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# Shrimp allergy: beyond avoidance diet

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*shrimp; allergy; food; hypersensitivity; immunotherapy; vaccine; tropomyosin*

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**List of abbreviations/acronyms**

House dust mites (HDM)  
Specific Immunoglobulin E (sIgE)  
Allergen-specific immunotherapy (ASIT)  
Sublingual immunotherapy (SLIT)  
Chinese herbal formulations (CHF)

**Introduction**

Popularly, “shellfish” and “seafood” are often used interchangeably, but they mean different things. “Seafood” is a general term that refers to any edible aquatic animals, whereas “shellfish” refers to invertebrate aquatic animals usually fitted with a rigid exoskeleton (crustaceans and mollusks), edible, and likely to be traded for human consumption (1). Crustaceans are classified among arthropods together with arachnids and insects, whereas mollusks include bivalves, gastropods and cephalopods (2). In

**Summary**

*Currently, the management of people diagnosed with shellfish allergy relies on the avoidance of those foods. HDM immunotherapy has been reported to induce both shrimp allergy in non-allergic patients, and shrimp tolerance in shrimp-allergic patients. This article summarizes therapeutic options other than avoidance diet for shrimp allergic patients available once the diagnostic is established, such as production of hypoallergenic shrimp, use of immunotherapy with modified allergens, probiotics and Chinese herbal formulations.*

the last years, shellfish consumption has increased in popularity and frequency worldwide. This growing demand for shellfish, with an increment of their extraction and cultivation, has been accompanied by increasing reports of adverse reactions, many of which of immune mechanism, produced by ingestion or manipulation, affecting both consumers and seafood workers (3-5). Shellfish is one of the leading causes of food allergy, with a prevalence of 2.8-8% among all food allergies (6,7), and it is a common cause of food-induced anaphylaxis (8,9). Cases of shrimp allergy-induced exercise and NSAID-dependent anaphylaxis are described (10,11). Shellfish allergy is much less frequent in children than in adults (12). Anaphylactic reactions are more frequent in young people, atopic individuals and asthmatics (13). The crustaceans (shrimp, lobster and crab) are the main cause of shellfish allergy. Usually, subjects with shrimp hypersensitivity react clinically to other types of crustaceans. Shrimp is the most studied crustacean from an allergenic point of view.

### Allergens

There are no differences between the protein bands from the extracts of boiled shrimp water and boiled shrimp (14). However, there are differences between extracts from cooked and raw shrimp (15).

Tropomyosin (Pen a 1), a protein from muscle, has been the first shrimp allergen detected (16). It is a major allergen of 38-41 kDa, and it is responsible for cross-reactivity between members of the shellfish family, particularly among the crustaceans. This led to its definition as an invertebrate panallergen (17). Tropomyosin has also been defined as a major allergen in other crustaceans (18), with very high homologies, up to 98%, among crustacean species including crawfish, crab and lobster (19,20). Tropomyosin is a panallergen responsible for the cross-reactivity between the members of the Arthropoda class, including shrimp (Pen a 1) and house dust mites (HDM) (Der p 10, Der f 10). The prevalence of shrimp allergy is higher in regions with high prevalence of HDM allergy, such as Canary Islands (21). In fact, almost all patients sensitized to shrimp showed positive skin prick test to HDM with/without clinical relevance, and 20-29% of HDM allergic patients showed sensitization to Der p 10 (22), tropomyosin from the HDM *Dermatophagoides pteronyssinus*. Frequently, HDM allergic patients are sensitized to shellfish with food tolerance. It is thought that inhaled tropomyosins from HDM are the primary sensitizer for shellfish allergy in warm and humid tropical climates (23).

There is also an important cross-reactivity with HDM Der p 10 and tropomyosin Pen a 1. There is not cross-reactivity between tropomyosins from filogenetically distant species. Therefore, tropomyosin from vertebrates is not allergenic.

Other minor allergens have been identified and characterized in shrimp. Arginine kinase is a 40 kDa allergen (Pen m 2) from muscle identified in shrimp (24,25) but also in mollusks (26). It was recognized in 27% out of a group of shrimp allergic subjects (25). In 2008, Ayuso et al. identified in Pacific white shrimp (*Litopenaeus vannamei*), a myosin light chain (Lit v 3) with high similarity to Bla g 8, a cockroach myosin light chain (27). Immunoblotting demonstrated immunoglobulin E (IgE) binding to a 20-kDa shrimp protein in 21 (55%) out of 38 sera of shrimp allergic subjects. One year later, the same group of investigators identified a sarcoplasmic-binding protein (Lit v 4) in *Litopenaeus vannamei* (28). Lit v 4 presents structural homology with Pen a 4 of *Penaeus aztecus* (29). Immunoblotting demonstrated IgE binding to a 20 kDa shrimp protein in 31 out of 52 (59.6%) sera of the shrimp allergic individuals. In addition,  $\alpha$ -actinin,  $\beta$ -actinin, fructose biphosphate aldolase, and ubiquitin have been identified as allergens in the *Solenocera melantho* (red shrimp) species (30), and other authors have identified the hemocyanin C subunit as an allergen in our shrimp-allergic patients (31). Hemocyanin is a hemolymph allergen with sequence homol-

ogy of 62.5 - 100% with several crustacea hemocyanins (32). Paramyosin, an invertebrate-specific myofibrillar protein, is a thermo-labile 100 kDa allergen recently identified as an allergen in various shellfish (33). An amino acid sequence homology as high as 70% was recognized between disc abalone *Haliotis discus discus* and Mediterranean mussel paramyosins.

Currently, the role of the allergens different to tropomyosin in shrimp allergy has not yet been well defined. Asero et al. showed that Italian adult shrimp-allergic individuals react to a wide variety of allergens, that tropomyosin is the relevant allergen only in a minority of patients, and that a large proportion of subjects react to not-identified to date high molecular weight allergen proteins (34).

### Current treatment for shrimp allergy

This section will not review the treatment of an acute allergic reaction, but the two currently existing etiological therapeutic approaches: desensitization and avoidance.

#### Desensitization

The natural course of shrimp allergy is to persist over time. Disappearance of reactivity to shrimp is rare. It is firmly established that Allergen Specific Immunotherapy (ASIT) is the only etiological treatment that can alter the natural course of allergic diseases, such as allergic rhino-conjunctivitis and asthma (35,36). The beneficial or harmful effect of HDM ASIT in shrimp allergy is still controversial. Usually, commercial HDM extracts used for SCIT contain quantified levels of group 1 and 2 allergens, but may also include low concentrations of other sensitizing allergens, such as tropomyosin (37). Pevec et al. studied 56 HDM-allergic patients treated with SCIT using HDM extract during 3 - 5.5 years. Specific gE (sIgE) to tropomyosin were found only in 5 patients, without clinical importance. Authors concluded that ASIT using HDM extracts does not induce clinically relevant sensitization to tropomyosin. Van Ree et al. studied 17 sera of HDM allergic patients receiving HDM immunotherapy (38). Serum samples were taken at the start of immunotherapy and 14-20 months later. At the beginning of immunotherapy, specific IgE for shrimp were positive in 3/17 subjects. After 14 to 20 months of immunotherapy, IgE responses for Der p 1 and Der p 2 were not increased. The 3 patients with initial positive specific IgE to shrimp were the only patients who had clinical symptoms after eating shrimps. So, it seems that immunotherapy for HDM does not increase the risk of reaction after ingestion of shrimp in previously non-sensitized patients. In a study with HDM allergic individuals non-sensitized to tropomyosin, Asero et al. observed that injection SIT with HDM extracts did not seem to induce de novo tropomyosin sensitization in mite-allergic patients after three years of ASIT

(39). Pajno et al. observed worsening of snail allergic reactions after several months of ASIT in children with previous combined mite-snail allergy (40).

Therefore, HDM immunotherapy has been reported to induce either shrimp allergy in non-allergic patients, shrimp tolerance in shrimp-allergic patients or no effect on shrimp sensitization. The contradictory results observed could be due to the different qualities of the HDM extracts used for immunotherapy, especially their content of minor allergens such as Der p 10. Possibly, ASIT with an extract containing quantified tropomyosin could induce desensitization in shellfish and HDM allergic patients. Actually, Cortellini et al. published a case report of a 15-year-old male diagnosed as having shrimp allergy and HDM allergy, who tolerated ingestion of shrimps after 12 months of sublingual immunotherapy (SLIT) for HDM (41). Authors hypothesized that the improvement in respiratory symptoms for HDM and in the food challenge for shrimps during mite immunotherapy with a known and high dosage of tropomyosin, may be dose dependent.

#### *Avoidance measures*

Food intake avoidance is the basic measure in managing food allergies. Generally, patients with food allergy to shrimp do not experience respiratory symptoms on inhalation of steam from cooking shrimp. But in some hypersensitive patients, airborne exposure might cause severe respiratory symptoms (15). Food avoidance seems theoretically easier than aeroallergens avoidance. Because of cross-reactivity, avoidance of all crustaceans is generally advised. Shrimp allergic patients are usually healthy, unless they suffer an acute episode by accidental ingestion of shellfish. So, these patients have no awareness of the disease and of the consequences of this problem. Therefore, educational programs are a keystone of the management of food allergy. The patient and her/his family should receive full information about the disease, its consequences, the recognition of the symptoms of an allergic reaction, and training about self-administration of drugs such as epinephrine. Re-education about diet intake of the patients and their families is also important. Patients should be alerted to possible hidden allergen exposure, particularly in restaurants where cooking equipment or serving utensils may be used for different foods. In addition, in many cases, the assessment by a specialist in nutrition would be adequate.

### **Future therapies for shrimp allergy**

#### *Production of hypoallergenic shrimp*

Hypoallergenic foods are those in which the allergenic capacity has been reduced by altering the structure of allergenic epitopes, reducing the risk of reaction when consumed by allergic pa-

tients. You can obtain hypoallergenic foods by physical, chemical and genetic modification procedures (42).

#### *Physical treatments*

Usui et al. investigated the effects of tropomyosin concentrations from cooked or raw shrimp (43). The risk of shrimp allergic reaction was not reduced significantly by different methods of preparing cooked shrimp.

#### *Chemical procedures: enzymatic hydrolysis*

Through enzymatic hydrolysis of shrimp, hypoallergenic products could be obtained which, while retaining some residual allergenicity, are tolerated by most shrimp allergic patients. Wang used proteases such as trypsin, papain and bromelain individually, to hydrolyze South American shrimp proteins (44). The results showed that hydrolysates from South American shrimp proteins digested by each of the three proteases, better with papain, could result in an attenuation of general allergic reactions.

#### *Modified immunotherapy*

##### *Vaccination with DNA plasmids*

Wai et al. constructed two hypoallergens of the shrimp tropomyosin Met e 1: MEM49 and MED171, and expressed them in plasmid pCI-Neo (45). Authors concluded that hypoallergen-based DNA vaccines could effectively protect against tropomyosin sensitization in mice via the establishment of Th1-oriented responses, recruitment of regulatory T cells, and induction of blocking IgG antibodies.

##### *T cell epitope immunotherapy*

Peptide-based immunotherapy (PIT) has been found to successfully treat allergic patients, and there are many opportunities for the application of PIT in this category (46). Wai et al. identified the immunodominant T cell epitopes of tropomyosin of *Metapenaeus ensis* (Met a 1), and evaluated their therapeutic effect in a Balb/c mouse model of Met e 1 hypersensitivity (47). Mice treated with the T cell epitope peptide mixture demonstrated an amelioration of systemic allergic symptoms, and a significant reduction in Th2-associated antibody and cytokine responses. More investigators are identifying CD4 T cell shrimp tropomyosin-derived epitopes for the design of PIT of shrimp-allergic patients (48).

##### *Probiotics*

The beneficial effect of probiotics has been demonstrated in the treatment of allergic diseases. Probiotics interact with the host immune system and may provide preventive and therapeutic effects on allergic diseases (49). Schiavi et al. investigated the therapeutic potential of VSL#3 probiotic mixture on specific immune responses and anaphylactic reaction induced in mice

**Table I** - Future therapies for shrimp allergy.

Production of hypoallergenic shrimp	physical treatments chemical procedures
Modified immunotherapy	vaccination with DNA plasmids T cell epitope immunotherapy
Probiotics	
Chinese herbal formulations	

by shrimp tropomyosin (50). Oral therapeutic administration of VSL#3 to tropomyosin sensitized mice significantly reduces symptom score and histamine release in faeces after allergen challenge. Measurements of IL-4, IL-5 and IL-13 were significantly reduced, whereas FOXP3 and IL-27 mRNA expression, IL-10, TGF- $\beta$  and IFN- $\gamma$  showed higher levels.

#### *Chinese Herbal Formulations (CHF)*

Plants have been used for medicinal purposes for thousands of years. Traditional Chinese medicine, which has been practiced for centuries in Asia, has awakened the interest of Western countries as an alternative or complementary therapy for some diseases, including allergic diseases such as food allergy. Li et al. tested the effect of a mixture of 11 herbs in an experimental model of mice with allergy to peanut. In this study protection was observed in the mouse, avoiding the appearance of anaphylactic reaction in the test of provocation with peanut (51). In addition, after two weeks of treatment levels of specific IgE were significantly reduced, and remained low for at least 4 weeks after discontinuation of treatment. Also a reduction in the synthesis of cytokines Th2, IL-4, IL-5 and IL-13 was observed, without altered IFN- $\gamma$  production. A major limitation of the current presentation of CHF is the inconveniently high daily dose. Therapeutic use of Chinese herbal formulations on food allergy is currently being investigated in several clinical trials with promising results in several food allergies including shellfish allergy (52).

In **Table I** we present the future therapies for shrimp allergy included in this review, summarized.

#### **Conclusions**

This article reviews as current as possible the future therapies for shrimp allergy. At the moment, there is a therapeutic need for this food allergy. The attempts in exploring new options, as alternative therapy, will lead to new treatments for this and for other food allergies. Our food allergic patients have been expecting for it for too many years.

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