

Asthma Exacerbation Associated with Glucosamine-Chondroitin Supplement

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Background: Although dietary supplements are in widespread use, and some have been endorsed by the medical community and complementary and alternative practitioners, not much is known about their potential side effects or drug interactions.

Methods: A case of asthma exacerbated by the use of a glucosamine-chondroitin supplement for osteoarthritis pain is described. The literature was searched from 1980 to 2002 using the terms "glucosamine," "chondroitin sulfate," "alternative medicine," and "dietary supplements," combined with "asthma."

Results and Conclusions: The biological link between both chondroitin and glucosamine and secretions from the respiratory tree of persons with asthma lends biologic plausibility to the hypothesis that the patient's asthmatic episode was related to the dietary substance. Physicians would be wise to question their patients about use of dietary supplements as self-medication and consider the possibility of such supplements causing exacerbations of underlying conditions. (*J Am Board Fam Pract* 2002;15:481-4.)

The use of over-the-counter dietary supplements is widespread in our society. Patients spend an estimated \$15 billion per year on these products, which are not regulated by the Food and Drug Administration.¹ Many of these supplements have found support for their use in the medical community or among parallel complementary-alternative medicine practitioners. Little is known, however, about potential side effects, untoward effects, or drug interactions of many of these substances, even those in widespread use.²

Arthritis, particularly degenerative osteoarthritis, which is more common in older persons, is a condition afflicting an increasing number of the US population.³ Although a broad range of traditional pharmaceuticals exist for the treatment of pain associated with this condition, many patients avail themselves of nonprescription supplements for pain relief. Glucosamine-chondroitin sulfate preparations are particularly popular, though there is

mixed evidence of efficacy.⁴⁻⁷ Available in various forms in many pharmacies, supermarkets, and health food stores, this drug combination is often recommended as an adjunct to traditional prescription pharmaceuticals and nonpharmacologic treatments.⁸ In this case report, we describe a probable side effect of this drug combination in a patient with underlying intermittent asthma.

Methods

A case is described in which a patient had exacerbation of her well-controlled asthma after starting to take a glucosamine-chondroitin sulfate compound to treat her pain caused by osteoarthritis. A MEDLINE literature search was undertaken using the key words "glucosamine," "chondroitin sulfate," "alternative medicine," and "dietary supplements," combined with "asthma."

Case Report

A 52-year-old woman with long-standing intermittent asthma came to the office complaining of exacerbation of her underlying asthma. This exacerbation was manifested by difficulty walking, climbing steps, and singing, all because of shortness of breath. She also began to wheeze more frequently and on a daily basis. Her usual rescue dose

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of inhaled albuterol for exacerbations, two puffs two to three times per day, was not sufficient to extinguish or diminish symptoms. Her health was otherwise unchanged, and she reported no history of exposure to any of her typical asthma triggers, either environmental or infectious. Specifically, she had no current or recent upper respiratory tract infection, recent exposure to allergens, cigarette smoke, or air pollution, or recent change in her work or home environment.

Aside from osteoarthritis of her knees and hips, mild stage 1 essential hypertension, and obesity, she was in reasonably stable health. The patient's asthma of 10 years' duration was manifested by periodic attacks of wheezing and shortness of breath usually after an upper respiratory tract infection or after singing, which she does often. Her main hobby was singing semiprofessionally in a local church-affiliated chorus. She had no history of smoking, and there was no history of allergies to medication. Her family history was notable for atopy and seasonal allergies. Her usual medications included inhaler-delivered albuterol, which she took as needed, but no more than once or twice per week, usually before singing, hydrochlorothiazide 25 mg daily, and over-the-counter ibuprofen 400 to 600 mg daily intermittently for pain relief. She worked in an office at a local university. There were no known environmental exposures either at work or at home.

When examined, she was a well-developed, obese woman in moderate respiratory discomfort caused by exertion. Her pulse was 90 beats per minute, respirations at rest were 20/min, increasing to 30/min with movement, blood pressure was 140/85 mmHg, and she was afebrile at 98.4°F. Her weight was 237 pounds, her height 5 feet 7 inches, and her body mass index 37. When examined, her head, ears, eyes, nose, and throat were unremarkable. Her chest had normal excursion with good air movement in all lung fields. There were diffusely scattered end-expiratory wheezes that did not clear with cough. Heart sounds were normal, as were findings of abdominal, skin, and neurological examinations. She had decreased range of motion in both hips with internal and external rotation and patellar crepitation of both knees. Compared with previous examinations, her pain with passive range of motion of both knee joints was diminished. Her peak expiratory flow rate was 350 mL/sec, representing a decrease from her normal personal best of

450 mL/sec to 500 mL/sec. Pulse oxygenation was 95%, also a decrement from her usual 98%.

During the course of the next 3 weeks, the patient's condition waxed and waned despite increased dosages of her albuterol inhaler and a course of tapering oral steroids begun early in the exacerbation. At a visit 3 weeks later, symptoms continued undiminished, and findings of her physical examination were unchanged. Her history was reviewed in detail, and the patient mentioned that her symptoms started after she began taking a glucosamine-chondroitin sulfate preparation three times per day for her arthritis. This preparation contained 500 mg of glucosamine and 400 mg of chondroitin sulfate.

Although we were not aware of any reports of drug side effects in asthma with these supplements, we followed the patient's suggestion and advised her to discontinue the preparation. Within 24 hours, the patient's asthma symptoms completely extinguished and did not return until 2 months later secondary to the infectious trigger of an upper respiratory tract virus. This exacerbation was brief and easily controlled with minimal increases of her albuterol. Subsequent use of nonsteroidal anti-inflammatory medications did not exacerbate her asthma symptoms. The patient has been unwilling to undergo a medication challenge with additional glucosamine-chondroitin preparation. Three months later in a subsequent office visit, the patient recalled that as a graduate student she had experienced an episode of wheezing during a biology laboratory session that included shark dissection. Chondroitin sulfate is a constituent of shark cartilage.

Literature Search

A MEDLINE electronic literature search was performed using the MeSH terms "glucosamine," "chondroitin sulfate," "alternative medicine," and "dietary supplements," which were combined with the term "asthma" for articles published from 1980 through 2002. Six articles were found using the terms "glucosamine" and "asthma," and five were found using the terms "chondroitin" and "asthma." Thirteen articles were found using "dietary supplements" and "asthma," and 72 were found combining "alternative medicine" and "asthma." A total of 117 articles on glucosamine therapy alone and 110 on chondroitin therapy alone were also found. A

review of all these articles found no case reports of asthma or asthma exacerbation with either of these dietary supplements alone or combined. It did find, however, a possible biochemical linkage between both substances and the respiratory tree of asthmatic patients, as described below.

Antibodies to chondroitin sulfate are found in higher concentrations in the airways of persons with asthma than in those without, even in the face of steroid administration.⁹ In a study by Huang and colleagues,¹⁰ deposition of chondroitin sulfate proteoglycan in the airways was increased significantly in asthmatic patients when compared with control subjects. Furthermore, the degree of proteoglycan immunoreactivity was significantly correlated with airway responsiveness in persons with asthma, suggesting proteoglycans such as chondroitin might play a role in airway wall remodeling and mechanics in asthma.

Glucosamine-containing antigen preparations have been found to be allergenic in asthmatic patients who have sea squirt allergy.¹¹ Whether glucosamine itself is responsible for the allergic response is unknown, but the possibility is plausible. These studies collectively provide a biochemical link to a possible immune response in asthmatic patients. Elucidation of the immunology of asthma is rapidly advancing.¹²

Discussion

In clinical epidemiology, Koch's postulates require satisfaction of several conditions before causality can be attributed. The specific agent should be found in all persons suffering from a specific disease but should not be found in healthy persons. The specific agent should be isolated from the afflicted person and should cause disease in an otherwise healthy person. The specific agent should be able to be reisolated in pure form from experimentally afflicted person. No other plausible explanations should exist for the observations.

Although we cannot say definitively that the dietary supplement was the cause of this patient's asthma exacerbation, several factors lead to the belief that such a conclusion is reasonable. The timing of the patient's onset of symptoms with the onset of supplement use, the persistence of symptoms while taking the supplement despite the administration of usually effective asthma treatment, and the symptom cessation with the cessation of the

supplement strongly suggest a link between the glucosamine-chondroitin sulfate preparation and the patient's asthma exacerbation. Furthermore, a biological link between both chondroitin and glucosamine and secretions from the respiratory tree of persons with asthma lends biologic plausibility to the hypothesis that the patient's asthmatic episode was related to the dietary substance.

Asthma exacerbations have been linked to infectious agents, environmental allergens and air pollution, certain medications, exercise, food additives such as sulfites and tartrazine, and emotional distress. Among prescription and over-the-counter drugs known as potential triggers are aspirin and other nonsteroidal anti-inflammatory agents, and β -adrenergic antagonists (β -blockers). Unfortunately, no registry exists for reporting possible adverse effects of over-the-counter products, including dietary supplements such as the product in this report. Physicians must therefore rely on case reports for information about the clinical effects of increasing numbers of unregulated dietary substances in use by consumers.

Conclusion

This report raises the possibility of a link between asthma exacerbation and a popular dietary substance. Glucosamine-chondroitin sulfate preparations are dietary supplements widely used by patients who have degenerative arthritis. The potential side effects of this medication are unknown. Asthma is a widespread condition affecting many, including persons with arthritis. Glucosamine and chondroitin have been linked to atopy and the respiratory tract secretions of asthmatic patients. Physicians would be wise to question their patients about use of dietary supplements as self-medication and consider the possibility of such supplements causing exacerbations of underlying conditions.

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