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Do shrimp-allergic individuals tolerate shrimp-derived glucosamine?

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Summary

Background There is concern that shrimp-allergic individuals may react to glucosamine-containing products as shrimp shells are a major source of glucosamine used for human consumption.

Objective The purpose of this study was to determine whether shrimp-allergic individuals can tolerate therapeutic doses of glucosamine.

Methods Subjects with a history of shrimp allergy were recruited and tested for both shrimp reactivity via a prick skin test and shrimp-specific IgE by an ImmunoCAP assay. Fifteen subjects with positive skin tests to shrimp and an ImmunoCAP class level of two or greater were selected for a double-blind placebo-controlled food challenge (DBPCFC) using glucosamine-chondroitin tablets containing 1500 mg of synthetically produced (control) or shrimp-derived glucosamine. Immediate reactions, including changes in peak flow and blood pressure, and delayed reactions (up to 24 h post-challenge) via questionnaire were noted and assessed.

Results All subjects tolerated 1500 mg of both shrimp-derived or synthetic glucosamine without incident of an immediate hypersensitivity response. Peak flows and blood pressures remained constant, and no subject had symptoms of a delayed reaction 24 h later.

Conclusion This study demonstrates that glucosamine supplements from specific manufacturers do not contain clinically relevant levels of shrimp allergen and therefore appear to pose no threat to shrimp-allergic individuals.

Keywords crustacean, glucosamine, IgE, shrimp allergy, supplement, tropomyosin

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Introduction

Glucosamine, a natural aminomonosaccharide found in human cartilage and other types of collagenous tissue, is becoming increasingly ubiquitous as a dietary supplement for joint health owing to its chondroprotective effects; yearly sales reached over 40 million units (standardized to 100 count bottles) in the United States in 2004 (Information Resources Inc., Chicago, IL, USA). In Europe and other countries around the world, glucosamine is a prescription drug with 1A classification for treatment of moderate

osteoarthritis of the knee [1]. Therapeutic administration of 25 mg/kg (about 1500 mg daily) has been found reproducibly to reduce symptoms of pain and stiffness while improving indicators of joint function for up to three years [1–5]. The supplement's widespread use is not without controversy, however. Although the supplement is becoming increasingly accepted as a safe and effective treatment for osteoarthritis, some have questioned both the safety and efficacy of the supplement [6–9].

A particular safety concern lies in glucosamine's potential allergenicity for a significant percentage of the United States population. One study has found glucosamine to exacerbate respiratory tree secretions in asthmatics, while another has reported an immediate-hypersensitivity reaction to the supplement in an average individual without a specific history of allergy [9, 10]. Glucosamine itself is too small a molecule to elicit an immune response, but its common industrial derivation from the shells of crustacea

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presents the possibility of its contamination by crustacean allergens from underlying fleshy tissue, including invertebrate tropomyosin, the highly allergenic 36 kDa muscle protein that accounts for 80% of shrimp allergenicity [11, 16]. Because tropomyosin is highly conserved among invertebrates and as such exhibits a high degree of cross-reactivity among crustacea and insects including crabs, lobster, crawfish, dust mites, and cockroaches, there is a significant number of potentially glucosamine-allergic individuals [17–21]. To ensure these individuals' safety, glucosamine products carry a warning label for shrimp and seafood-allergic individuals, which ultimately denies them of glucosamine's reported antireactive, antiarthritic effects.

Considering that one study estimates crustacea allergy to afflict as much as 2% of the United States population, the question of glucosamine products' allergenicity in crustacea-allergic individuals is of great interest [22]. A 2004 letter to the editor of the *Journal of Allergy and Clinical Immunology* posed the question of glucosamine product allergenicity in the shellfish-allergic individual and provided a pilot study that seemed to repudiate the allergenicity claims [23]. This paper intends to improve upon the methods performed in this letter's study by evaluating the effect of therapeutic doses (1500 mg) of glucosamine products upon shrimp-allergic individuals.

Methods

Subjects

Approval from the Tulane University School of Medicine and the Medical Center of Louisiana School of Medicine at New Orleans (MCLNO) Institutional Review Boards as well as the Tulane-LSU General Clinical Research Center (GCRC) Advisory Committee were obtained. A variety of methods were used to recruit shrimp-allergic patients. They included newspaper ads, letters to local allergists, and fliers posted locally in the greater New Orleans region.

Responding patients were screened initially with a preliminary questionnaire. Those with a history typical for immediate hypersensitivity to shrimp were contacted, informed consent was obtained, and a detailed interview and physical exam were performed at the GCRC. Subjects reporting a history of anaphylactic shock were excluded from the study. Those with a history consistent with immediate hypersensitivity after ingestion of shrimp were skin tested using allergen extracts from both commercial and laboratory sources. Patients were skin prick tested (SPT) with a QuinTest device (Hollister Stier, Spokane, WA, USA) to histamine (10 mg/mL) and saline controls, as well as commercial shrimp, crab, crawfish, and lobster extracts (1 : 10 w/v). Skin test results were quantified as a mean of measuring the largest weal diameter and the corresponding perpendicular diameter. In addition, serology was obtained to detect shrimp-specific IgE via

the ImmunoCAP assay (Quest, Lyndhurst, NJ, USA). Results were expressed as Class 1–6.

Oral challenge

Individuals with immediate hypersensitivity histories, positive skin tests to shellfish extracts, and an ImmunoCAP Class level of 2 or greater were asked to return for a DBPCFC with a pair of tablets containing 1500 mg of glucosamine hydrochloride and 1200 mg chondroitin sulfphate (provided by Weider Nutrition Group, Salt Lake City, USA). One pair of tablets contained shrimp-derived glucosamine, and a second (control) contained synthetic glucosamine fermented by fungi from corn (Cargill Acidulants Regenasue[®], Eddyville, IA, USA); tablets were administered to each patient in random order 1 h apart. All patients had IV access and were monitored closely for vital signs and peak flows every 15 min. Patients were kept under observation for 1 h after the last tablet was consumed. They were then given a questionnaire that was to be completed 24 h later to assess delayed symptoms.

Results

A total of 15 subjects were recruited to participate in the oral glucosamine challenge (Table 1). Eleven were male and four were female. All were over the age of 18, and the oldest was 49 years of age. By history, all had typical symptoms of an IgE-mediated reaction (urticaria, pruritus, wheezing, and/or angioedema to shrimp) shortly after the consumption of shrimp. The primary subject complaint was pruritus and urticaria (hives) (Table 1).

All subjects reacted to shrimp upon prick skin testing (Table 2). Additionally, all subjects reacted to more than one shellfish, probably due to the large degree of crustacean cross-reactivity. Results are expressed in millimetres of weal diameter when a reaction was present. In the oral challenge, all subjects tolerated 1500 mg of shell-derived glucosamine without incident of an immediate hypersensitivity response. Peak flows and blood pressure remained consistent in all subjects during challenge; there was no objective or subjective evidence of any systemic symptoms to the glucosamine. None of the individuals responded with symptoms of a delayed reaction within the 24 h following the challenge.

Discussion

Based on estimates of crustacean allergy prevalence, the chondroprotective supplement potentially dangerous to at least 2% of the United States population. This number may be larger, considering it estimates only those with crustacean allergies; including allergies to other arthropods such as dust mites and cockroaches could increase the potential affected population. Determining the safety of glucosamine

Table 1. Age, gender and shrimp allergy: history of the study population

Subject	Age, gender	Immediate symptoms (by history to shrimp)
1	36, F	Shortness of breath, wheezing, syncope, 'throat closed'
2	49, M	'Throat itch', angioedema, Shortness of breath, pruritus to face
3	20, M	'Swollen throat', wheezing, pruritus, hives, angioedema, Shortness of breath, wheezing
4	19, M	Angioedema, pruritus, nausea, vomiting, hives, Shortness of breath, wheezing, fatigued
5	18, F	'Tightening throat', Shortness of breath, swelling, wheezing
6	21, M	'Tightening throat', lip swollen (angioedema), pruritus, hives
7	28, M	Lip swollen (angioedema), pruritus, hives, nausea, vomiting
8	20, M	Angioedema, Shortness of breath, 'itchy mouth', pruritus, hives
9	21, M	Hives, 'throat closed', Shortness of breath, pruritus, hives, wheezing
10	20, M	'Throat swollen', lip edema (angioedema), pruritus, Shortness of breath, cough, wheezing
11	25, M	Throat swollen, eyes swelling (angioedema), pruritus, hives, Shortness of breath
12	21, M	Tongue, throat, lip swelling (angioedema), pruritus, hives, swelling, Shortness of breath
13	36, F	Shortness of breath, pruritus, hives, wheezing
14	48, F	Eyes swelling (angioedema), wheezing, pruritus, Shortness of breath, 'stomach cramps'
15	19, M	Angioedema, pruritus, wheezing

consumption in allergic individuals will make available glucosamine's chondroprotective benefits to any of these 600 000+ individuals who may require such treatment.

Although, the subjects tested reported significant histories of shrimp allergy manifested by pruritus, urticaria, angioedema, dyspnea, nausea, vomiting, or diarrhoea, all the shellfish-allergic individuals challenged with shrimp-derived glucosamine tolerated the tablets without evidence of an immediate systemic reaction. All subjects maintained constant peak flow and blood pressure measurements. None of the subjects reported symptoms consistent with hypersensitivity 1 day after the glucosamine supplement oral challenge as self-reported by their mail-in questionnaire.

Because glucosamine is additionally used as a filler in many other medications, its allergenic safety determined by

this study additionally allows the benefits of these various medications available to these crustacean-allergic individuals. Those wary of glucosamine products' allergenic risk as printed on the sides of many product containers should feel more comfortable in taking these products. While additional testing with larger sample numbers should be executed to determine with more precision the safety of these products, especially from other original sources, this investigation demonstrates that low-protein-concentration (less than 0.1%) glucosamine products pose no threat to shrimp-allergic individuals.

A possible explanation for the absence of contaminating allergen in these supplements lies in the method of their extraction from crustacean shells. The extraction involves several hydrolysis and washing steps, which

Table 2. Shrimp IgE immunoCAP, skin test results and glucosamine challenge reactions in subjects with a history of shrimp allergy

Subject	IgE ImmunoCAP Class	Shrimp	Crab	Lobster	Crawfish	Histamine	Saline	Immediate Glucosamine challenge Reaction	Delayed Glucosamine challenge Reaction
1	2	4.3*	1.0	3.1	3.2	4.2	Neg.	Neg.	Neg.
2	5	8.0	Neg.	8.5	Neg.	6.2	Neg.	Neg.	Neg.
3	4	4.8	3.8	7.9	7.1	6.0	Neg.	Neg.	Neg.
4	4	7.5	6.2	10.1	10.0	7.1	Neg.	Neg.	Neg.
5	3	9.3	9.8	8.3	6.5	7.8	Neg.	Neg.	Neg.
6	5	4.6	5.8	4.8	4.0	5.8	Neg.	Neg.	Neg.
7	2	7.8	6.0	5.4	Neg.	8.4	Neg.	Neg.	Neg.
8	2	11.3	2.2	8.3	9.5	6.2	Neg.	Neg.	Neg.
9	3	8.1	10.0	19.8	7.5	7.2	Neg.	Neg.	Neg.
10	4	4.0	6.8	6.8	3.5	4.3	Neg.	Neg.	Neg.
11	4	13.3	Neg.	8.0	7.8	7.1	Neg.	Neg.	Neg.
12	6	10.6	8.6	13.0	10.0	5.3	Neg.	Neg.	Neg.
13	2	4.7	3.8	3.5	3.6	4.9	Neg.	Neg.	Neg.
14	2	11.5	12.5	13.6	Neg.	7.3	Neg.	Neg.	Neg.
15	3	6.4	6.8	4.0	3.6	4.8	Neg.	Neg.	Neg.

*Skin reaction as mean weal diameter in millimeter.

Neg. negative.

presumably alter or destroy all allergens present in the sample, including tropomyosin. Thus, there should not be any detectable allergenic material such as tropomyosin (e.g. Pen a 1) or other allergens in shrimp shell-derived glucosamine supplements extracted under pressure, and our results corroborate this hypothesis. Our results further agree with the manufacturer (Weider Nutrition Group), which has shown that the protein content in these tablets is virtually undetectable (< 0.1%) due to the extraction process. This further suggests the supplements used in this study do not contain clinically relevant levels of shrimp allergen.

This claim stands only for the extraction process performed by the specific manufacturer of supplements used in this study. Less diligent derivation of crustacean glucosamine could result in products contaminated with allergenic protein; thus safety claims are only for glucosamine products derived through a process similar to the specific tablets used within this study.

Recently a letter published in the *Journal of Allergy and Clinical Immunology* questioned glucosamine product's safety in seafood-allergic individuals [22]. This letter concluded in a similar fashion as our study but fails to address two important aspects of the product's allergenicity. As aforementioned, the glucosamine dose required to safely maximize its chondroprotective effects is up to 1500 mg daily [1–5]. Thus 1500 mg is commonly accepted as the typical therapeutic dose. The published letter's study failed to test this accepted therapeutic dosage; it used 500 mg, or one-third of the therapeutic dosage, which does not accurately test glucosamine product's potential for allergenicity at a clinically-relevant dosage. Furthermore, while its small sample size of six subjects does yield some insight into the issue at hand, increasing this number certainly leads to a more effective conclusion on glucosamine's safety. Our study therefore confirms the tolerance described in this letter in shrimp-allergic individuals challenged with a typical therapeutic dose of one specific brand (Schiff®) of shrimp-shell-derived glucosamine.

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References

- Jordan KM, Arden NK Standing Committee for International Clinical Studies Including Therapeutic Trials ESCISIT *et al.* EULAR Recommendations 2003: an evidence based approach to

- the management of knee osteoarthritis: Report of a Task Force of the Standing Committee for International Clinical Studies Including Therapeutic Trials (ESCISIT). *Ann Rheum Dis* 2003; 62:1145–55.
- McAlindon TF, La Valley MP, Felson DT. *et al.* Glucosamine and chondroitin for the treatment of osteoarthritis: a systemic quality assessment and meta-analysis. *JAMA* 2000; 283:1469–75.
- Anderson JW, Nicolosi RJ, Borzelleca JF. Glucosamine effects in humans: a review of effects on glucose metabolism, side effects, safety considerations and efficacy. *Food Chem Toxicol* 2005; 43:187–201.
- Richy F, Bruyere O, Ethgen O, Cucherat M, Henrotin Y, Reginster JY. Structural and symptomatic efficacy of glucosamine and chondroitin in knee osteoarthritis: a comprehensive meta-analysis. *Arch Intern Med* 2003; 163:1514–22.
- Towheed T, Maxwell L, Anastassiades T *et al.* Glucosamine therapy for treating osteoarthritis. *Cochrane Database Syst Rev* 2005, CD02946.
- Hooper M. Is glucosamine an effective treatment for osteoarthritic pain? *Cleve Clin J Med* 2001; 68:494–5.
- Phoon S, Manolios N. Glucosamine. A nutraceutical in osteoarthritis. *Aust Fam Physician* 2002; 31:539–41.
- Danao-Camara T. Potential side effects of treatment with glucosamine and chondroitin. *Arthritis Rheum* 2000; 43:2853.
- Tallia A, Cardone D. Asthma exacerbation associated with glucosamine–chondroitin supplement. *J Am Board Fam Pract* 2002; 15:481–4.
- Matheu V, Gracia Bara MT, Pelta R, Vivas E, Rubio M. Immediate-hypersensitivity reaction to glucosamine sulfate. *Allergy* 1999; 54:643.
- Leung PS, Chow WK, Duffey S, Kwan HS, Gershwin ME, Chu KH. IgE reactivity against a cross-reactive allergen in crustacea and mollusca: evidence for tropomyosin as the common allergen. *J Allergy Clin Immunol* 1999; 98:954–61.
- Leung PS, Chu KH. Molecular and immunological characterization of shellfish allergens. *Front Biosci* 1998; 3:d306–12 (Review).
- Ayuso R, Lehrer SB, Reese G. Identification of continuous, allergenic regions of the major shrimp allergen Pen a 1 (tropomyosin). *Int Arch Allergy Immunol* 2002; 127:27–37.
- Leung PS, Chu KH, Chow WK *et al.* Cloning, expression, and primary structure of *Metapenaeus ensis* tropomyosin, the major heat-stable shrimp allergen. *J Allergy Clin Immunol* 1994; 94:882–90.
- Shanti KN, Martin BM, Nagpal S, Metcalfe DD, Rao PV. Identification of tropomyosin as the major shrimp allergen and characterization of its IgE-binding epitopes. *J Immunol* 1993; 151:5354–63.
- Dahl CB, Slattery M, Reese G, Lehrer SB. Identification of the major brown shrimp (*Penaeus aztecus*) allergen as the muscle protein tropomyosin. *Int Arch Allergy Immunol* 1994; 105:49–55.
- Reese G, Ayuso R, Lehrer SB. Tropomyosin: an invertebrate pan-allergen. *Int Arch Allergy Immunol* 1999; 119:247–58 (Review).
- Borrego T, Cuevas M, Garcia T. Cross Reactivity between fish and shellfish. *Allergol Immunopathol* 2003; 3:146–51.
- Goetz DW, Whisman BA. Occupational asthma in a seafood restaurant worker: cross-reactivity of shrimp and scallops. *Ann Allergy Asthma Immunol* 2000; 85:461–6.
- Ayuso R, Reese G, Leong-Kee S, Plante M, Lehrer SB. Molecular basis of arthropod cross-reactivity: IGE-binding cross-reactive

- epitopes of shrimp, house dust mite and cockroach tropomyosins. *Int Arch Allergy Immunol* 2002; 129:38–48.
- 21 Santos AB, Chapman MD, Aalberse RC *et al.* Cockroach allergens and asthma in Brazil: identification of tropomyosin as a major allergen with potential cross-reactivity with mite and shrimp allergens. *J Allergy Clin Immunol* 1999; 104:329–37.
- 22 Sicherer SH, Munoz-Furlong A, Sampson HA. Prevalence of seafood allergy in the United States determined by a random telephone survey. *J Allergy Clin Immunol* 2004; 114: 159–65.
- 23 Gray HC. Is glucosamine safe in patients with seafood allergy? *J Allergy Clin Immunol* 2004; 114:459–6.