

# Food intolerance

**Food intolerance** (or **non-allergic food hypersensitivity**) is a detrimental reaction, often delayed, to a food, beverage, **food additive**, or compound found in foods that produces symptoms in one or more body organs and systems, but generally refers to reactions other than **food allergy**. Food allergies are immune reactions, involving mast cells in which food triggers release of **mast cell mediators**, such as **histamine** when the food allergen binds to pre-formed **IgE antibodies** already bound to the mast cell. This mechanism causing allergies to typically give immediate reaction (a few minutes to a few hours) to foods,<sup>[1]</sup> There are numerous causes for other types of food sensitivities, most of which, in contrast to food allergies, cause delayed hypersensitivity reactions to the food.

Food intolerances can be classified according to their mechanism. Intolerance can result from the absence of specific **chemicals** or **enzymes** needed to **digest** a food substance, as in **hereditary fructose intolerance**. It may be a result of an abnormality in the body's ability to absorb nutrients, as occurs in **fructose malabsorption**. Food intolerance reactions can occur to naturally occurring chemicals in foods, as in **salicylate sensitivity**. Drugs sourced from plants, such as aspirin, can also cause these kinds of reactions. Finally, it may be the result of non-IgE-mediated immune responses.

## 1 Definitions

*Non-allergic food hypersensitivity* is the medical name for food intolerance, loosely referred to as *food hypersensitivity*, or previously as *pseudo-allergic reactions*. Non-allergic food hypersensitivity should not be confused with true **food allergies**.<sup>[2][3][4]</sup>

Food intolerance reactions can include **pharmacologic**, **metabolic**, and **gastro-intestinal** responses to foods or food compounds. Food intolerance does not include either **psychological responses**<sup>[4]</sup> or **foodborne illness**.

A non-allergic food hypersensitivity is an abnormal physiological response. It can be difficult to determine the poorly tolerated substance as reactions can be delayed, dose-dependent, and a particular reaction-causing compound may be found in many foods.<sup>[5]</sup>

- Metabolic food reactions are due to **inborn** or **acquired errors of metabolism** of nutrients, such as in **diabetes mellitus**, **lactase deficiency**, **phenylketonuria** and **favism**.

- Pharmacological reactions are generally due to low-molecular-weight chemicals which occur either as natural compounds, such as **salicylates** and amines, or to **food additives**, such as **preservatives**, **colouring**, **emulsifiers** and **taste enhancers**. These chemicals are capable of causing drug-like (biochemical) side effects in susceptible individuals.<sup>[6]</sup>
- Gastro-intestinal reactions can be due to **malabsorption** or other GI Tract abnormalities.
- Immunological responses are mediated by non-IgE immunoglobulins, where the immune system recognises a particular food as a foreign body.
- Toxins may either be present naturally in food, be released by bacteria, or be due to contamination of food products.<sup>[6]</sup> Toxic food reactions are caused by the direct action of a food or substance without immune involvement.<sup>[6]</sup>
- Psychological reactions involve manifestation of clinical symptoms caused not by food but by **emotions** associated with food. These symptoms do not occur when the food is given in an unrecognisable form.<sup>[6]</sup>

**Elimination diets** are useful to assist in the diagnosis of food intolerance. There are specific diagnostic tests for certain food intolerances.<sup>[6][7][8]</sup>

## 2 Signs and symptoms

Non-IgE-mediated food hypersensitivity (food intolerance) is more chronic, less acute, less obvious in its presentation, and often more difficult to diagnose than a food allergy.<sup>[9]</sup> Symptoms of food intolerance vary greatly, and can be mistaken for the symptoms of a **food allergy**. While true allergies are associated with fast-acting immunoglobulin IgE responses, it can be difficult to determine the offending food causing a food intolerance because the response generally takes place over a prolonged period of time. Thus, the causative agent and the response are separated in time, and may not be obviously related. Food intolerance symptoms usually begin about half an hour after eating or drinking the food in question, but sometimes symptoms may be delayed by up to 48 h.<sup>[10]</sup>

Food intolerance can present with symptoms affecting the skin, respiratory tract, **gastrointestinal tract (GIT)** either individually or in combination. On the skin may

include skin rashes, urticaria (hives),<sup>[11]</sup> angioedema,<sup>[12]</sup> dermatitis,<sup>[13]</sup> and eczema.<sup>[14]</sup> Respiratory tract symptoms can include nasal congestion, sinusitis, pharyngeal irritations, asthma and an unproductive cough. GIT symptoms include mouth ulcers, abdominal cramp, nausea, gas, intermittent diarrhea, constipation, irritable bowel syndrome,<sup>[7][8][10]</sup> and may include anaphylaxis.<sup>[14]</sup>

Food intolerance has been found associated with; irritable bowel syndrome and inflammatory bowel disease,<sup>[15]</sup> chronic constipation,<sup>[16]</sup> chronic hepatitis C infection,<sup>[17]</sup> eczema,<sup>[18]</sup> NSAID intolerance,<sup>[19]</sup> respiratory complaints,<sup>[20]</sup> including asthma,<sup>[21]</sup> rhinitis and headache,<sup>[22][23]</sup> functional dyspepsia,<sup>[24]</sup> eosinophilic esophagitis<sup>[10]</sup> and ENT illnesses.<sup>[22][25]</sup>

### 3 Causes

Reactions to chemical components of the diet are more common than true food allergies. They are caused by various organic chemicals occurring naturally in a wide variety of foods, both of animal and vegetable origin more often than to food additives, preservatives, colourings and flavourings, such as sulfites or dyes.<sup>[14]</sup> Both natural and artificial ingredients may cause adverse reactions in sensitive people if consumed in sufficient amount, the degree of sensitivity varying between individuals.

Pharmacological responses to naturally occurring compounds in food, or chemical intolerance, can occur in individuals from both allergic and non-allergic family backgrounds. Symptoms may begin at any age, and may develop quickly or slowly. Triggers may range from a viral infection or illness to environmental chemical exposure. It occurs more commonly in women, which may be because of hormone differences, as many food chemicals mimic hormones.

A deficiency in digestive enzymes can also cause some types of food intolerances. Lactose intolerance is a result of the body not producing sufficient lactase to digest the lactose in milk;<sup>[26][27]</sup> dairy foods which are lower in lactose, such as cheese, are less likely to trigger a reaction in this case. Another carbohydrate intolerance caused by enzyme deficiency is hereditary fructose intolerance.

Celiac disease, an autoimmune disorder caused by an immune response to the protein gluten, results in gluten intolerance and can lead to temporary lactose intolerance.<sup>[28][29]</sup>

The most widely distributed naturally occurring food chemical capable of provoking reactions is salicylate,<sup>[19]</sup> although tartrazine and benzoic acid are well recognised in susceptible individuals.<sup>[30][31][32]</sup> Benzoates and salicylates occur naturally in many foods, including fruits, juices, vegetables, spices, herbs, nuts, tea, wines, and coffee. Salicylate sensitivity causes reactions to not only aspirin and NSAIDs but also foods in which salicylates naturally occur, such as cherries.

Other natural chemicals which commonly cause reactions and cross reactivity include amines, nitrates, sulphites and some antioxidants. Chemicals involved in aroma and flavour are often suspect.<sup>[21][33][34][35]</sup>

The classification or avoidance of foods based on botanical families bears no relationship to their chemical content and is not relevant in the management of food intolerance.

Salicylate-containing foods include apples, citrus fruits, strawberries, tomatoes, and wine, while reactions to chocolate, cheese, bananas, avocado, tomato or wine point to amines as the likely food chemical. Thus, exclusion of single foods does not necessarily identify the chemical responsible as several chemicals can be present in a food, the patient may be sensitive to multiple food chemicals and reaction more likely to occur when foods containing the triggering substance are eaten in a combined quantity that exceeds the patient's sensitivity thresholds. People with food sensitivities have different sensitivity thresholds, and so more sensitive people will react to much smaller amounts of the substance.<sup>[6][10][21][34][35][36][37][38][39][40]</sup>

### 4 Pathogenesis

The term food allergy is widely misused for all adverse reactions to food. Food allergy (FA) is a food hypersensitivity occurring in susceptible individuals, which is mediated by a classical immune mechanism specific for the food itself. The best established mechanism in FA is due to the presence of IgE antibodies against the offending food. Food intolerance (FI) are all other adverse reactions to food. Subgroups of FI are enzymatic (e.g. lactose intolerance due to lactase deficiency), pharmacological (e.g. reactions against biogenic amines, histamine intolerance), and undefined food intolerance (e.g. against some food additives).<sup>[41]</sup> As knowledge of mechanisms and causes of food intolerance improve, nomenclature will be updated.<sup>[42]</sup> There is no worldwide scientific consensus on the pathogenesis of food intolerance.

Food intolerances can be caused by enzymatic defects in the digestive system, can also result from pharmacological effects of vasoactive amines present in foods (e.g. Histamine),<sup>[7]</sup> among other metabolic, pharmacological and digestive abnormalities.

A frequent misconception among the public is confusion between cow's milk allergy (CMA) and cow's milk intolerance, which is usually intolerance to lactose. There are at least two, and possibly more, distinct pathologies. Hypersensitivity to milk is often broadly classified into immunoglobulin E (IgE)-mediated allergy and non-IgE-mediated intolerance. The immunopathological mechanisms of non-IgE-mediated intolerance in particular remain poorly understood, and this has hindered the development of simple and reliable diagnostics. Adults

with non-IgE-mediated intolerance to milk tend to suffer ongoing reactions without the development of tolerance. The precise immunopathological mechanisms of non-IgE-mediated intolerance remain unclear. A number of mechanisms have been implicated, including type-1 T helper cell (Th1) mediated reactions, the formation of immune complexes leading to the activation of Complement, or T-cell/mast cell/neuron interactions inducing functional changes in smooth muscle action and intestinal motility. Food antigens contact the immune system throughout the intestinal tract via the **gut associated lymphoid tissue** (GALT), where interactions between antigen presenting cells and T cells direct the type of immune response mounted. Unresponsiveness of the immune system to dietary antigens is termed “oral tolerance” and is believed to involve the deletion or switching off of reactive antigen-specific T cells and the production of regulatory T cells (T reg) that quell inflammatory responses to benign antigens. In the case of IgE-mediated allergies, a deficiency in regulation and a polarisation of specific effector T cells towards type-2 T helper cells (Th2) lead to signalling of B-cells to produce milk protein-specific IgE. Whereas non-IgE-mediated reactions (intolerances) may be due to Th1 mediated inflammation. Dysfunctional T reg cell activity has been identified as a factor in both allergy/ intolerance mechanisms.<sup>[43]</sup>

## 5 Diagnosis

Diagnosis of food intolerance can include **hydrogen breath testing for lactose intolerance and fructose malabsorption**, professionally supervised **elimination diets**, and ELISA testing for IgG-mediated immune responses to specific foods. It is important to be able to distinguish between food allergy, food intolerance, and autoimmune disease in the management of these disorders.<sup>[44]</sup> Non-IgE-mediated intolerance is more chronic, less acute, less obvious in its clinical presentation, and often more difficult to diagnose than allergy, as skin tests and standard immunological studies are not helpful.<sup>[9]</sup> Elimination diets must remove all poorly tolerated foods, or all foods containing offending compounds. Clinical investigation is generally undertaken only for more serious cases, as for minor complaints which do not significantly limit the person’s lifestyle the cure may be more inconvenient than the problem.<sup>[6]</sup>

The Hemocode Food Intolerance System and Rocky Mountain Analytical Food Allergy Test are unvalidated yet heavily marketed examples of ELISA testing of IgG4 to foods. IgG4 against foods indicates that the person has been repeatedly exposed to food proteins recognized as foreign by the immune system. However, its presence should not be considered a factor which induces intolerance. Food-specific IgG4 does not indicate food allergy or intolerance, but rather a normal physiological response of the immune system after exposure to food

components.<sup>[45]</sup> Although elimination of foods based on IgG-4 testing in IBS patients resulted in an improvement in symptoms,<sup>[46]</sup> the positive effects of food elimination were more likely due to wheat and milk elimination than IgG-4 test-determined factors.<sup>[47]</sup> The IgG-4 test specificity is questionable as healthy individuals with no symptoms of food intolerance also test positive for IgG-4 to several foods.<sup>[48]</sup>

Diagnosis is made using medical history and cutaneous and serological tests to exclude other causes, but to obtain final confirmation a Double Blind Controlled Food Challenge must be performed.<sup>[7]</sup> Treatment can involve long-term avoidance,<sup>[49]</sup> or if possible re-establishing a level of tolerance.

The **antigen leukocyte cellular antibody test** (ALCAT) has been commercially promoted as an alternative, but has not been reliably shown to be of clinical value.<sup>[50][51][52]</sup>

## 6 Prevention

There is emerging evidence from studies of cord bloods that both sensitization and the acquisition of tolerance can begin in pregnancy, however the window of main danger for sensitization to foods extends prenatally, remaining most critical during early infancy when the immune system and intestinal tract are still maturing. There is no conclusive evidence to support the restriction of dairy intake in the maternal diet during pregnancy in order to prevent. This is generally not recommended since the drawbacks in terms of loss of nutrition can outweigh the benefits. However, further randomised, controlled trials are required to examine if dietary exclusion by lactating mothers can truly minimize risk to a significant degree and if any reduction in risk is outweighed by deleterious impacts on maternal nutrition.<sup>[43]</sup>

A Cochrane review has concluded feeding with a soy formula cannot be recommended for prevention of allergy or food intolerance in infants. Further research may be warranted to determine the role of soy formulas for prevention of allergy or food intolerance in infants unable to be breast fed with a strong family history of allergy or cow’s milk protein intolerance.<sup>[53]</sup> In the case of allergy and celiac disease others recommend a dietary regimen is effective in the prevention of allergic diseases in high-risk infants, particularly in early infancy regarding food allergy and eczema. The most effective dietary regimen is exclusively breastfeeding for at least 4–6 months or, in absence of breast milk, formulas with documented reduced allergenicity for at least the first 4 months, combined with avoidance of solid food and cow’s milk for the first 4 months.<sup>[54][55]</sup>

## 7 Management

Individuals can try minor changes of diet to exclude foods causing obvious reactions, and for many this may be adequate without the need for professional assistance. For reasons mentioned above foods causing problems may not be so obvious since food sensitivities may not be noticed for hours or even days after one has digested food. Persons unable to isolate foods and those more sensitive or with disabling symptoms should seek expert medical and dietitian help. The dietetic department of a teaching hospital is a good start. (see links below)

Guidance can also be given to your general practitioner to assist in diagnosis and management. Food elimination diets have been designed to exclude food compounds likely to cause reactions and foods commonly causing true allergies and those foods where enzyme deficiency cause symptoms. These elimination diets are not everyday diets but intended to isolate problem foods and chemicals. Avoidance of foods with additives is also essential in this process.

Individuals and practitioners need to be aware that during the elimination process patients can display aspects of food addiction, masking, withdrawals, and further sensitization and intolerance. Those foods that an individual considers as 'must have every day' are suspect addictions, this includes tea, coffee, chocolate and health foods and drinks, as they all contain food chemicals. Individuals are also unlikely to associate foods causing problems because of masking or where separation of time between eating and symptoms occur. The elimination process can overcome addiction and unmask problem foods so that the patients can associate cause and effect.

It takes around five days of total abstinence to unmask a food or chemical, during the first week on an elimination diet withdrawal symptoms can occur but it takes at least two weeks to remove residual traces. If symptoms have not subsided after six weeks, food intolerance is unlikely to be involved and a normal diet should be restarted. Withdrawals are often associated with a lowering of the threshold for sensitivity which assists in challenge testing, but in this period individuals can be ultra-sensitive even to food smells so care must be taken to avoid all exposures.

After two or more weeks if the symptoms have reduced considerably or gone for at least five days then challenge testing can begin. This can be carried out with selected foods containing only one food chemical, to isolate it if reactions occur. In Australia, purified food chemicals in capsule form are available to doctors for patient testing. These are often combined with placebo capsules for control purposes. This type of challenge is more definitive. New challenges should only be given after 48 hours if no reactions occur or after five days of no symptoms if reactions occur.

Once all food chemical sensitivities are identified a dietitian can prescribe an appropriate diet for the individ-

ual to avoid foods with those chemicals. Lists of suitable foods are available from various hospitals and patient support groups can give local food brand advice. A dietitian will ensure adequate nutrition is achieved with safe foods and supplements if need be.

Over a period of time it is possible for individuals avoiding food chemicals to build up a level of resistance by regular exposure to small amounts in a controlled way, but care must be taken, the aim being to build up a varied diet with adequate composition.<sup>[61][151][161][441][561][571][581]</sup>

## 8 Prognosis

The prognosis of children diagnosed with intolerance to milk is good: patients respond to diet which excludes cow's milk protein and the majority of patients succeed in forming tolerance.<sup>[59]</sup> Children with non-IgE-mediated cows milk intolerance have a good prognosis, whereas children with IgE-mediated cows milk allergy in early childhood have a significantly increased risk for persistent allergy, development of other food allergies, asthma and rhinoconjunctivitis.<sup>[60]</sup>

A study has demonstrated that identifying and appropriately addressing food sensitivity in IBS patients not previously responding to standard therapy results in a sustained clinical improvement and increased overall well being and quality of life.<sup>[58]</sup>

## 9 Epidemiology

Estimates of the prevalence of food intolerance vary widely from 2% to over 20% of the population.<sup>[61]</sup> So far only three prevalence studies in Dutch and English adults have been based on double-blind, placebo-controlled food challenges. The reported prevalences of food allergy/intolerance (by questionnaires) were 12% to 19%, whereas the confirmed prevalences varied from 0.8% to 2.4%. For intolerance to food additives the prevalence varied between 0.01 to 0.23%.<sup>[62]</sup>

Food intolerance rates were found to be similar in the population in Norway. Out of 4,622 subjects with adequately filled-in questionnaires, 84 were included in the study (1.8%) Perceived food intolerance is a common problem with significant nutritional consequences in a population with IBS. Of these 59 (70%) had symptoms related to intake of food, 62% limited or excluded food items from the diet. Tests were performed for food allergy and malabsorption, but not for intolerance. There were no associations between the tests for food allergy and malabsorption and perceived food intolerance, among those with IBS. Perceived food intolerance was unrelated to musculoskeletal pain and mood disorders.<sup>[63]</sup>

According to the RACP working group, "Though not considered a "cause" of CFS, some patients with chronic

fatigue report food intolerances that can exacerbate symptoms.”<sup>[64]</sup>

## 10 History

In 1978 Australian researchers published details of an 'exclusion diet' to exclude specific food chemicals from the diet of patients. This provided a basis for challenge with these additives and natural chemicals. Using this approach the role played by dietary chemical factors in the pathogenesis of chronic idiopathic urticaria (CIU) was first established and set the stage for future DBPCT trials of such substances in food intolerance studies.<sup>[65][66]</sup>

In 1995 the European Academy of Allergology and Clinical Immunology suggested a classification on the basis of the responsible pathogenetic mechanism; according to this classification, non-toxic reactions can be divided into 'food allergies' when they recognize immunological mechanisms, and 'food intolerances' when there are no immunological implications. Reactions secondary to food ingestion are defined generally as 'adverse reactions to food'.<sup>[67]</sup>

In 2003 the Nomenclature Review Committee of the World Allergy Organization issued a report of revised nomenclature for global use on food allergy and food intolerance, that has had general acceptance. Food intolerance is described as a 'non allergic hypersensitivity' to food.<sup>[68]</sup>

## 11 Society and culture

In the UK, scepticism about food intolerance as a specific condition influenced doctors' (GPs') perceptions of patients and of the patients' underlying problems. However, rather than risk damaging the **doctor-patient relationship**, GPs chose - despite their scepticism and guided by an element of awareness of the limitations of modern medicine - to negotiate mutually acceptable ground with patients and with patients' beliefs. As a result, whether due to a placebo effect, a secondary benefit, or a biophysical result of excluding a food from the diet, the GPs acknowledge both personal and therapeutic benefits.<sup>[61]</sup>

In the Netherlands, patients and their doctors (GPs) have different perceptions of the efficacy of diagnostic and dietary interventions in IBS. Patients consider food intolerance and GPs regard lack of fibre as the main etiologic dietary factor. GPs should explore the patients' expectations and incorporate these in their approach to IBS patients.<sup>[69]</sup>

New food labeling regulations were introduced into the USA and Europe in 2006,<sup>[70]</sup> which are said to benefit people with intolerances.<sup>[71]</sup> In general, food-allergic consumers were not satisfied with the current labelling

practices.<sup>[72]</sup> In the USA food companies propose distinguishing between food allergy and food intolerance and use a mechanism-based (i.e., immunoglobulin-E-mediated), acute life-threatening anaphylaxis that is standardized and measurable and reflects the severity of health risk, as the principal inclusion criterion for food allergen labeling.<sup>[73]</sup> Symptoms due to, or exacerbated by, food additives usually involve non-IgE-mediated mechanisms (food intolerance) and are usually less severe than those induced by food allergy, but can include anaphylaxis.<sup>[14]</sup>

## 12 Research directions

A Low **FODMAP** diet now has an evidence base sufficiently strong to recommend its widespread application in conditions such as **IBS** and **IBD**.<sup>[74]</sup> Restriction of Fermentable Oligo-, Di- and Mono- saccharides and Polyols globally, rather than individually, controls the symptoms of functional gut disorders (e.g. IBS), and the majority of IBD patients respond just as well. It is more successful than restricting only Fructose and Fructans, which are also FODMAPs, as is recommended for those with **Fructose malabsorption**. Longer term compliance with the diet was high.

A randomised controlled trial on IBS patients found relaxing an IgG-mediated food intolerance diet led to a 24% greater deterioration in symptoms compared to those on the elimination diet and concluded food elimination based on IgG antibodies may be effective in reducing IBS symptoms and is worthy of further biomedical research.<sup>[75]</sup>

Intestinal or bowel hyperpermeability, so called **leaky gut**, has been linked to food allergies<sup>[76]</sup> and some food intolerances.<sup>[77][78]</sup> Research is currently focussing on specific conditions<sup>[79][80][81]</sup> and effects of certain food constituents.<sup>[82][83][84]</sup> At present there are a number of ways to limit the increased permeability, but additional studies are required to assess if this approach reduces the prevalence and severity of specific conditions.<sup>[78][82]</sup>

## 13 See also

- **Sucrose intolerance**
- **Fructose intolerance**
- **Fructose malabsorption**
- **Lactose intolerance**
- **Egg intolerance**
- **Gluten sensitivity**
  - **Gluten-sensitive enteropathy**

- Salicylate sensitivity
- Sodium phosphates
- Drug intolerance
- Elimination diet
- Milk soy protein intolerance

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## 15 External links

- Food Intolerance Awareness from British Allergy Foundation

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