no effect on corticosteroid requirements but vitamin C had a modest corticosteroid sparing effect. This study was rated as limited because of its small sample size, relatively short period of time, low statistical power, and various other limitations.

Pearson37 conducted a parallel-group randomized, placebo-controlled trial to investigate the effect of vitamin E on bronchial hyperresponsiveness in adults with asthma. This 6-week study involved 72 participants who were randomized to received 500-mg natural vitamin E or a matched placebo. There was no difference in corticosteroid reduction between the magnesium and placebo groups. The authors concluded that oral magnesium supplementation for 26 weeks had no effect on corticosteroid requirements but vitamin C had a modest corticosteroid sparing effect. This study was rated as limited because of its small sample size, relatively short period of time, low statistical power, and various other limitations.

Fogarty38 conducted a parallel-group randomized, placebo-controlled trial to determine whether the findings of epidemiologic studies that suggest that higher intakes of dietary vitamin C and magnesium may be associated with reduced risk of asthma would apply to the clinical control of asthma. Three hundred adults with medically controlled asthma were randomized to 1 of the 3 groups: supplementation of 1 g/d vitamin C, 450-mg chelated magnesium, or a matched placebo. After 16 weeks, there were no significant differences in any of the outcome markers between the treatment or placebo groups. The negative results might be explained by the subjects being well controlled and having relatively high baseline levels of these nutrients. This study was rated as good because of its research design, sample size, and adherence level.

Fogarty38 conducted a parallel-group randomized, placebo-controlled trial to determine whether the findings of epidemiologic studies that suggest that higher intakes of dietary vitamin C and magnesium may be associated with reduced risk of asthma would apply to the clinical control of asthma. Three hundred adults with medically controlled asthma were randomized to 1 of the 3 groups: supplementation of 1 g/d vitamin C, 450-mg chelated magnesium, or a matched placebo. After 16 weeks, there were no significant differences in any of the outcome markers between the treatment or placebo groups. The negative results might be explained by the subjects being well controlled and having relatively high baseline levels of these nutrients. This study was rated as good because of its research design, sample size, and adherence level.
DIET STUDIES

Ochs and Balcom\(^3\) conducted a cross-sectional study in which antioxidant dietary intake and serum levels were measured in 218 individuals with chronic airflow limitation. Serum and dietary β-cryptoxanthin, lutein/zeaxanthin, and retinol, and dietary β-carotene, vitamin C, and lycopene were positively associated with forced expiratory volume 1 percentage \((P < .05, \text{ all associations})\). Serum vitamins β-cryptoxanthin, lutein/zeaxanthin, and lycopene; dietary β-cryptoxanthin, β-carotene, vitamin C; and lutein/zeaxanthin were positively associated with forced vital capacity percentage \((P < .05, \text{ all associations})\). Erythrocytic glutathione was negatively associated with forced expiratory volume 1 percentage, whereas plasma thiobarbituric acid-reactive substances were negatively associated with forced vital capacity percentage \((P < .05)\). The data infer that a dietary and serum antioxidant/oxidant imbalance is involved in reduced pulmonary function in individuals with chronic airflow limitation. The cross-sectional nature and low participation resulted in a fair rating.

Romeiu et al\(^4\) investigated fruit intake and the incidence of asthma, using 68,535 women cohorts from the Etude Epidémologique auprès des femmes de la MGEN (E3N) study, a prospective investigation of major chronic diseases that was conducted in France. A decreasing trend in asthma prevalence was observed with increasing intake of apples from the first quartile \((Q1)\) to the fourth quartile \((Q4)\) \((\text{odds ratio, } Q1-Q4 = 0.90; \text{ 95\% confidence interval, 0.80–1.02; test for trend } P = .03)\). Leafy vegetable intake was inversely related to asthma prevalence, with a significant decreasing trend when intake was increased. Intake of fruity vegetables, such as carrots and tomatoes, was inversely associated with asthma \((\text{test for trend, } P = .01)\). The results suggest that a higher intake of antioxidants through diet, especially leafy vegetables, carrots, and tomatoes may help prevent and manage adult asthma. This study used a large cohort and was rated good.

Patel et al\(^5\) conducted a nested case-control study to determine whether the apparent association between dietary antioxidants and asthma can be attributed to a “healthy diet” and lifestyle or to the protective effect of specific foods or nutrients. High versus low or no intake of fruits and vegetables showed protective effects of asthma risk; however, only fruit intake was significantly associated with a reduced risk of diagnosed asthma after adjustment \((P = .0003)\). Specifically, citrus fruits were associated with decreased risk of asthma \((P = .008)\). Symptomatic cases showed a trend toward reduced risk of symptomatic asthma with increased fruit consumption \((P = .009)\), but not with vegetables. After adjustment, only the nutrients manganese \((P = .002)\) and vitamin C \((P = .003)\) were significant between symptomatic and asymptomatic cases. The authors concluded that symptomatic asthma in adults is associated with low intake of the dietary antioxidants vitamin C and manganese, with vitamin C found predominantly in fruit. This study was rated as fair because it was an observational study; however, it did match 515 subjects with controls, was part of a large cohort, and was consistent with other studies.

REVIEWS

Kirkham and Rahman\(^6\) reviewed the potential impact of antioxidant supplementation as adjunctive therapy for asthma, based on the premise that reactive oxygen species (ROS) may play a role in the inflammatory response of asthma. The complex mechanisms of oxidative stress may lead to an ineffective response to corticosteroids. Several therapeutic approaches have been tested, including increasing endogenous antioxidant enzyme defenses or by enhancing the nonenzymatic defenses through dietary or pharmacological methods. They divided these therapies into 6 categories for the review: dietary, thiols, spin traps, redox sensors, enzymes, and polyphenols. Further studies are needed to identify new and more efficacious antioxidant therapies and their specific mechanisms.
Mak and Chan-Yeung reviewed studies on the oxidant to antioxidant balance in people with asthma. Although they found conflicting results, the data do support increased ROS and reactive nitrogen species levels in people with asthma. There is an accompanying decrease in plasma antioxidant capacity in people with asthma and glutathione peroxidase activity; however, there is increased activity of superoxide dismutase and erythrocyte catalase. It seems as though endogenous antioxidants both scavenge free radicals, yet at the same time promote ROS and nitric oxide synthase production. Reducing exposure to ROS or increasing endogenous antioxidant levels may reestablish a balance in people with asthma and may play a role in the treatment of asthma.

Misso and Thompson reviewed research looking at oxidative stress, antioxidant deficiencies in asthma, and potential modification by diet. Biomarkers of oxidative stress must be indirectly measured through exhaled breath condensate, except for nitric oxide. Highly reactive oxygen and nitrogen species have been measured in the exhaled air and sputum of adult patients with asthma. Reduced glutathione levels caused by oxidative stress inactivates antioxidant enzymes, leading to increased apoptosis, shedding of airway epithelial cells, and airway remodeling. Studies have found that the oxidant/antioxidant equilibrium is further challenged by low intakes of vitamins C and E, selenium, and flavonoids, although clinical trials have not shown a benefit of antioxidant supplementation. An area of interest may be the genetic variation in glutathione S-transferase and whether this genotype may influence the efficacy of dietary supplementation in asthma. The need for more long-term prospective trials exploring whether modifying dietary intake is beneficial for the prevention or management of asthma are needed.

CONCLUSIONS

On the basis of the extensive review of literature, there is insufficient evidence to support the addition of antioxidant supplementation to the current clinical practice guidelines for asthma management at this time, independently or as an adjunctive therapy. However, there is good evidence to support the promotion of increased dietary fruit and vegetable intake in adults with asthma, as recommended by the MyPyramid Food Guidance System. The Mediterranean diet is another food guidance system that may effectively increase fruit and vegetable intake, as well as other antioxidant compounds, such as omega-3 fatty acids. Although in the studies cited in this article fruit was the only food group that was statistically significantly and inversely associated with asthma, it is feasible that increasing intake of other foods high in antioxidants would be prudent.

Although NH chose to take antioxidants in supplement form, the available evidence supports obtaining these nutrients through whole-food sources rather than commercial supplements. In addition, such diet recommendations are consistent with the general health guidelines of MyPyramid.gov. Because her diet is already relatively balanced and healthy, she should be encouraged to regularly consume a variety of foods high in antioxidants and phytochemicals, such as apples, dried plums (prunes), blueberries, blackberries, strawberries, raisins, kale, raspberries, oranges, plums, red grapes, cherries, bell peppers, beets, Brussels sprouts, corn, spinach, onions, broccoli, eggplant, alfalfa sprouts, tea, red wine, tomato-rich products, chocolate, and fish high in omega-3 fatty acids.

Future research needs to focus on the mechanisms behind the protective effects of antioxidants, the synergistic effect of antioxidants, and other nutrients, whether benefits can be obtained through food or supplementation, and the genetic-environmental link. Large prospective clinical trials would provide a more accurate assessment of the long-term effects and may help identify the ideal amounts/doses under various conditions. A key component of research would be to measure clinical indicators of asthma, including...
the prevalence of asthma as defined by the National Heart, Lung, and Blood Institute and NAEPP and mortality rates.

Asthma is a controllable disease with proper medical care and self-management. Despite that fact, asthma is a disease currently without a cure that impacts morbidity and mortality rates. It is imperative that research continues to explore potential genetic and environmental factors in the onset and management of asthma, including diet and antioxidants.

REFERENCES


