

REVIEW

Shellfish allergy

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Summary

Seafood plays an important role in human nutrition and health. The growing international trade in seafood species and products has added to the popularity and frequency of consumption of a variety of seafood products across many countries. This increased production and consumption of seafood has been accompanied by more frequent reports of adverse health problems among consumers as well as processors of seafood. Adverse reactions to seafood are often generated by contaminants but can also be mediated by the immune system and cause allergies. These reactions can result from exposure to the seafood itself or various non-seafood components in the product. Non-immunological reactions to seafood can be triggered by contaminants such as parasites, bacteria, viruses, marine toxins and biogenic amines. Ingredients added during processing and canning of seafood can also cause adverse reactions. Importantly all these substances are able to trigger symptoms which are similar to true allergic reactions, which are mediated by antibodies produced by the immune system against specific allergens. Allergic reactions to 'shellfish', which comprises the groups of crustaceans and molluscs, can generate clinical symptoms ranging from mild urticaria and oral allergy syndrome to life-threatening anaphylactic reactions. The prevalence of crustacean allergy seems to vary largely between geographical locations, most probably as a result of the availability of seafood. The major shellfish allergen is tropomyosin, although other allergens may play an important part in allergenicity such as arginine kinase and myosin light chain. Current observations regard tropomyosin to be the major allergen responsible for molecular and clinical cross-reactivity between crustaceans and molluscs, but also to other inhaled invertebrates such as house dust mites and insects. Future research on the molecular structure of tropomyosins with a focus on the immunological and particularly clinical cross-reactivity will improve diagnosis and management of this potentially life-threatening allergy and is essential for future immunotherapy.

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Introduction

Seafood plays an important role in human nutrition and health. The highest consumption of seafood in Europe is Iceland (consumption of crustacean and fish of about 91 kg live weight per capita) followed by Portugal (59 kg), Norway (47 kg), Spain (43 kg), France (27 kg), United Kingdom (19 kg) and Germany (13 kg) as compared with Japan (60 kg) [1], Australia (11 kg) [2] and United States (8 kg). Data for only shellfish consumption are difficult to retrieve but the average American eats about 16.3 pounds of fish and shellfish per capita, and the top choice with 4.1 pounds are shrimps. America is the third largest consumer of seafood after China and Japan and imports over 84% of

its consumed seafood (http://www.noaa.gov/stories/2008/20080717_seafood.html).

The growing international trade in seafood products has added to the popularity and frequency of consumption of a variety of seafood products across many countries. This increased consumption of seafood has been accompanied by more frequent reports of adverse health problems among consumers but also among processors of seafood. The following review focuses on adverse reactions to shellfish that can result from reactions mediated by the immune system (allergies) as well as non-immunological reactions [3, 4]. Importantly various substances found in shellfish can trigger clinical symptoms which although non-allergic in origin are similar to true IgE-mediated

Table 1. Adverse reactions to shellfish generated by different triggers

Aetiology	Shellfish implicated	Clinical symptoms	Time of onset
<i>Bacterial</i> Aeromonas, Listeria, Salmonella, Vibrio	Crustacean, Mollusc	Dermatological	Minutes to several hours
<i>Viral</i> Rota-, Astrovirus, Hepatitis A, small round viruses, etc.	Crustacean, Mollusc	Gastrointestinal	
<i>Parasites</i> Anisakis	Crustacean and Cephalopods (e.g. squid)	Respiratory	
<i>Toxins</i> Algae toxins	All Mollusc species	Neurological	
<i>Allergens</i>	Crustacean, Mollusc		

allergic reactions (Table 1). Because of the similarity in clinical reactions of affected individuals, it is of fundamental importance to differentiate adverse reactions from true shellfish allergy and understand the underlying mechanisms of allergic reactions and the molecular nature of these allergens. The epidemiology, diagnosis and clinically cross-reactive allergens are discussed below.

Classification of seafood groups

Patients with allergy to shellfish may fail to identify the offending seafood species, often as a result of confusion regarding the diversity of shellfish consumed and the different common names used to describe shellfish. The three most important seafood groupings include the fish, crustacean and molluscs. The two invertebrate phyla of crustacean and molluscs are generally referred to as 'shellfish' in the context of seafood consumption (Table 2).

Crustaceans are classified as arthropods together with arachnids and insects. Over 50 000 living crustacean species are found world-wide and a large number of varieties are consumed raw or cooked. Molluscs is also a large and diverse group, subdivided into the classes Bivalve, Gastropods and Cephalopods (Table 2) and comprises almost 100 000 different species, including several economically important seafood groups such as mussels, oysters, abalone and squid (calamari). The last of the seafood groups are the fish, which belong to the group of vertebra, contain very different allergens and are not part of this review.

Adverse reactions to shellfish

Adverse reactions to shellfish can be generated via immunological and non-immunological reactions, resulting from exposure to the shellfish itself or various non-seafood components in the product (Table 1). These reactions can be triggered by a range of substances including parasites (e.g. *Anisakis*) [5, 6], protochordates (*Hoya*), bacteria (e.g. *Vibrio*; *Klebsiella*; *Pseudomonas*), viruses

Table 2. Classification of seafood species and the shellfish group

	Phylum	Group	Common name
	Arthropods	Crustacean	Crab, rock lobster, prawn, shrimp
Shellfish	Molluscs	Gastropods	Abalone, snail, whelk
		Bivalves	Clam, oyster, scallop, mussel, cockles
		Cephalopods	Squid (cuttlefish), octopus
	Chordate	Teleostie	Tuna, salmon, carp, trout

(e.g. hepatitis A), marine toxins (e.g. saxitoxins, ciguatera) and biogenic amines [7]. Additionally, ingredients such as preservatives, flavours and colourings added during processing of shellfish can cause adverse reactions such as chemical additives (e.g. sodium benzoate; metabisulphites) [8, 9], spices (e.g. mustard, flour additives, garlic) [10] and some such as casein that are not always obvious (hidden ingredients) [3].

Prevalence and epidemiology of shellfish allergy

As with all food allergies, accurate epidemiological data on the prevalence of seafood allergy generally and shellfish allergy in particular are limited by the lack of controlled population-based studies incorporating the gold standard of double-blind placebo-controlled oral food challenge (DBPCFC). While the consumption of seafood is steadily increasing world-wide, it is generally considered that shellfish and fish are among the four foods most commonly provoking severe food anaphylaxis [11–14].

It is estimated that about 30 000 food-induced anaphylactic events are seen annually in the United States alone, of which up to 200 are fatal (<http://www.fda.gov/ForConsumers/ConsumerUpdates/ucm089307.htm>). A telephone survey established perhaps surprisingly that individuals identified 'seafood allergy' as a major source of health concern affecting an estimated 6.5 million people in the United States – more than twice as common as reported

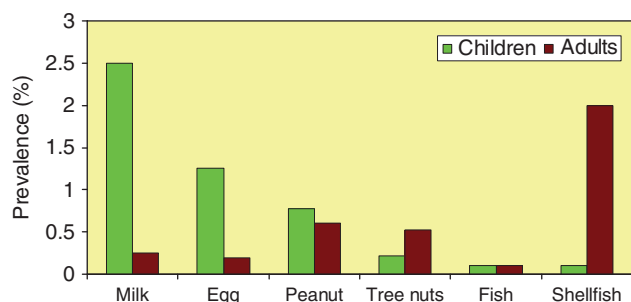


Fig. 1. Prevalence profile of food allergy among children and adults in the United States [80].

peanut allergy. From this survey of 14 948 individuals, 2% described that shellfish allergy and seafood allergy was almost five times more common in adults than in children [12] (Fig. 1). Of the subjects with perceived allergies to crustaceans and molluscs only 38% and 49%, respectively, reported reactions to multiple species and only 14% reacted to both shellfish groups, suggesting less than expected clinical cross-reactivity between the crustacean and molluscs. Telephone surveys, however, are unable to discriminate adverse reactions, for example due to shellfish poisoning, from true IgE-mediated clinical allergy [15]. A study by Crespo et al. [16] in Spain among 355 children established that 6.8% of patients reacted to crustaceans by skin prick test (SPT). A study from South Africa on 105 individuals with perceived adverse reactions to seafood confirmed sensitization to prawns and rock lobster in 47% and 44%, respectively [17]. Of the 131 positive reactions by ImmunoCAP, 50% reacted to four different crustacean species. However, clinical cross-reactivity may not always be similar to that of molecular cross-reactivity to allergens.

Shellfish allergy is common in western countries such as Europe, United States and Australia, but seems to be more prevalent in Asian countries where allergic reactions to seafood and particularly shellfish are very common among children and adults [18–21].

Furthermore, more shellfish is readily available to a wider range of populations and countries due to improved transportation, shipping and general globalization of food supply as well as increasing socio-economic standards. The likelihood of becoming sensitized to a particular food allergen seems to correlate with geographical eating habits, so seafood allergy to a particular seafood species is more prevalent in countries where this seafood is part of the staple diet.

Clinical features and diagnostic approaches of shellfish allergy

The pattern of allergic symptoms after ingestion of shellfish appears similar to the symptoms experienced due to other allergenic foods. Reactions are immediate, reported

mostly within 2 h; however, late-phase reactions have been reported up to 8 h after ingestion, particularly to snow crab, cuttlefish, limpet and abalone [22, 23]. Patients may have a single symptom but often there is multi-organ involvement. Importantly respiratory reactions are often seen after ingestion of allergenic seafood and frequently with anaphylactic reactions. In particular, the oral allergy syndrome is often experienced by crustacean allergic subjects. Symptoms occur within minutes after ingestion of crustaceans and include itching and angioedema of the lips, mouth and pharynx. One of the first clinical reports highlighting the existence of exercise-induced anaphylaxis due to food was presented by Maulitz et al. [24] after the ingestion of oysters. Similar findings have subsequently been reported for abalone [25], squid [26] and shrimp [27]. While atopic individuals are at greater risk of developing anaphylactic reactions to food allergens, it is interesting to note that shellfish allergy results less frequent to fatal anaphylaxis as compared with peanut allergy.

The appearance of allergic symptoms results not only from ingestion of seafood, but can also be triggered by inhaling cooking vapours and handling seafood in the domestic as well as in the occupational environment [28–30]. Symptoms manifest mainly as upper and lower airway respiratory symptoms and dermatitis, while systemic anaphylaxis is rarely seen with this type of exposure.

Notably, there are a number of individuals who have reacted to shellfish but wish to continue to eat seafood. It is important to establish that any adverse reaction was indeed IgE mediated and correctly identify the specific seafood species implicated. While a detailed history is essential, the identification of the implicated seafood species using specific diagnostic procedures is of importance, particularly if the seafood product is not properly identified. Sensitized individuals need to be advised of the potential dangerous consequences of continued exposure.

Diagnostic methods include SPT and quantification of specific IgE antibodies using assays such as the ImmunoCAP or allergen-microarray. However, positive test results are not necessarily proof of clinical sensitivity. Possible cross-reactivity between tropomyosin from crustacean and molluscs with tropomyosin from insects and mites may have clinical significance and is discussed below. In addition, other allergens have been recently identified in crustacean such as sarcoplasmic calcium-binding protein [31], myosin light chain [32] and arginine kinase [15, 33]. The later allergen has been previously characterized as allergen from a moth [34] and one might speculate that this particular allergen could also be a cross-reactive pan-allergen such as tropomyosin.

The dose of ingested shellfish causing anaphylactic reactions varies between different studies. Wu and Williams [35] reported that fatal anaphylaxis occurred after

ingestion of three snails. A different study using DBPCFC reported the accumulated amount of as little as 120 mg of dried snail causing a significant decrease in lung function FEV₁ [36]. For crustacean, Bernstein *et al.* [37] reported that patients in a DBPCFC reacted to 14 g of shrimp. Similar results were confirmed by Daul *et al.* [38] who reported that the equivalent dose of 32 mg of protein extract, equivalent to the amount obtained from about four medium-sized shrimps (16 g) caused reactions in DBPCFC.

Occupational exposure to shellfish allergens

The fishing and fish-processing industry has experienced tremendous growth in recent years. The Food and Agriculture Organization estimated that the number of people engaged in fishing, aquaculture and related activities world-wide increased to about 38 million in 2002. Increased levels of production and processing of seafood result in more frequent reporting of occupational health problems such as rhinitis, urticaria and asthma and other allergic reactions. The prevalence of occupational asthma in shellfish-processing workers is estimated as between 2% and 36% and occupational protein contact dermatitis is 3–11% [4, 28, 39]. Occupational sensitization has also been reported to molluscs such as scallops among restaurant workers [40] and scallop processors [41]. From the limited scientific data available for all seafood groups, it seems that crustacean stimulate a particularly strong allergic response in the work-place with sensitization rates of up to 26% (SPT) of workers in plants that process king-, rock- and snow crab [42–44].

Allergic reactions during processing of seafood are the result of exposure to seafood itself or to various non-seafood components present in the product. Aerosols generated by snow crab and king crab processing contain not only allergenic muscle proteins, but also crab exoskeleton, gills, kanimiso (internal organs) as well as background material such as cellulose, synthetic fibres and inorganic particles (silicon, aluminium, iron) [43]. Limited

evidence from dose–response relation studies indicate that development of symptoms is related to duration and intensity of exposure [28, 45, 46].

Biochemical and biological characteristics of shellfish allergens

The major allergens responsible for ingestion-related allergic reactions due to crustaceans are tropomyosins, while molluscs contain other less well-characterized allergens in addition to tropomyosin (Table 3). It is noteworthy that crustacean and mollusc allergens do not cross-react with fish allergens and no reactivity between known allergens or homologous proteins has currently been demonstrated [47].

Already in the early 1980s Hoffman *et al.* identified a heat-stable IgE antibody-binding allergen in shrimps, which was later identified by Lehrer and colleagues in the brown shrimps as tropomyosin [48–50]. Shrimp tropomyosin has a slightly acidic isoelectric point, seems to have minor glycan modifications and is water soluble and heat stable. While tropomyosin migrates in SDS-PAGE as a single band between 34 and 39 kDa, the protein in its native state is a coiled-coil homodimer with much higher molecular weight. Tropomyosin has a highly conserved amino acid sequence among different invertebrate organisms, with up to eight IgE-binding regions in shrimp, and is present in muscle and non-muscle cells.

In addition to tropomyosin, other allergens have been identified and characterized in crustaceans. Proteomic analysis of the black tiger shrimp *Penaeus monodon* has identified a novel allergen, Pen m 2 [51]. Protein sequence analysis of Pen m 2 has interestingly shown the protein to be very similar to arginine kinase, suggesting that the allergen may be a new class of invertebrate pan allergens [33]. In addition a sarcoplasmic calcium-binding protein and a 20 kDa myosin light chain have been identified in the black tiger prawn (*P. monodon*) and Pacific white shrimp (*Litopenaeus vannamei*) [31, 32, 52]. These allergenic proteins have similar homologues among different

Table 3. Overview of characterized shellfish allergens

Allergens identified	Molecular weight (kDa) (approximately)	Allergen nature and function	Species implicated
Tropomyosin	34–39	Major muscle protein with highly conserved amino acid structure; α -helix coiled-coil structure; three isoforms identified	Crab, rock lobster, prawn, shrimp, krill, barnacle
Arginine kinase	40	Phosphagen kinase; key enzyme in energy metabolism in invertebrates; evolutionary relationship to vertebrate creatine kinase	Tiger prawn, white shrimp
Myosin light chain	20	Two light chains are bound to each myosin heavy chain	White shrimp
Sarcoplasmic calcium-binding protein	20	Calcium-binding muscle protein; EF-hand-type	White shrimp, tiger prawn

invertebrates but the significance for clinical cross-reactivity is not known. Interestingly the sarcoplasmic calcium-binding protein seems to be an important allergen particularly among the paediatric population. A number of other IgE-binding proteins with molecular masses ranging from 8 to 89 kDa have also been demonstrated in various studies, although not identified immunochemically. It is well documented that tropomyosin, myosin light chain and sarcoplasmic protein are heat stable. However, it is possible that the heating process, particularly of the whole prawn, generates smaller or larger IgE-binding fragments/aggregates.

Importantly, tropomyosin is not only a crustacean allergen but has been confirmed in a number of mollusc species [53]. It has become apparent that molluscs such as mussel, oyster, squid, limpet and abalone can be significant food allergens in exposed populations. Tropomyosin has been demonstrated as one of the major allergens in squid, oysters, scallops, snails and abalone [23]. In addition, molluscs contain other allergens such as myosin heavy chain, haemocyanin and amylase [53]. Furthermore, arginine kinase as mentioned above seems to be also allergenic in molluscs, accounting perhaps for an additional degree of cross-reactivity among these two seafood groups.

Immunoglobulin-E cross-reactivity of shellfish allergens

Within the shellfish group

Cross-reactivity occurs frequently to seafoods within a certain group or family such as crab, lobster, shrimp among the crustaceans [27,54–58], suggesting that cross-reactivity frequently occurs between phylogenetically related organisms. However, Lehrer and Mccants [59], demonstrated already in the late 1980s that crustacean sensitized sera had significant IgE antibody reactivity to oyster extract by RAST analysis, highlighting the cross-reactivity within shellfish. Crustacean allergic subjects often react to species of the mollusc group, such as squid (cuttlefish), abalone, limpet, squid, oyster, mussel, scallop and clam. A study by Leung et al. [60] confirmed the presence of a 38 kDa IgE-binding protein in all 10 mollusc species tested, using sera from nine crustacean allergic patients. Furthermore, varying reactivity of the sera with a number of other mollusc allergens was observed, such as oyster [4, 61]. Serological and clinical cross-reactivity is also often observed between crustaceans and the mollusc squid (*Todarodes pacificus*) [62, 63]. This allergen was identified as the tropomyosin Tod p 1 and seems to cross-react with other squid species (*Loligo vulgaris*) and also shrimp, lobster and crab. Crespo's group [64] showed in Spain that nine of 10 children with sensitization to molluscs reacted by SPT and serum-specific IgE to crustaceans. However, most cross-reactivity studies are based on

molecular and immunological findings and not necessarily on clinical reactivity.

Even though IgE cross-reactivity among crustaceans and molluscs is commonly reported, until recently there had been only limited molecular characterization of these cross-reactive allergens. Molecular investigation of these allergens suggests that a high homology in the primary amino acid sequence of an allergen results in a high homology of the 3-D structure (protein folding) of the protein and thus potentially leads to cross-reactivity [65–67]. Molecular comparison of tropomyosin from many different crustacean species reveals very high homologies of up to 98%, whereas the amino acid sequence identity of shrimp tropomyosin with mussels and abalone is lower with 57% and 61%, respectively. The relationship of molecular cross-reactivity with clinical reactivity has, however, not been adequately defined. In addition clinical cross-reactivity cannot be confirmed by skin test positivity, because of possible co-sensitization in highly atopic individuals as demonstrated by Wu and Williams [35]. While DBPCFC are not easy to perform to confirm clinical allergy to particular shellfish species, cross-inhibition assays might give more insight into whether sensitization to one of the shellfish groups results in clinical reactivity. Nevertheless, species-specific allergic reactions to particular crustacean species have been reported and are probably of clinical relevance. Whether these specific reactions are based on differential IgE responses to specific epitopes or perhaps a reflection of the first shellfish exposure is not known.

Between shellfish and other invertebrates

Allergic reactions in shellfish allergic patients have also been reported to mites and insects [56,64,68–75]. Clinically relevant cross-reactivity between crustacean and house dust mite (HDM) allergens has been described [76] and the term 'mite–crustaceans–mollusc syndrome' is sometimes used. The primary sensitization is believed mostly to be 'respiratory' allergy to dust mites, which then sometimes cause food allergic reactions to crustaceans or molluscs in some individuals. There are also observations on allergy to mites or cockroaches possible occurring subsequent to sensitization to crustaceans [69].

Other possible IgE reactivities to tropomyosin-containing allergen sources have been documented, such as the cross-reactivity to the fish parasite *Anisakis* [62, 68]. The possible clinical cross-reactivity is supported by high (74%) amino acid sequence homology of crustacean and *Anisakis* nematode tropomyosin (Ani s 3) [5, 77–80].

This seemingly frequently encountered cross-reactivity is probably due to tropomyosin and may have significant clinical implications. This has been shown particularly for shellfish allergens and tropomyosins from insects and mites, which are all part of the phylum arthropod [81, 82].

A recent study demonstrated sensitization to shrimp tropomyosin in orthodox Jews, who are prohibited by religious dietary laws from eating shellfish, which could be indicative of sensitization to tropomyosin from non-crustacean, such as HDM and cockroaches, via the inhalation route [83]. Exposure to invertebrate tropomyosins via the inhalation route might generate these cross-reacting IgE antibodies demonstrated in this study. Inhalational routes of sensitization have not been well documented but seem to be predominant in workers sensitized in the food-processing industry [28, 45, 84, 85].

A recent review by Mills and colleagues [66] highlighted that almost all animal food allergens have homologs in the human proteome. In general the vertebrate tropomyosin sequences have significant similarity with over 90% homology and none of these has been reported as allergenic. In contrast, allergenic tropomyosins are always found among the invertebrates such as crustaceans, molluscs, insects and some nematodes (*Anisakis*) and demonstrate lower sequence identity to human tropomyosin of 54% (<http://www.allergome.org/>, GenBank and SwissProt). Furthermore, inhalant arthropod-derived tropomyosins share high sequence identities to shellfish tropomyosins of up to 84%. These allergenic tropomyosins are found in two cockroaches (*Per a 7* and *Bla g 7*) as well as in the HDM (*Der p 10* and *Der f 10*) [55, 86, 87].

These observations were recently supported by two separate studies. During immunotherapy to HDM patients developed sensitization to shellfish tropomyosin, which did not exist before therapy [36, 75, 88, 89]. However, sensitization to shellfish tropomyosin is not always observed as stated by Asero [90] and these differential responses might be due to various amounts of tropomyosin present in the immunotherapy preparations. These immunological findings strongly indicate that the documented cross-reactivity between tropomyosins from different allergen sources can result in cellular activation and subsequently asthmatic reactions.

T cell cross-reactivity of shellfish allergens

The mainstream treatment for shellfish allergy is still allergen avoidance where feasible. Although this is effective for most patients, accidental exposure to shellfish allergens results frequently in anaphylaxis. In addition clinical cross-reactivity of tropomyosin from shellfish with other invertebrate allergen sources such as HDM and insect could play a significant role. Therefore allergen-specific immunotherapy could be important as it selectively modulates the allergen-specific immune response and is potentially curative [91]. An attractive approach is the use of short, linear peptides corresponding to T cell epitopes of allergens. Allergen-specific T cell lines and T cell clones are produced and mapped for peptide specificity to determine dominant T cell epitopes of

allergens. While these molecular and cellular approaches for immunotherapy are already progressed for cat dander, ragweed and bee venom, there are no published data on shellfish allergen T cell epitopes. Hopefully these developing procedures may provide alternative methods of treatment for shellfish allergic subjects.

Conclusion

Shellfish are an increasingly important cause of IgE-mediated food allergy. The recent designation of the mollusc group as commonly allergenic foods, separate from crustacea, in the European Union and Canada has added to their public health importance. The prevalence of shellfish allergy seems to vary largely between geographical locations, most probably as a result of the availability of seafood as part of the staple diet.

The major shellfish allergens are tropomyosin, although other allergens may play an important part in allergenicity such as arginine kinase and myosin light chain. Tropomyosin seems to be the major allergen responsible for molecular and clinical cross-reactivity between crustaceans and molluscs, but also to other inhaled invertebrates such as HDM and insects. While shellfish allergens do not cross-react with fish allergens, allergic reactivity to *Anisakis*-contaminated fish might result from cross-reactivity to invertebrate tropomyosin.

Future research on the molecular structure of tropomyosins and other cross-reactive shellfish allergens, with a focus on the immunological and particularly clinical cross-reactivity will improve diagnosis and management of this potentially life-threatening allergy and is essential for future immunotherapy.

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