

Role of Adverse Reactions to Food in Urticaria and Exercise-Induced Anaphylaxis

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Key Words

Food · Allergy · Pseudoallergy · Urticaria · Exercise-induced anaphylaxis

Abstract

In urticaria, adverse reactions to food are only a frequent finding in the subset of patients with chronic continuous urticaria. Mostly these reactions are of pseudoallergic nature, directed against artificial additives as well as naturally occurring aromatic components. IgE-mediated allergic reactions are a rare cause in acute urticaria as well as in recurrent chronic urticaria. In other types of urticaria, e.g. physical urticaria, food plays hardly any role as an eliciting agent with the exception of ice-cold drinks in cold urticaria. By contrast, exercise-induced anaphylaxis is frequently food-dependent. Two subtypes are distinguished: unspecific food-dependent exercise-induced anaphylaxis (FDEIA), where the filling of the stomach independently of the kind of food ingested prior to exercise is responsible for the symptoms. In specific FDEIA, an IgE-mediated food allergy causes symptoms only in combination with exercise. In the latter group, wheat is an important allergen.

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Definition of Urticaria and Exercise-Induced Anaphylaxis

Urticaria is defined by the occurrence of wheals and in some cases angioedema. Wheals are characterized by a surrounding reflex erythema, associated itching and the fleeting nature (persistence of the wheal <24 h). Urticaria is the heading for a heterogeneous group of distinct entities. These subgroups are distinguished by disease duration, pathogenesis, eliciting agents and clinical features. In order to compare results from different studies it is of highest importance to differentiate clearly between the different subtypes and to adhere to the consensus classification of urticaria [1] (table 1).

Exercise-induced anaphylaxis (EIA) is characterized by airway obstruction, urticaria and hypotension following physical exercise. A subtype of EIA related to the intake of specific food is known as food-dependent, exercise-induced anaphylaxis (FDEIA). In some cases, specific foods cause anaphylaxis when exercise follows ingestion, but are tolerated if not followed by exercise (specific FDEIA). Others suffer from EIA after any meal followed by exercise, regardless of the food eaten (nonspecific FDEIA) [2]. In specific FDEIA an IgE-mediated mechanism is likely, as skin prick testing and IgE for specific foods ingested prior to exercise are positive in most patients [3]. Serum histamine and tryptase levels are increased during symptomatic attacks, indicating degranulation of mast cells in FDEIA [4, 5].

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Table 1. Classification of urticaria on the basis of its duration, frequency and causes [from 1]

	Duration	Frequency
a. Spontaneous urticaria		
1. Acute urticaria	<6 weeks	Spontaneous wheals appearing most days
2. Chronic urticaria	>6 weeks	Spontaneous appearance of wheals
± Chronic continuous urticaria	Daily or on most days of the week	
± Chronic recurrent urticaria	Symptom-free intervals ranging from days to weeks	
b. Physical urticaria	<i>Eliciting factor</i>	
1. Dermographic urticaria	Mechanical shearing forces (wheals arising after 1–5 min)	
2. Delayed pressure urticaria	Vertical pressure (wheals arising with a 3–8 h latency)	
3. Cold contact urticaria	Cold air/water/wind	
4. Heat contact urticaria	Localized heat	
5. Solar urticaria	UV and/or visible light	
6. Vibratory urticaria/ angioedema	Vibratory forces, e.g. pneumatic hammer	
c. Special types of urticaria		
1. Cholinergic urticaria		
2. Adrenergic urticaria		
3. Contact urticaria (allergic or pseudoallergic)		
4. Aquagenic urticaria		
d. Different diseases related to urticaria for historical reasons		
1. Urticaria pigmentosa (mastocytosis)		
2. Urticarial vasculitis		
3. Familial cold urticaria (a vasculitis)		

The following part is divided into urticaria and FDEIA, since different aspects of these diseases will need to be considered.

Role of Food in Urticaria

Data concerning food as an eliciting factor in urticaria are limited. The reasons are mainly the difficulties in the diagnosis of food allergy and especially of food pseudoallergy with the necessity of double-blind, placebo-controlled food challenge (DBPCFC) and the fact that not only the elicitation of wheals but also the augmentation of disease activity needs to be kept in mind.

Acute Urticaria

Acute urticaria is a frequent disease affecting approximately 15–23% of the population at least once in their lifetime [6]. Patient's history is important but often not reliable since the role of food is generally overestimated;

63% of patients with acute urticaria suspect food as an eliciting factor [6]. In acute urticaria IgE-mediated adverse reactions to food have been confirmed in less than 1% of patients [6, 7], whereas in recurrent episodes of acute whealing this rate was reported to be higher in the past (10%) [7a]. In general food appears to be of higher importance for acute urticaria in early childhood. Here, in up to 15% IgE-mediated reactions were reported in the age group from 6 months to 16 years [8]. Pseudoallergic reactions against food were not reported in any of these studies, but pseudoallergic reactions against NSAID are reported to be the second most frequent cause, responsible for 9% of acute urticaria cases while as the most frequent cause an upper respiratory tract infection [9] was identified.

Chronic Urticaria

Similar to acute urticaria, type I-allergic reactions were rarely reported to be responsible for the development of chronic urticaria [6, 10]. However, a type I allergy should

Table 2. Survey of studies on the role of food in the pathogenesis of urticaria [from 1]

Author(s)	Number of patients investigated	Number of positive reactions to food additives	Method of provocation	Response to diet
Warin and Smith, 1976 [37]	111	59.5% (incl. ASS)	Single-blind, placebo-controlled (antihistamine treatment)	75% ¹
Genton et al., 1985 [38]	17	88.2% (incl. ASS)	Single-blind	93.3% ¹
Michaelsson and Juhlin, 1973 [39]	52	75% (incl. ASS)	Single-blind	81.3% free of symptoms ¹ 6.3% clear improvement ¹
Thune and Granhold, 1975 [40]	100	62% (incl. ASS)	Single-blind	80.6% clear improvement ¹ 19.4% spontaneous clearance ¹
Wüthrich and Fabro, 1981 [41]	620	26.6% (incl. ASS)	Single-blind	> 60% clear improvement ¹
Juhlin, 1981 [42]	330	31%	Single-blind	No data
Ortolani et al., 1984 [43]	70	59.6% (incl. ASS)	Single-blind, placebo controlled	No data
Rudzki et al., 1980 [44]	158	31.6%		No data
Ros et al., 1976 [45]	75		Follow-up study	24% free of symptoms ¹ 57% clear improvement ¹
Verschave et al., 1983 [46]	67	None		55% of all patients
Gibson and Clancy, 1980 [47]	76	Up to 54%	Single-blind, placebo-controlled	Of all patients: 71.1% free of symptoms 19.7% clear improvement 9.2% refused diet
Kirchhof et al., 1982 [48]	100	39%	Double-blind, placebo-controlled	44% ¹
Suprananiam and Warner, 1986 [49]	43	24%	Double-blind, placebo-controlled	87.5% ¹
Zuberbier et al., 1995 [9]	67	19%	Double-blind, placebo-controlled	73% of all patients
Pigatto and Valsecchi, 2000 [11]	202 of a total group of 348	37.3%	Double-blind, placebo-controlled	Of all patients: 62.4% clear improvement 17.3% no benefit 20.3% discontinued diet

¹ Number referring to the group of patients put on diet after positive reactions.

be ruled out in those patients who suffer from intermittent attacks of whealing lasting for a few hours only shortly after the ingestion of food. By contrast, in adult patients with chronic continuous urticaria with daily whealing a type I-allergic mechanism is unlikely since the eliciting allergens would need to be ingested several times daily. In this subset of patients, pseudoallergic reactions against food and food additives have been repeatedly discussed previously (table 2) apart from infectious or autoimmune etiology due to the distinct nature of this reaction.

The clinical symptoms of pseudoallergy cannot be clearly distinguished from a type I-allergic reaction. They occur frequently with a latency of more than 4 h and cease only after a prolonged omission of the suspected pseudoallergen for more than 10–14 days [9]. This is in contrast to type I allergies where the symptoms usually appear after 0–120 min and clear after a few hours or at the latest after 24–48 h. These aspects of pseudoallergy are important to be kept in mind also in interpreting different studies (table 2). Only a few studies have used the gold standard of DBPCFC tests and in some of the mentioned studies elimination diets were only adhered to for a

few days. Results may also differ due to heterogeneous study populations and study conditions. Some studies have included not only patients with chronic urticaria but also patients with physical urticaria. Also approximately 50% of patients do not show a total clearance of symptoms but have an improvement in disease intensity, pointing to the involvement of cofactors. Finally, a study outcome may also depend on the country where the study was performed (e.g. parasitic infections are more frequent in developing countries, hepatitis B is more frequent in southern than northern Europe) and on the differences in health systems. The latter is important since none of the studies are cross-sectional population-based investigations, and in some countries referrals to specialists are only possible in severe cases. In our own study [9] unselected patients with chronic continuous urticaria were included who had not previously received a diagnostic work-up. In this group a high incidence of pseudoallergic reactions against food was seen. These results were only recently confirmed by Pigatto and Valsecchi [11], who investigated a group of 202 patients with chronic urticaria using the same diet and study conditions. In this study

126 patients improved on the diet, whereas 35 patients did not show any benefit from the diet and 41 patients dropped out. In both studies positive oral provocation tests to food additives were only seen in a minority of patients (19 and 37%, respectively), which points to the relevance of naturally occurring pseudoallergens. Especially aromatic compounds found in vegetables appear to be important. An open oral provocation test in 31 chronic urticaria patients showed that 71% of patients responding to a low pseudoallergen diet reacted to tomatoes, and 44% to distillates of tomatoes containing aromatic compounds free of protein and salicylic acid. In contrast, less than 7% reacted to the histamine, protein and salicylate-rich residue [12].

Only little knowledge was gained during the last years regarding the mechanisms of pseudoallergic reactions against food. Synergism with other eliciting factors might be of importance; one possibility appears to be the permeability of gastric mucosa. Initial results show that only the gastric but not the intestinal permeability is decreased in patients with chronic continuous urticaria benefiting from a low pseudoallergen diet. Furthermore, this pathologic intestinal permeability is restored after performing a pseudoallergen diet lasting 3 weeks [13].

In another study the occurrence of anti-FcεRI-α autoantibodies was investigated, which has been described to be of pathophysiologic relevance in up to 30% of patients with chronic urticaria [14, 15]. In our studies these autoantibodies were found at the same frequency as described earlier, but they were not detectable in patients with idiopathic chronic urticaria (7 of 22) or in patients with pseudoallergy against food whose symptoms cleared on stopping the diet (6 of 17) [16]. There are two possible explanations for these findings. First, the FcεRI-α autoantibodies are not of pathophysiologic relevance in these patients with chronic urticaria, and second, a synergism between the autoantibodies and other eliciting stimuli, e.g., food, is necessary for the appearance of clinical symptoms in some patients.

Physical Urticaria and Special Types of Urticaria

Both type I-allergic and pseudoallergic reactions against food rarely play any role as eliciting factor of physical urticaria. However, the temperature of food is an important factor in the elicitation of cold urticaria. The ingestion of ice-cold drinks may induce severe symptoms and patients need to be instructed about this possibility

[17]. Also in contact urticaria, food is an important factor. Both immunological and non-immunological reactions have been described [18]. Contact urticaria to food may present an important health problem in the food-processing industry and in restaurants with food preparation. For an extensive review, compare Wakelin [18]. For special types of urticaria, food may play a role, thus in cholinergic urticaria, hot food, spices and strong liquors can increase body temperature and elicit wheals [19].

Diagnosis of Adverse Reactions to Food in Urticaria

The recommended diagnostic procedures in urticaria have been published in a recent consensus report [1]. Regarding the diagnosis of adverse type I allergy reactions to food, a detailed description is given below in the section on diagnosis of FDEIA. For diagnosis of pseudoallergy as an eliciting factor, patients with chronic continuous urticaria should be given a low pseudoallergen diet (table 3). It is important to instruct patients about possible pitfalls, also handing out recipes is regarded as helpful [17]. The diet should be performed for at least 3 weeks and a detailed diary about the food eaten is advisable to double check involuntary mistakes. This should be accompanied by a symptom protocol using a simple symptom score of 0–3 [1]. In case of symptom score improvement, a DBPCFC following the diet is the diagnostic gold standard for urticaria but difficult to perform on an out-patient basis.

Treatment of Urticaria

The treatment of urticaria has extensively been described in the recent consensus paper [20]. H₁-antihistamines often at a higher dosage than that recommended are most important. However, in cases with pseudoallergy a high chance of complete remission of the disease after several months of diet is possible. It is helpful to encourage the patients to maintain the diet for a longer period. However, it is not necessary to adhere to the diet as strictly as stated in table 3. A large number of food items is only extremely rarely responsible for pseudoallergic reactions and it is possible to include one further item every 3 days into the diet. In order to monitor possible reactions, patients should be advised to continue a diary of symptoms.

Table 3. Low pseudoallergen diet [from 14]

	Allowed	Forbidden
Basic food	Preservative-free bread, potatoes, rice, unprocessed cereals, flour (not self-raising), rice cakes, durum wheat pasta (without egg)	All others (e.g. pasta with eggs, cake, biscuits, potato chips, crisps)
Fats	Butter, cold pressed plant oils	All others (e.g. margarine, mayonnaise)
Milk products	Fresh milk, cream without stabilizers, white cheese, fromage frais, mild Gouda in small amounts	All others
Food from animals	Fresh meat without seasoning	All others including eggs, seafood, smoked meat
Vegetables	All except those listed as forbidden (e.g. lettuce, carrots, zucchini, cabbage, broccoli, asparagus)	Artichokes, peas, mushrooms, spinach, rhubarb, tomatoes and tomato products, olives, sweet peppers
Fruit	None	All including dried fruits or fruit juices
Herbs, spices	Salt, sugar, chives, onions	All others including garlic and herbs
Sweets	None	All including chewing gum
Beverages	Milk, mineral water, coffee, black tea	All others including beer, wine, spirits and herbal teas
Spreads	Honey	All others

Food-Dependent Exercise-Induced Anaphylaxis

Reports of FDEIA seem to be increasing, possibly due to the increased popularity of exercising over the past decade [21]. However, only rare epidemiological data about the frequency of FDEIA in the general population are available. Aihara et al. [22] documented that the frequency of FDEIA in junior high school students in a Japanese high school was <0.02%. Here, it has to be noted that the mean age of FDEIA is between 25 and 35 years [23]. Since symptoms may vary, many persons with FDEIA are often unaware of their condition and FDEIA is often undiagnosed [24]. Regarding the course of disease, data are only available for EIA in general. Nancy et al. published a 10-year follow-up study with 365 US-American patients with EIA. 47% of those who replied a questionnaire stated that the frequency of attacks had decreased since the primary onset. In 46% of patients the frequency of attacks had remained the same [23].

FDEIA was first reported by Maulitz et al. [26] in 1979. They described a case of a 31-year-old woman who developed anaphylaxis during long-distance running after eating shellfish. Since then, numerous foods have been implicated as causes of FDEIA. Shellfish, tomatoes and alcoholic drinks were the most frequently causes pub-

Table 4. Food eliciting FDEIA [from 23]

Food eliciting FDEIA	n	%
Shellfish	45	16
Alcohol	31	11
Tomatoes	23	8
Cheese	22	8
Celery	18	7
Strawberries	15	5
Milk	13	4
Wheat products	14	5
Peaches	13	5

lished by Shadick et al. [23]. This spectrum of eliciting factors is however quite different from other countries where other foods have been identified as aggravating allergens. In contrast to data from European and Japanese investigators, wheat products were identified by only 5% of patients as contributing to an episode of FDEIA [23] (table 4).

In 125 Japanese individuals with FDEIA, the most frequently food determined was wheat followed by shrimps [3]. According to Morita et al., soluble proteins in wheat

have been identified as allergens in baker's asthma, whereas insoluble proteins (gluten) are allergens for wheat-dependent EIA [27]. Among the insoluble proteins, Palosou et al. [27] have identified α -gliadin (40 kDa) and a novel γ -gliadin-like protein as allergens in European patients with wheat-dependent EIA.

Interestingly, the antigenicity of gluten was increased in patients with FDEIA when gluten was digested with pepsin, but decreased when digested with trypsin. This suggests that the antigenicity of gluten is enhanced in the stomach and attenuated in the duodenum. Based on these observations, it was hypothesized that exercise might induce an increase in mucosal absorption of food peptides, including pepsin-digested gluten, in the gut, resulting in IgE-mediated allergic reactions in sensitized subjects [28].

The mechanism of FDEIA is unclear so far, but it has been suspected that exercise triggers allergic reactions in patients who have low-grade type I allergies specific for certain foods. Participation of the autonomic nervous system, intake of certain drugs, weather, humidity, stress, family tendency [29], menstruation cycle in females and the general condition of the individual patient might contribute to induction of FDEIA symptoms [30]. Also, exercise might change food allergen absorption by changes in splanchnic blood flow. A dysfunction of the autonomic nervous system and the ability of gastrin to increase cutaneous mast cell mediator release have also been hypothesized to play a part in the pathogenesis [3]. Romano et al. [2] documented that the pollen season in which subjects suffer from pollinosis and were active in sports seems also to be an important contributing factor. With regard to pollen sensitization, 9 of 14 subjects with FDEIA in whom tomatoes were the suspected food, suffered from seasonal allergic rhinitis against grass pollen which have structures cross-reacting with tomatoes. In all cases, seasonal rhinitis preceded FDEIA for some years, supporting the hypothesis that sensitization to pollen allergens represents the primary event leading to the induction of IgE antibodies that may then cross-react with homologous food allergens [2].

Diagnosis of FDEIA

If the patient's history is suggestive for FDEIA, a thorough allergological work-up is mandatory. This should include specific IgE, skin prick testing with common inhalant allergens, possibly cross-reacting foods, as well as suspected foods. Prick-to-prick test with native allergens

should be performed since this offers a high sensitivity [25].

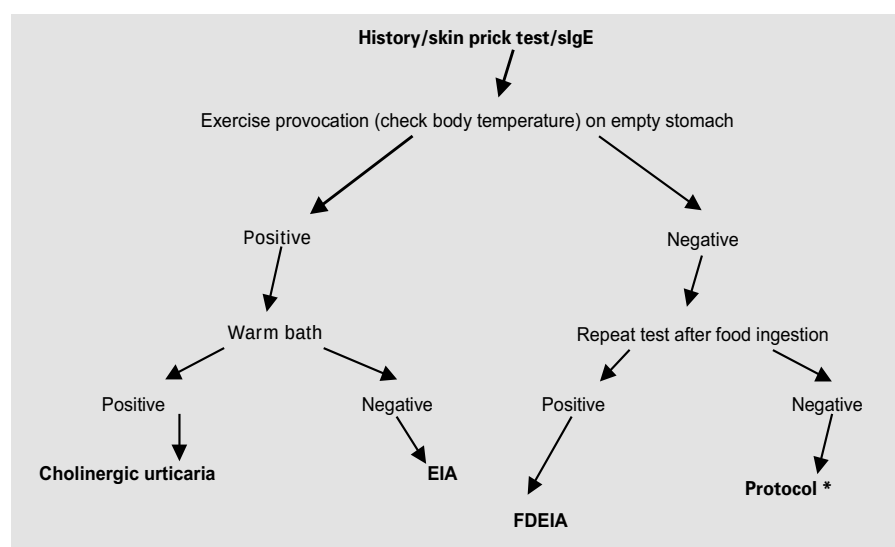
Finally, a food challenge test followed by exercise is required for the confirmation of the diagnosis and is mandatory to avoid unnecessary diets or exercise restrictions. Provocation tests should be performed in the hospital due to the possible severe and sometimes delayed reactions. DBPCFC is the gold standard but open challenge may be sufficient if no reaction occurs. However, it needs to be considered that some patients fail to develop clinical symptoms in provocation tests. Reasons for false-negative test results may depend on the method of provocation. Suko et al. proposed that insufficient amounts of food allergen ingested or inappropriate exercise could be the cause of false-negative clinical responses to challenge tests [31]. Hanakawa et al. [31] published a case of a young woman whose positive reaction of FDEIA depended on the amount of wheat allergen ingested. These authors concluded that an insufficient amount of food allergen ingested or subthreshold exercise levels may be reasons for unsuccessful challenge tests noted in several previous reports [31]. On the other hand, Aihara et al. [32] described a case of a 14-year-old boy who did not develop symptoms of FDEIA after ingestion of rice or 'umeboshi' (Japanese plum) alone but clearly after ingestion of the two foods together.

In conclusion, a positive provocation test confirms clearly the diagnosis but a negative provocation test never completely rules out the presence of FDEIA in an individual [24]. In our own experience it is helpful to imitate the meals and amounts ingested if single food challenge is negative, although this is sometimes difficult to realize under DBPCFC conditions. Especially if alcoholic beverages have been ingested they need to be included in the protocol since they increase gastric allergen absorption and augment histamine release. Another eliciting factor may be associated drug intake, especially of drugs which enhance gastric mucosa permeability such as acetylsalicylic acid (ASA).

Thus, Aihara et al. [3] showed that prior ingestion of ASA augments symptoms of FDEIA. In 5 of 7 patients who were tested negative with food and exercise, only the combination with ASA induced a positive provocation test. Therefore it was suggested to include ASA pre-treatment in provocation tests for patients with suspected FDEIA in whom food challenge associated with exercise is not sufficient to induce anaphylactic reactions.

Apart from an impairment of the gastric mucosa, ASA inhibits cyclooxygenase function in the arachidonic acid cascade, which results in a decrease of prostaglandin syn-

Fig. 1. Flowsheet for the diagnosis of FDEIA and cholinergic urticaria. Try warm bath for cholinergic urticaria or protocol to search for individual factors.



thesis and an increase of leukotriene synthesis. Increased leukotriene levels may be a cofactor in FDEIA. Prostaglandin E₂ may also play an important role for the enhancement of histamine release. Prostaglandins are synthesized via the COX pathway from arachidonic acid released from phospholipids in the plasma membrane by phospholipase A₂ in response to extracellular stimuli. Marone et al. [33] reported a linear correlation between the ability of NSAIDs to potentiate IgE-mediated histamine release from basophils and their ability to inhibit COX activity. Moreover, it has been documented that PGEs inhibits the release of histamine and other inflammatory mediators from mast cells and basophils, which express the receptor for PGE. These authors speculated therefore that ASA enhances histamine release by the suppression of PGEs, which inhibits histamine release in patients with immediate-type hypersensitivity [33].

Differential Diagnoses of FDEIA

If a positive reaction after physical exercise occurs independently of food intake, EIA is possible, but it needs to be distinguished from cholinergic urticaria. Wheals in FDEIA are often larger and passive warmth does not elicit wheals [17] (fig. 1).

Food as well as exercise need also to be considered as an augmenting factor in patients with systemic mastocytosis. Mainly unspecific histamine release from mast cells, causing diarrhea, flush and pruritus, has been described

after the ingestion of very hot or very cold food, alcohol and spicy meals [34]. In order not to overlook this differential diagnosis, serum tryptase levels should be analyzed in all patients suspected of having EIA accompanied by an inspection of the complete integument for the presence of urticaria pigmentosa-like lesions.

Therapy of FDEIA

Avoidance of the combination of the individual food and exercise is an appropriate and effective treatment in specific FDEIA. In unspecific FDEIA, patients should be educated to avoid exercise 1–6 h after eating and in addition to avoid ASA, NSAIDs and alcoholic beverages before exercising [35] depending on the patient's individual history. It is necessary to instruct the patient to always carry an emergency kit including antihistamines, corticosteroids and epinephrine when exercising. Recently, usage of leukotriene antagonists in the treatment of FDEIA has been discussed [2]. Successful prophylaxis by antihistamines is documented in individual cases [36], but controlled prospective clinical trials for both drugs are lacking.

References

- Zuberbier T, Greaves M, Juhlin L, Lennart J, Kobza-Black A, Maurer D, Stingl G, Henz B: Definition, classification and routine diagnosis of urticaria: A consensus report. *J Invest Dermatol Symp Proc* 2001;6:123–127.
- Romano A, Di Fonso M, Giuffreda F, Papa G, Artesani MC, Viola M, Venuti A, Palmieri V, Zeppilli P: Food-dependent exercise-induced anaphylaxis: Clinical and laboratory findings in 54 subjects. *Int Arch Allergy Immunol* 2001; 125:265–272.
- Aihara M, Miyazawa M, Osuna H, Tsubaki K, Ikebe T, Aihara Y, Ikezawa Z: Food-dependent exercise-induced anaphylaxis: Influence of concurrent aspirin administration on skin testing and provocation. *Br J Dermatol* 2002;146: 466–467.
- Briner WW Jr: Introduction: Exercise and allergy. *Med Sci Sports Exerc* 1992;24:843–844.
- Schwartz HJ: Elevated serum tryptase in exercise-induced anaphylaxis. *J Allergy Clin Immunol* 1995;95:917–919.
- Zuberbier T: The role of allergens and pseudoallergens in urticaria. *J Invest Dermatol Symp Proc* 2001;6:132–134.
- Aoki T, Kojima M, Horiko T: Acute urticaria: History and natural course of 50 patients. *J Dermatol* 1994;21:73–77.
- Wüthrich B, Haeckl-Hermann D: Zur Ätiologie der Urtikaria. Eine retrospektive Studie anhand von 316 konsekutiven Fällen. *Z Hautkr* 1980;55:102–111.
- Kauppinen K, Juntunen K, Lanki H: Urticaria in children. Retrospective evaluation and follow-up. *Allergy* 1984;39:469–472.
- Zuberbier T, Chantraine-Hess S, Hartmann K, Czarnetzki BM: Pseudoallergen-free diet in the treatment of chronic urticaria – A prospective study. *Acta Derm Venereol* 1995;75:484–487.
- Juhlin L: Recurrent urticaria: Clinical investigation of 330 patients. *Br J Dermatol* 1981; 104:369–381.
- Pigatto PD, Valsecchi RH: Chronic urticaria: A mystery. *Allergy* 2000;55:306–308.
- Zuberbier T, Pfrommer C, Specht K, Vieths S, Bastl-Borrmann R, Worm M, Henz BM: Aromatic components of food as novel eliciting factors of pseudoallergic reactions in chronic urticaria. *J Allergy Clin Immunol* 2002;109: 343–348.
- Buehner S, Ehlers I, Kuehl F, Zuberbier T, Lochs H: Gastrointestinal barrier in patients with chronic recurrent urticaria: Influence of a low pseudoallergen diet. *Gastroenterology* 1998;114:A868.
- Hide M, Francis DM, Grattan GEH, Hakimi J, Kochan JP, Greaves MW: Autoantibodies against the high-affinity IgE receptor as a cause of histamine release in chronic urticaria. *N Engl J Med* 1983;328:1599–1604.
- Fiebiger E, Hammerschmid F, Stingl G, Maurer D: Anti-FcεRI antibodies in autoimmune-mediated disorders. *J Clin Invest* 1998; 101:243–251.
- Zuberbier T, Fiebiger E, Maurer D, Stingl G, Henz BM: Anti-FcεRI serum autoantibodies in different subtypes of urticaria. *Allergy* 2000; 55:951–954.
- Henz BM, Zuberbier T, Grabbe J, Monroe E: Urticaria: Clinical, Diagnostic and Therapeutic Aspects. Berlin, Springer, 1998, pp 69–78, 196.
- Wakelin SH: Contact urticaria. *Clin Exp Dermatol* 2001;26:132–136.
- Zuberbier T, Althaus C, Chantraine-Hess S, Czarnetzki B: Prevalence of cholinergic urticaria in young adults. *J Am Acad Dermatol* 1994;31: 978–981.
- Zuberbier T, Greaves M, Lennart J, Merk H, Stingl G, Henz B: Management of urticaria: A consensus report. *J Invest Dermatol Symp Proc* 2001;6:128–131.
- Kutting B, Brehler R: Exercise-induced anaphylaxis. *Allergy* 2000;55:585–586.
- Aihara Y, Takahashi Y, Kotoyori T, Mitsuda T, Ito R, Aihara M, Ikezawa Z, Yokota S: Frequency of food-dependent, exercise-induced anaphylaxis in Japanese junior high school students. *J Allergy Clin Immunol* 2001;108:1035–1039.
- Shadick NA, Liang MH, Partridge AJ, Bingham C, Wright E, Fossel AH, Sheffer AL: The natural history of exercise-induced anaphylaxis: Survey results from a 10-year follow-up study. *J Allergy Clin Immunol* 1999;104:123–127.
- Hosey RG, Carek PJ, Goo A: Exercise-induced anaphylaxis and urticaria. *Am Fam Physician* 2001;64:1367–1372.
- Norgaard A, Skov PS, Bindslev-Jensen C: Egg and milk allergy in adults: Comparison between fresh foods and commercial allergen extracts in skin prick test and histamine release from basophils. *Clin Exp Allergy* 1992;22:940–947.
- Maulitz RM, Pratt DS, Schocket AL: Exercise-induced anaphylactic reaction to shellfish. *J Allergy Clin Immunol* 1979;63:433–434.
- Palosuo K, Alenius H, Varjonen E, Koivuluhta M, Mikkola J, Keskinen H, Kalkkinen N, Reunala T: A novel wheat gliadin as a cause of exercise-induced anaphylaxis. *J Allergy Clin Immunol* 1999;103:912–917.
- Harada S, Horikawa T, Ashida M, Kamo T, Nishioka E, Ichihashi M: Aspirin enhances the induction of type I allergic symptoms when combined with food and exercise in patients with food-dependent, exercise-induced anaphylaxis. *Br J Dermatol* 2001;145:336–339.
- Senna G, Mezzelani P, Pacor ML: Anaphylaxis induced by exertion. *Recent Prog Med* 1993; 84:203–209.
- Von Vigier R, Sheffer AL, Pichler WJ: Exercise-induced urticaria and anaphylaxis. *Dtsch Med Wochenschr* 1995;120:1381–1386.
- Hanakawa Y, Tohyama M, Shirakata Y, Murakami S, Hashimoto K: Food-dependent exercise-induced anaphylaxis: A case related to the amount of food allergen ingested. *Br J Dermatol* 1998;138:898–900.
- Aihara Y, Kotoyori T, Takahashi Y, Osuna H, Ohnuma S, Ikezawa Z: The necessity for dual food intake to provoke food-dependent, exercise-induced anaphylaxis (FEIA): A case report of FEIA with simultaneous intake of wheat and umeboshi. *J Allergy Clin Immunol* 2001;107: 1100–1105.
- Marone G, Kagey-Sobotka A, Lichtenstein LM: Effects of arachidonic acid and its metabolites on antigen-induced histamine release from human basophils in vitro. *J Immunol* 1979; 123:1669–1677.
- Bandmann HJ, Kaess H, Langer HD: Mastocytosis simulating a food allergy. *Hautarzt* 1983; 34:217–220.
- Guinpepain MT, Eloit C, Raffard M, Brunet-Moret MJ, Rassemont R, Laurent J: Exercise-induced anaphylaxis: Useful screening of food sensitization. *Ann Allergy Asthma Immunol* 1996;77:491–496.
- Fujimoto S, Kurihara N, Hirata K, Kamimori T, Tanaka S, Takeda T: Successful prophylaxis of wheat-dependent exercise-induced anaphylaxis with terfenadine. *Intern Med* 1995;34: 654–656.
- Warin RP, Smith RJ: Challenge test battery in chronic urticaria. *Br J Dermatol* 1976;94:401–405.
- Genton C, Frei PC, Pecoud A: Value of oral provocation tests to aspirin and food additives in routine investigation of asthma and chronic urticaria. *J Allergy Clin Immunol* 1985;76:40–45.
- Michaelsson G, Juhlin L: Urticaria induced by preservatives and dye additives in food and drugs. *Br J Dermatol* 1973;88:525–532.
- Thune P, Granholt A: Provocation tests with antiphlogistica and food additives in recurrent urticaria. *Dermatologica* 1975;151:360–367.
- Wüthrich B, Fabro L: Acetylsalicylsäure- und Lebensmitteladditiva-Intoleranz bei Urtikaria, Asthma bronchiale und chronischer Rhinopathie. *Schweiz Med Wochenschr* 1981;111: 1445–1450.
- Juhlin L: Recurrent urticaria: Clinical investigation of 330 patients. *Br J Dermatol* 1981; 104:369–381.
- Ortolani C, Pastorello E, Luraghi MT, Della Torre F, Bellani M, Zanussi C: Diagnosis of intolerance to food additives. *Ann Allergy* 1984;53:587–591.
- Rudzi E, Czubalski K, Grzywa Z: Detection of urticaria with food additives intolerance by means of diet. *Dermatologica* 1980;161:57–62.
- Ros AM, Juhlin L, Michaelsson G: A follow-up study of patients with recurrent urticaria and hypersensitivity to aspirin, benzoates and azo dyes. *Br J Dermatol* 1976;95:19–24.
- Verschave A, Stevens E, Degreef H: Pseudoallergen-free diet in chronic urticaria. *Dermatologica* 1983;167:256–259.
- Gibson A, Clancy R: Management of chronic idiopathic urticaria by the identification and exclusion of dietary factors. *Clin Allergy* 1980; 10:699–704.
- Kirchhof B, Hausteil UF, Rytter M: Azetylsalicylsäure-Additiva-Intoleranzphänomene bei chronisch rezidivierender Urtikaria. *Dermatol Monatsschr* 1982;168:513–519.
- Supramaniam G, Warner JO: Artificial food additive intolerance in patients with angio-oedema and urticaria. *Lancet* 1986;ii:907–909.