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# Diagnosis and Elimination Diets in Pediatric Food Allergy vs Sensitization

From Theory to Practice

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## **ABSTRACT**

Food allergy is an increasing health problem, especially among children with atopic dermatitis, in which food sensitization (specific IgE antibodies without clinical relevance) is also common. Its management can be challenging, and may lead to overdiagnosis and overtreatment. In order to compare theoretical attitude and actual clinical practice, we did a literature search and conducted a small study and survey. In the study we obtained 25 children with atopic dermatitis and food sensitizations but no clear symptoms of IgE-mediated food allergy at referral to our service (Allergy and Respiratory Disease section of the Pediatrics service in External Examination Rooms of Araba University Hospital - HUA CCEE). An important proportion of them had had unjustified referral (28%), unjustified IgE screening (48%) and unjustified therapeutic elimination diet (40%). Besides, nearly all (96.67%) performed oral food challenges were negative. We conclude that there may be overdiagnosis and overtreatment of food sensitizations in children with atopic dermatitis referred to our service. Moreover, sensitizations should always be confirmed by an appropriate diagnostic test (usually an oral food challenge), probably sooner than we are doing nowadays. Likewise, sensitizations alone should not be an indication for therapeutic elimination diets, despite being often viewed as safe and prudent in doubtful cases, as those diets imply potential risks such as loss of tolerance, nutritional deficiencies and patient and parent preoccupation.

## **KEY WORDS**

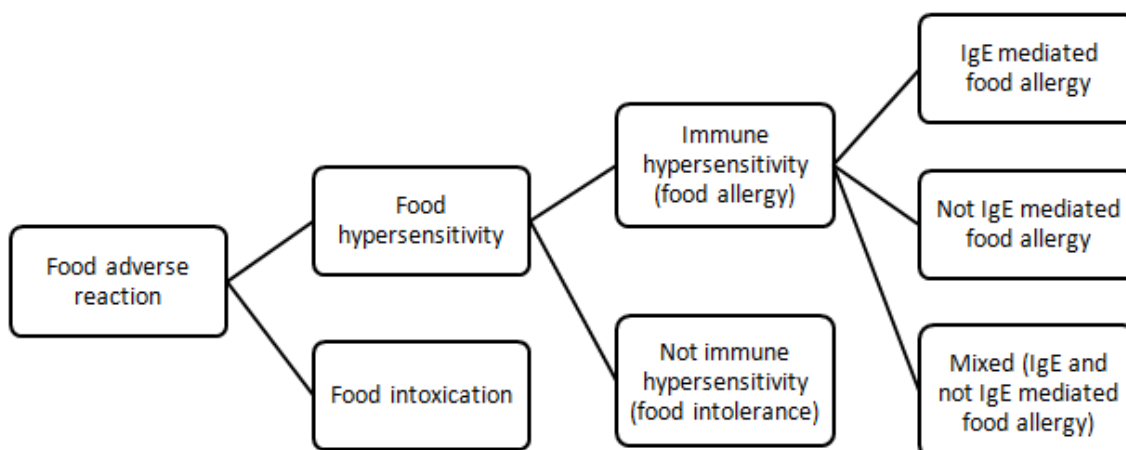
"food allergy", "food sensitization", "IgE-mediated", "food allergy management", "elimination diet", "atopic dermatitis".

## 1. BACKGROUND

### 1.1. GENERAL OVERVIEW

An adverse reaction to food ingestion is a very common event. It can happen to anyone if the food is in poor conditions (food intoxication), but sometimes certain food is harmless to some people while affecting others (food hypersensitivity). This last event is an increasing healthcare problem<sup>1,2,3,4</sup>, especially among children; it is estimated that 1-3% of adult population and 6-8% of less than 4 year-old children are affected<sup>1,3</sup>.

Food hypersensitivity can be classified by the type of reaction responsible for the adverse effect: immune response (food allergy) or not-immune response (formerly known as food intolerance)<sup>1,5,6,7</sup>, as we can see in **Figure 1**.



**Figure 1. Classification of food adverse reactions.** Adapted from References 1, 5, 6 and 7.

#### 1.1.1. Immune hypersensitivity (food allergy)

The reaction is dose-independent, and it can involve IgE antibodies (type I hypersensitivity reaction) or not (type III-IV hypersensitivity reactions).

#### 1.1.1.1. IgE mediated food allergy

The symptoms appear in less than 2 hours from the ingestion, and can be cutaneous (urticaria, angioedema, atopic dermatitis), digestive (oral, perioral and/or faringeal itchiness, erythema and swelling, dysphagia, vomiting, diarrhea, abdominal pain), respiratory (rhinitis, cough, dysphonia, bronchospasm, asthma) or general (hypotension, cardiorespiratory arrest), and if more than two organs are affected simultaneously it is called anaphylaxis<sup>1,2,5,6</sup>.

These IgE reactions can be potentially life-threatening in a short period of time, so they require diets that strictly avoid the culprit foods (usually milk, egg, peanut, tree nuts, shellfish and fish<sup>3</sup>). This is the main reaction type that we will discuss.

#### 1.1.1.2. Not IgE mediated food allergy

The patient reacts to the food with an immune response that does not include specific IgE antibodies. The symptoms appear in more than 2 hours from the ingestion, and are usually gastrointestinal, mild and not life-threatening in the short-term. They generally appear in less than 6 month-old infants and are commonly self-limited, so elimination diets can be recommended but they can be less strict<sup>2</sup>.

#### 1.1.1.3. Mixed (IgE and not IgE mediated food allergy)

In some cases we can have both types of food allergy at the same time, as it may be the case of atopic dermatitis (discussed in section "1.4. Allergy risk factor: atopic dermatitis" of this paper).

### **1.1.2. Not immune hypersensitivity (food intolerance)**

The reaction is dose-dependent, and can be due to an enzymatic defect, pharmacological interactions, an irritating food (like spicy or hot food)... or to functional and behavioural factors<sup>5,7</sup>, and will not be discussed in this paper.

## **1.2. IgE MEDIATED ALLERGY FORMATION**

This allergy is an overreaction to a protein contained in a specific food, otherwise harmless to others, due to a mistake in the immune tolerance of a susceptible patient<sup>5</sup>.

### **1.2.1. Process**

#### 1.2.1.1. Sensitization phase

The process starts when the patient's organism contacts with the culprit protein for the first time. The immune system detects the protein as foreign and dangerous, and therefore creates specific IgE antibodies against an specific site of the culprit protein that the food contains (called antigen). At this point, the patient has specific IgE antibodies but no symptoms, so the patient is sensitized to the food.

The sensitization can happen via ingestion or inhalation of the allergen<sup>5</sup>:

- Via ingestion: this is the way of the type-I antigens, thermoresistant and stable proteins that are not affected by the digestion or cooking process, and usually cause more severe symptoms.
- Via inhalation: this is the way of type-II antigens, thermolabile and commonly destroyed during digestion or cooking, and usually cause milder and not-systemic symptoms<sup>7,8,9</sup>.

#### 1.2.1.2. Effector phase

In the second time the patient contacts with the culprit antigen, the specific IgE antibodies may bind to it and also to mastocytes and basophils, activating them and provoking their degranulation, causing the mentioned symptoms in less than 2h from the contact with the antigen<sup>5</sup>.

#### 1.2.1.3. Chronic phase

The repetition of effector phases due to continued contact with the culprit antigen can result in tissue infiltration by immune cells (eosinophils, neutrophils and T-helper lymphocytes), causing structural changes with tissue fibrosis and malfunction<sup>5</sup>.

#### 1.2.1.4. Considerations

Nevertheless, the sensitization phase does not always proceed to the effector phase; in fact, sensitization to many food antigens without effector phase symptoms is common, especially among children<sup>6</sup>.

Moreover, it is also frequent that one antigen, typically an inhaled or airborne type-II allergen, is molecularly similar to other antigens, inducing the formation of IgE antibodies that react with the original antigen but also with those similar to it<sup>1,9</sup>. Actually, it is estimated that 60% of food allergies in older children and adults are linked with an inhalant allergy<sup>9</sup>. This process is called cross-reactivity, and can be a source of multiple sensitizations that do not necessarily mean a progression to the effector phase and thus an actual food allergy.

#### 1.2.2. Food allergy vs sensitization

Summarizing, in an IgE mediated food allergy the patient has produced specific IgE antibodies against certain food's antigen. Those IgE antibodies can react to the food's antigen when ingested and produce symptoms (actual food allergy) or exist but not produce any symptoms when the culprit food is ingested (food sensitization). Therefore, in the case of food sensitization the patient can safely eat said food despite having specific IgE antibodies against it, and does not require any elimination diet.

This is especially relevant if we take into account the alteration of the quality of life an elimination diet implies: constant food label review, fear of eating third-person made meals (at restaurants or school), keeping up the guard for possible reactions, limitation of the diet and food curiosity (especially relevant in growing children)...<sup>1,2</sup> Thus, it is essential that we differentiate food allergy and sensitization, to ensure that we do not prescribe unnecessary elimination diets.

### 1.3. DIAGNOSIS OF FOOD ALLERGY AND SENSITIZATION

#### 1.3.1. IgE antibody detection tests: types

The presence of IgE antibodies can be detected in many ways, but these are the main and most used ones:



#### 1.3.1.1. Laboratory IgE detection

This in vitro test is based on a blood-sample extraction and the laboratory detection of the IgE antibodies in the serum of the patient.

We can detect the specific IgE against a certain antigen (IgE for selected components or s-IgE), the IgE antibodies against a certain whole food (which will be the sum of all the s-IgE antibodies against all known and detectable antigens of said food) and the total amount of IgE (against all antigens, not only food-induced ones, usually a non-specific fact)<sup>7,10</sup>.

Nowadays, with microarray technology and allergen panels, we can detect many specific IgE antibodies at the same time<sup>7,10</sup>, but this kind of tests is not recommended as a screening method for the high rates of clinical false-positives which could lead to diagnostic issues and unnecessary dietary eliminations<sup>2,9</sup>.

#### 1.3.1.2. Prick test

In this in vivo test, the antigen is injected just below the epidermis using a needle, and the skin reaction is evaluated. If the patient has specific IgE antibodies against that antigen, the mastocytes and basophils in his or her tissue will degranulate and create a wheal in the injection site of the skin<sup>2,10</sup>.

The injected antigen-containing solution can be a standard extract (commercially made, with all the antigens of a certain food or with only one of them) or a sample of the suspected food that the patient brings ("prick-prick")<sup>9</sup>.

#### 1.3.1.3. Others

Aside from these IgE detection tests, there are other ones less used in allergy: in vitro tests (Basophil Activation Test), in vivo tests (intradermal test and patch test) and not-validated ones (IgG detection, cytotoxic test, hair analysis, iridology, kinesiology, electrodermal testing...).

### **1.3.2. IgE antibody detection tests: interpretation**

On the one hand, an specific IgE detection test is considered negative if its  $<0.35$  kU/L (for laboratory detection)<sup>11</sup> and/or  $<3$ mm in diameter (for prick-tests)<sup>2,10</sup>,

whereas higher results are considered positive. On the other hand, the illustrative cutoff point where a test is considered very likely to have clinical relevance (Positive Predictive Value or PPV  $\geq 95\%$ ) varies with the different allergens (see **Table 1**).

Both laboratory IgE detection and prick-tests have a relatively high negative predictive value ( $>90\%$ )<sup>2,3,4</sup> but a low positive predictive value ( $<50\%$ )<sup>2,4</sup> due to possible cross-reactivity, which indicates that only suspected food allergens should be tested in order to avoid false positives (sensitizations with no clinical allergy)<sup>2,4</sup>. We should take into account that these tests only detect sensitization (the presence of specific IgE antibodies) and directly relate to the likelihood of symptom onset<sup>2</sup>, but do not predict clinical hypersensitivity or its severity<sup>2,3,7,9,12,13</sup>.

**Table 1. Specific IgE detection tests' illustrative cutoff points.** The level at which it is considered very likely to have clinical relevance (Positive Predictive Value or PPV  $\geq 95\%$ ) has been proposed for the most common foods involved in food allergy, and varies between allergen types and patient age. Adapted from References 2, 3 and 8.

Allergen	Specific IgE level (PPV $\geq 95\%$ )	Prick-test (PPV $\geq 95\%$ )
Cow's milk	$\geq 15$ kU/L (5 kU/L in $\leq 2$ year-olds)	$\geq 8$ mm
Hen egg white	$\geq 7$ kU/L (2 kU/L in $\leq 2$ year-olds)	$\geq 7$ mm
Peanut	$\geq 14$ kU/L	$\geq 8$ mm
Wheat	$\geq 26$ kU/L	-
Soybean	$\geq 30$ kU/L	-
Fish	$\geq 20$ kU/L	-
Tree nuts	$\geq 15$ kU/L	-

### 1.3.3. Oral food challenge or provocation test

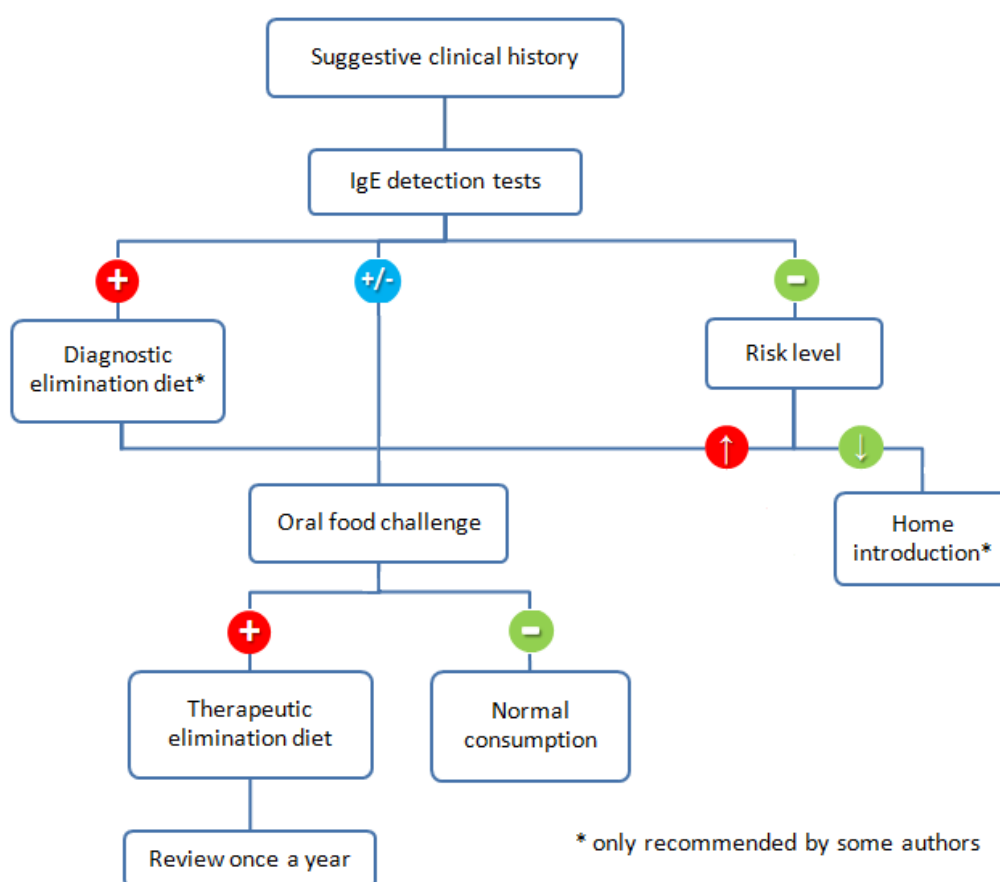
It consists on giving the culprit food to the patient for ingestion, in increasing amounts (doses determined by the type of food and type of patient) at 15-30min intervals, until the top dose has been reached or an adverse reaction appears. In all cases, an observational period of at least 2 hours must be kept after the last dose<sup>13</sup>.

It is used to determine if there is an actual adverse reaction to the suspected food, and also establish the threshold value at where it appears (indicates patient sensitivity)<sup>13</sup>.

As it is potentially dangerous, it must be carried out in a controlled environment, with trained healthcare professionals and appropriate equipment for possible adverse reactions, especially anaphylaxis<sup>3,7</sup>. Although double blind test is the way to go in adults and older children, an open challenge is usually sufficient in infants and younger children<sup>13</sup>.

### 1.3.4. Diagnostic algorithm

We designed a summarized algorithm for the food allergy diagnostic process recommended by recent studies<sup>1,2,3,4,9,12,14</sup>, shown in **Figure 2**. Each step's characteristics and indications are explained below.



**Figure 2. General diagnostic algorithm for food allergies.** Adapted from References 1, 2, 3, 4, 9, 12, 14.

- Clinical history: in case of an adverse reaction suspicion, a detailed anamnesis must be developed exhaustively, documenting the symptoms that appeared, the context (looking for other foods and possible cofactors like exercise, infections, drugs...), time of latency between ingestion and reaction, other exposures to said food... as well as a physical exam, to determine if a food allergy is suspected<sup>1</sup>. If so, it is considered a suggestive clinical history and the diagnostic algorithm should be started.
- IgE detection tests: after the determination of a suggestive clinical history, IgE detection tests (laboratory IgE detection and prick tests) are carried out to evaluate the presence of specific IgE antibodies against the suspected food<sup>1</sup>. We should take into account that most of the specific IgE detection test results are usually uncertain (higher than the negative cut-point and lower than the PPV  $\geq 95\%$ )<sup>14</sup>.
- Diagnostic elimination diet: a diet that avoids the suspected food can be sometimes recommended for diagnostic purposes, especially if there are positive specific IgE detection tests as well as chronic gastrointestinal or skin reactions (namely, atopic dermatitis)<sup>3</sup>, but should always have a defined objective and be limited to 2 weeks and followed by an oral food challenge<sup>3,4,12,14</sup>. If there is an actual food allergy, significant clinical improvement usually happens<sup>14</sup>.
- Oral food challenge: it is the gold standard of diagnostics, and must be carried out to confirm a food allergy, especially if the clinical history is suggestive but both the IgE detection tests are negative or not concluding<sup>1,4,9</sup>. It is relatively contraindicated if the suspected reaction has been life-threatening<sup>12,13</sup>, and the doses and timing must be determined according to its severity<sup>12</sup>, but it is stated that all suspected allergies should be confirmed by an oral food challenge<sup>3,9</sup>.
- Home introduction: if the clinical history is suggestive but the IgE detection tests are negative and the risk is low, some authors defend the possibility of consuming the suspected food at home<sup>2</sup>, and not in an oral food challenge.
- Therapeutic elimination diet: it should be established only if the food allergy is confirmed by an oral food challenge, and not only based on a suggestive clinical history and positive IgE detection tests<sup>3,9,14</sup>.

- Review: as a tolerance is often acquired over time<sup>3,14,15</sup>, it is advisable to repeat the sequence once a year in order to confirm that the food allergy still exists<sup>3</sup>.
- Normal consumption: if a food allergy is ruled out, the suspected food can be consumed. Furthermore, if there is a sensitization (specific IgE antibodies against the food), usual consumption (at least once every 2 weeks) is highly recommended for the maintenance of tolerance and reduction of anaphylactic risk<sup>4</sup>. In this sense, if a food the patient is sensitized to has not been consumed in more than 2 weeks, an oral food challenge is recommended for the checking of the tolerance maintenance<sup>4</sup>.

#### **1.4. ALLERGY RISK FACTOR: ATOPIC DERMATITIS**

Atopic dermatitis is the most common inflammatory skin disease in children (incidence of 15-30% in childhood in industrialized countries<sup>4,15</sup>), and it is considered the major risk factor for the development of food allergies<sup>14</sup>. The pathogenesis is multifactorial, but the key point appears to be the defective skin barrier which allows the penetration of allergens and therefore leads to cutaneous sensitization<sup>4,15</sup>.

In this sense, we find that the prevalence of allergy and sensitization is higher in patients with atopic dermatitis<sup>4,14</sup>, both to airborne allergens (with their classical cross-reactivity) and to foods (10 to 20% of allergy in patients with atopic dermatitis<sup>14</sup>, as opposed to the 1 to 3% in the general population<sup>1,3</sup>). The most frequent foods to which atopic patients are sensitized and allergic to are hen egg white, cow's milk and peanut<sup>4,15</sup>. Besides, the severity of the atopic dermatitis appears to be directly related to the prevalence of food allergy<sup>4,14</sup>.

Moreover, these patients can develop into the "atopic march", in which there is a progression of allergic disorders from early atopic dermatitis to food allergy or sensitization and respiratory symptoms (allergic rhinitis and asthma)<sup>4</sup>. Nevertheless, we should remark that up to 65% of children with atopic dermatitis do not show sensitization<sup>15</sup>.

### **1.4.1. Types of allergic reactions**

In these patients, food allergens can produce two types of reactions:

#### **1.4.1.1. Immediate (type I hypersensitivity)**

The typical IgE-mediated reaction (urticaria, flushing, dysphagia, asthma...), occurring within 2h of ingestion<sup>4</sup>. In this sense, the suspected food has to have been recently introduced into the diet<sup>14</sup>; therefore, we assume that foods that have been previously often eaten and well-tolerated are not responsible for a newly appeared outbreak (despite the possibility of being sensitized to them), especially if there has been a period in which the food was consumed and the skin was clear<sup>14</sup>.

#### **1.4.1.2. Delayed (type IV hypersensitivity)**

Flares of eczema (exacerbation of the atopic dermatitis) that appear 6-48h after the ingestion<sup>4</sup>. Evidence suggests this type of reaction is not very common, but when it occurs a significant skin improvement upon an elimination diet takes place<sup>4,6</sup>. As it is presumably not IgE-mediated, IgE detection tests are not valid for the confirmation of this type of reaction, and therefore it can only be proven by skin improvement upon an elimination diet or by an oral food challenge<sup>4,6</sup>.

Nevertheless, specific IgE levels are thought to be indirectly linked to this kind of hypersensitivity reaction, and so they can be evaluated in cases of moderate to severe atopic dermatitis after optimal skin care has been taken<sup>4</sup>. We should evaluate foods that are frequently consumed (by the patient or the mother if breastfed) and commonly related (such as egg and cow's milk)<sup>15</sup>, as these are the ones most prone to be the cause of the delayed reaction.

### **1.4.2. Diagnostic precautions**

As we know, sensitization does not necessarily mean clinical reactivity (actual food allergy): it is estimated that 50 to 80% of patients with atopic dermatitis have food sensitizations, of which only 10 to 20% are actual food allergies (mostly immediate reactions)<sup>4,14</sup>.

Besides, the diagnosis can be further challenged by the variable course of the atopic dermatitis (with the alternation of milder and more severe periods)<sup>4,15</sup>, skin reactions to other triggers (irritants, airborne allergens, bacteria...), overall higher IgE levels... and also by the high parent and patient perception of food triggers (which interestingly decreases when optimal skin care is taken)<sup>4</sup>. In this sense, it has been shown that many families attempt elimination diets without medical direction<sup>4</sup>.

Due to the known high clinical false-positive rate of specific IgE detection tests (meaning there is no clinical reaction), it has been shown that IgE screening (specific IgE detection without an specific clinical suspicion) has little utility in determining the probability of developing an IgE-mediated food allergy<sup>4,9</sup>. Thus, the allergy diagnosis process should only take place in these situations:

- Evidence of an immediate reaction after food ingestion: testing is strongly recommended<sup>4</sup>.
- Moderate to severe atopic dermatitis after optimal skin care: testing should be considered, in order to identify potential trigger foods of a delayed reaction<sup>4</sup>.

### **1.4.3. Potential risks of elimination diets**

It may seem harmless and even prudent to establish an elimination diet upon allergy suspicion (for example, if a sensitization is detected), but there are some potential risks to be considered:

#### **1.4.3.1. Nutritional deficiencies**

Studies show that children with atopic dermatitis and food allergies are at significant risk of growth deficiency<sup>4</sup>, especially younger ones and those with cow milk elimination diets (which are associated to slower growth, decreased expected height and decreased nutritional intake of calcium)<sup>4</sup>. On this matter, it is important to reassure that this potential risk can be overcome with adequate dietary supplementation, close monitoring and consideration for referral to a dietician<sup>2,4</sup>.

#### 1.4.3.2. Patient and parent preoccupation

The diagnosis of a food allergy and the establishment of an elimination usually lead to an important amount of worry and work for the patient's environment, with constant reading of labels, anxiety and limitations when eating out or at school...<sup>2</sup>

#### 1.4.3.3. Loss of tolerance

When a patient has a food sensitization but usually consumes that food (without an actual food allergy, because there is clinical tolerance), an elimination diet of said food can lead to a loss of that tolerance and the development of an actual food allergy (even anaphylaxis) upon food reintroduction<sup>4</sup>. Studies show that this can happen in 19-50% of patients who undergo elimination diets with previous tolerance, and can develop in as fast as 14 days of elimination diet<sup>4</sup>. This is the reason why diagnostic elimination diets should not exceed this period of time.

#### 1.4.3.4. Late introduction of foods

If a food allergy is suspected but not proven (as in a patient with atopic dermatitis, in which allergies are more frequent but not certain), it has been commonly thought that a delay in the dietary introduction of said food would mean better future tolerance. Nowadays, the opposite has been observed and is recommended: early introduction of common allergenic foods is now recommended<sup>2,3,4</sup>, as avoidance in high-risk newborns (like those with severe atopic dermatitis or allergies in first-degree relatives) has not proven to be effective<sup>3,4</sup>. Moreover, studies on peanut allergy have even shown benefit (a significant decrease in allergy) with its early introduction as opposed to strict avoidance, as well as not affecting the severity or duration of the atopic dermatitis<sup>4</sup>.

#### 1.4.3.5. Neglecting of the skin care

In some cases, an elimination diet could be considered a sufficient treatment and lead to a decrease in the attention to skin care, which usually means a worsening of the atopic dermatitis and potential epidermal barrier dysfunction, opening the door to new potential cutaneous sensitizations<sup>4</sup>. In fact, it has been shown that skin care



treatment of high risk infants with hydrating lotions since the moment of birth reduces the likelihood of atopic dermatitis and food sensitizations<sup>1</sup>.

Thus, we can conclude that a valid and coherent allergy suspicion should always be confirmed with the proper diagnostic algorithm, and no elimination diet should be established in atopic patients based solely on their sensitizations<sup>9</sup>.

## **2. OBJECTIVES**

The main factors that led to this paper are the fact that food allergy is an increasing health problem, that its perception seems to be overestimated by the population and that its diagnosis can be challenging. These facts lead up to a notable chance of misdiagnosis and overtreatment, with the usual elimination diets (and their potential risks) it implies.

We established 4 objectives for this paper:

- N° 1: update and clarify the current definitions and management recommendations on IgE-mediated food allergy and sensitization.
- N° 2: observe the allergic characteristics of a local population sample and compare them to the general worldwide characteristics reflected in studies, analyzing their possible differences.
- N° 3: observe the actual management of food sensitizations in local clinical practice and compare them to the theoretical ones, analyzing their possible differences.
- N° 4: observe the actual knowledge of food sensitizations in local clinical practice.

## **3. MATERIALS AND METHODS**

### **3.1. LITERATURE SEARCH**

Firstly, in order to achieve objective n° 1, we performed a literature search on PubMed and UpToDate databases and webpage of the Spanish Society of Clinical Immunology, Allergology and Pediatric Asthma (SEICAP: (Sociedad Española de

Inmunología Clínica, Alergología y Asma Pediátrica). Some of the studies were also found for being referenced in the already selected studies.

We searched studies from year 2004 up until year 2020, combining the key words "food allergy" (MeSH term), "sensitization", "IgE-mediated" "diagnosis", "management" and "atopic dermatitis" (MeSH term), associated to several filters ("Free full text" and "Review") and combined with the logical operator AND when needed. The articles returned by the search were selected based on the relevance to this paper by reading the title and the abstract, thus obtaining those mentioned in the References. They were all read and their key points and ideas are those explained and synthesized in the Introduction.

Besides, we did an online course on Food Allergy by the FSA foundation<sup>11</sup> to add up to the updated general knowledge of food allergies.

### **3.2. STUDY**

Secondly, geared towards objectives nº 2 and nº 3, we decided to conduct an observational study on pediatric patients diagnosed with atopic dermatitis, a known risk factor for food allergies and sensitizations (especially in the younger years).

Therefore, we reviewed the group of patients seen in one of the exam rooms of the Allergy and Respiratory Disease section of the Pediatrics service (External Examination Rooms of Araba University Hospital - HUA CCEE) in the lapse of one year (from 1<sup>st</sup> March 2020 to 28<sup>th</sup> February 2021), using the Osabide Global program. From those, we selected and anonymized the patients whose reason for referral was atopic dermatitis and suspicion of food sensitization or allergy (due to positive IgE detection tests or existence of atopic dermatitis). We excluded those who at the moment of referral had already been diagnosed with food allergy or had a clear history of immediate allergic reactions, in order to better study the management of food sensitization.

Data was compiled about the patients' referral (reason and date of the first consultation), age, sex, signs and symptoms (severity of the dermatitis, previous tolerance and reactions to food and airborne allergens, existence of asthma), previous and current IgE detection tests (laboratory IgE detection performed by immunological

CAP technique, considered the reference standard<sup>10</sup>), conducted oral food challenges and established diagnostic and therapeutic elimination diets. We mainly focused on hen egg white and cow's milk, as they are the foods to which atopic patients are most frequently sensitized and allergic to (besides peanut, which is not so often consumed in our environment as it is in the United States)<sup>4,15</sup>. After that, the data was coded and analyzed with the program Stata: Software for Statistics and Data Science.

### 3.3. SURVEY

Finally, in order to explore objective n° 4, we conducted a simple and anonymous survey among pediatricians in the Basque Country through Google Forms.

The survey's aim was to determine whether the professionals would consider safe to establish an elimination diet longer than 2 weeks in a patient sensitized to a certain food but with tolerance towards it. As we know, elimination diets longer than those 2 weeks imply risk of tolerance loss and so risk of an allergic reaction upon ingestion.

The survey was the following:

*A 15-month old toddler with mild-moderate atopic dermatitis comes to your Primary Healthcare exam room. She has a good growth chart and normally consumes eggs and cow's milk since the 9<sup>th</sup> month. Her father tells us that the atopic dermatitis has worsened in the last month, and links it to egg ingestion because a cousin is allergic. You request an analysis with specific IgEs and you obtain 1'99 kU/L of IgE against egg white (normal <0'35 kU/L). What would you consider to be the right next step?*

- a) Establish a definitive egg-free diet. The existence of specific IgE mean food allergy to egg.*
- b) Refer to the allergy specialist (appointment in 1 month) and meanwhile establish an egg-free diet. Having detected specific IgEs against egg it's prudent to establish a diet without it until the specialist sees the patient in 1 month.*
- c) Maintain the egg in the diet and refer to the allergy specialist (appointment in 1 month). The existence of IgE is a reason for referral and needs a complete study.*
- d) Maintain the egg in the diet and calm the father down, because there is no egg allergy (the IgE analysis should not have been asked for this reason).*

## 4. RESULTS

### 4.1. LITERATURE SEARCH

The selected articles were read and their key points and ideas explained and synthesized in the Introduction.

### 4.2. STUDY

#### 4.2.1. General information

We obtained 25 patients.

- Age: the patients had been born between 2007 and 2018, and had an approximate mean of 14 months of age (ranging from 4 months to 4 years and 6 months) at the first consultation in the specialized exam room.
- Sex: we had 9 female (36%) and 16 male (64%).
- Severity of atopic dermatitis: patients were evenly distributed between the established severity levels of mild (24%), mild-moderate (20%), moderate (24%), moderate-severe (16%) and severe (16%) atopic dermatitis, as we can see in **Figure 3**.

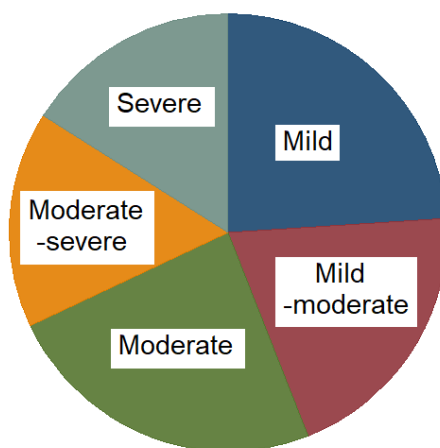


Figure 3. Patient distribution among atopic dermatitis severity levels.

- IgE screening: specific IgE detection without a defined clinical suspicion had been performed in 48% (12 patients). No statistically significant correlation was found between the performing of IgE screening and the severity of the atopic dermatitis.
- Main reason for referral: of the total number of patients with atopic dermatitis, 24% (6 patients) had been referred to the specialist mainly for suspicion of an IgE-mediated immediate reaction. The remaining 76% (19 patients) had been referred solely for their atopic dermatitis, and of those 37% (7 patients) had mild or mild-moderate atopic dermatitis while 63% (12 patients) had moderate to severe type. These results are reflected in **Figure 4**.

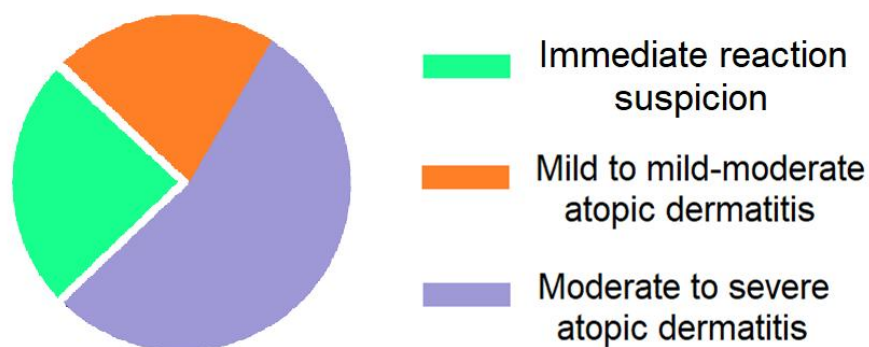
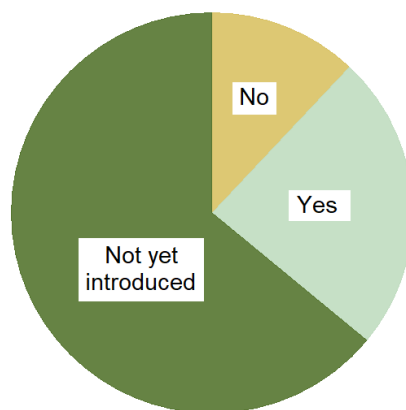


Figure 4. Patient distribution among the main reasons for referral.

#### 4.2.2. Hen egg white

##### 4.2.2.1. Tolerance

Hen egg white was tolerated by 24% of patients (6 patients), produced an adverse reaction in 12% (3 patients) and had not been yet introduced in the diet of 64% (16 patients), as depicted in **Figure 5**.



**Figure 5. Patients' tolerance to hen egg white.**

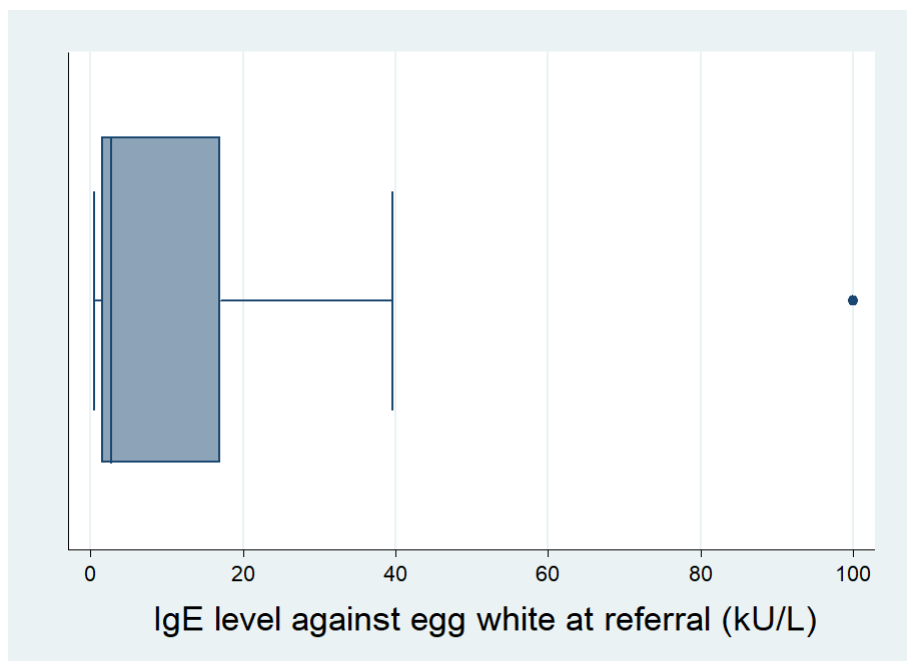
#### 4.2.2.2. IgE determination

Nearly all of them (92%, 23 patients) had had their IgE against egg white determined at referral (in Primary Care or in the first specialised visit), and of those all (100%) were positive in specific IgE laboratory determination (with a median of 2'75 kU/L, ranging from 0'5 to 100 kU/L) and 73'9% (17 patients) were positive in the prick test.

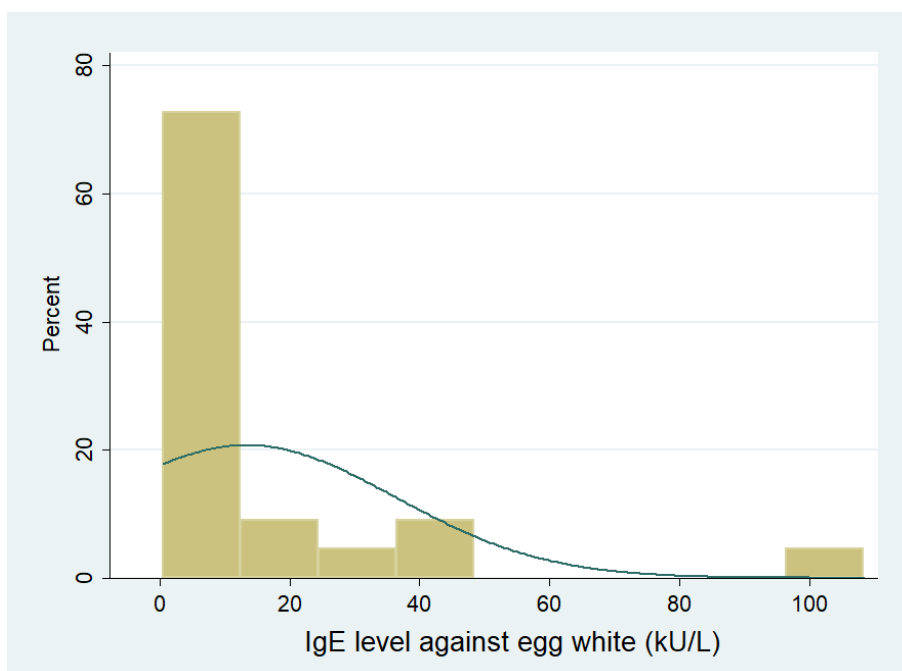
As we can see in **Figure 6**, most of the specific IgE values are low, making their distribution asymmetric and leptokurtic: most of the values gather around the median (2'75 kU/L), which is significantly lower than the mean (13'26 kU/L). This is due to the fact that more than half the values (63'63%) are lower than 4 kU/L, almost all values (95'45%) are lower than 40 kU/L and there is one outlier (4'54%).

To statistically prove it, the kurtosis coefficient is positive (10'16, meaning that those values gather around a central point) and the skewness coefficient is also positive (2'67, meaning there are more values lower than the mean than higher), and therefore said levels do not follow a normal distribution (better viewed in **Figure 7**).

All this makes the median the most representative measure of central tendency, and this is the reason why we have preferably used the median as a central tendency measure in this paper.

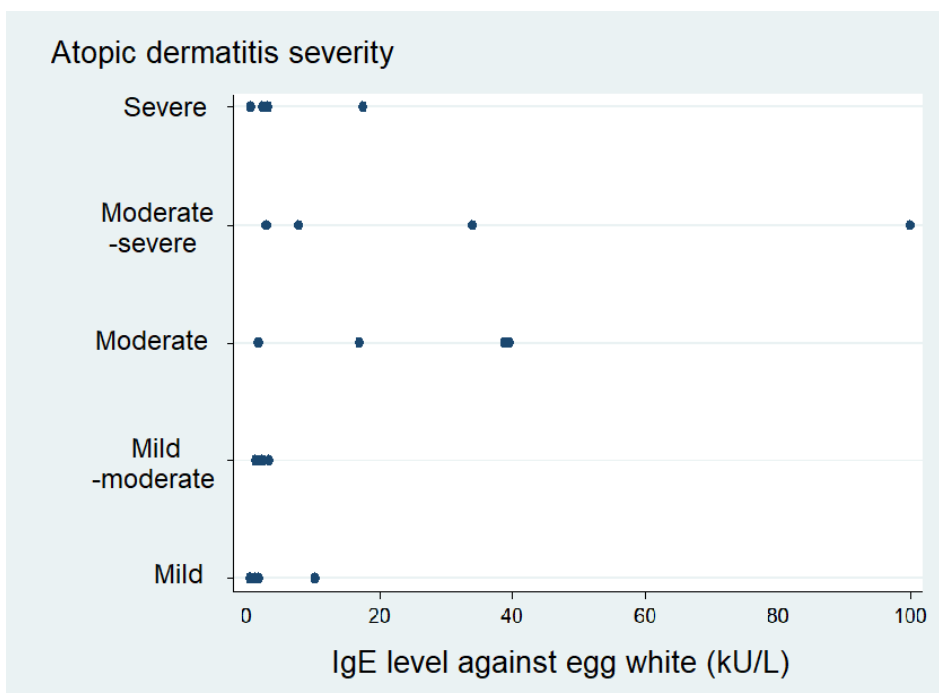


**Figure 6. Distribution of patients' IgE levels against egg white at referral (1).** Most of the values are low, making the median (2'75 kU/L) significantly lower and more representative of the sample than the mean (13'26 kU/L). Almost all values are lower than 40 kU/L, and there is one outlier (at 100 kU/L).



**Figure 7. Distribution of patients' IgE levels against egg white at referral (1).** Most of the values are low, making their distribution asymmetric and leptokurtic, and making the median (2'75 kU/L) significantly lower and more representative of the sample than the mean (13'26 kU/L).

Besides, we found a slight positive correlation (0'258) between the severity of the atopic dermatitis and the IgE levels against egg white, as depicted in **Figure 8**, but it was not statistically significant (95% confidence interval of -0'012 to 0'044).



**Figure 8.** Different IgE levels against egg white in the atopic dermatitis severity groups. No statistically significant correlation was found.

#### 4.2.2.3. Elimination diets

A therapeutic elimination diet (longer than 2 weeks) had been established in Primary Care without an actual diagnostic confirmation (no oral food challenge or diagnostic elimination diet) in 40% (10 patients). No statistically significant correlation was found between this establishment and the IgE levels against egg white.

A diagnostic elimination diet was established in the specialized exam room in 12% (3 patients), and was negative in all cases (no improvement was found).

#### 4.2.2.4. Oral food challenge

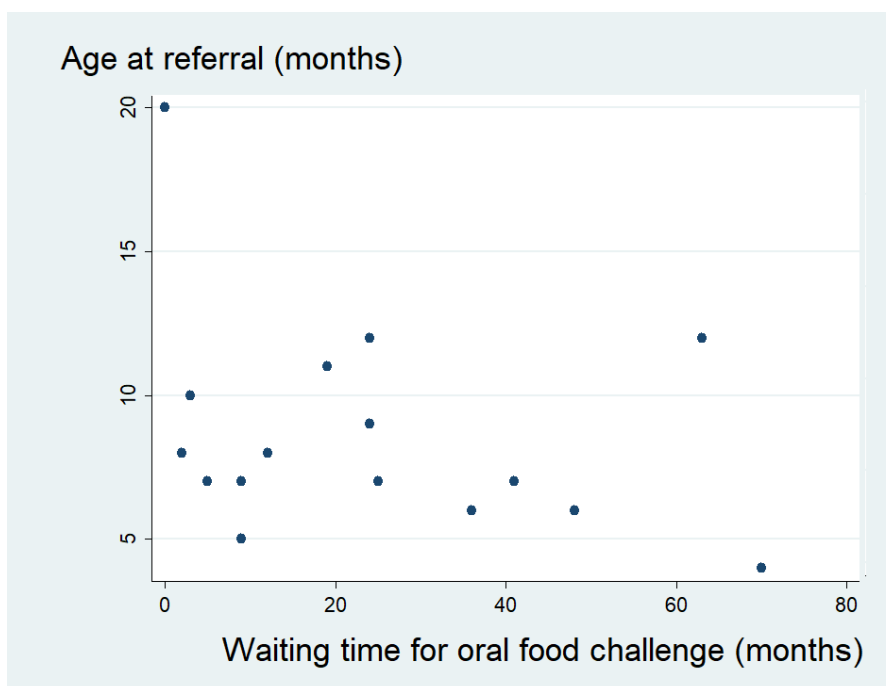
The sensitization detected in the mentioned 92% of patients (23 patients) was followed by an oral food challenge in 21 cases (91'30%, being 82'60% or 19 patients



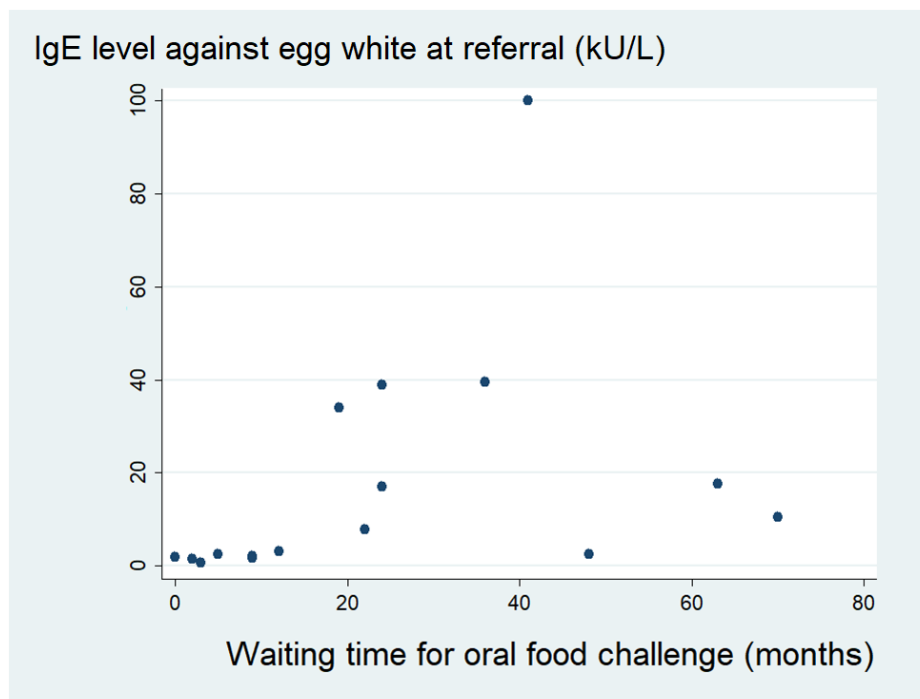
in the exam room and 17'40% or 4 patients at home, depending on the risk level). The reasons not to perform it were previous tolerance or a clear history of an immediate reaction.

Since the first specialised consultation, an approximate median of 19 months lapsed until the oral food challenge took place in the exam room. It was performed when the patients were 30 months of age (median) and with specific IgE levels of 1'33 kU/L (median), ranging from 0'22 to 34 kU/L. The results of the challenge were negative in all patients (100%).

We analyzed the possible factors that could modify the waiting time for the oral food challenge, but we found no statistically significant correlation between it and: the age of the patients at referral (as shown in **Figure 9**), the initial specific IgE levels (see **Figure 10**), the severity of the atopic dermatitis or the current age of the patients.



**Figure 9. Conditions for the oral food challenge (1).** There was no statistically significant correlation between the patients' age at referral and the waiting time for the oral food challenge in the exam room.



**Figure 10. Conditions for the oral food challenge (2).** There was no statistically significant correlation between the specific IgE level at referral and the waiting time for the oral food challenge in the exam room.

#### 4.2.3. Cow's milk

- Tolerance: cow's milk was tolerated by 64% of patients (16 patients), produced an adverse reaction in 12% (3 patients) and had not been yet introduced in the diet in 24% (6 patients), as depicted in **Figure 11**.
- IgE determination: 76% of them (19 patients) had had their IgE against cow's milk determined, and of those 63'15% (12 patients, 48% of the total of patients) were positive in specific IgE laboratory determination (with a mean of 7'27 kU/L, ranging from 0'61 to 51 kU/L) and 42'10% (8 patients, 32% of the total of patients) were positive in prick tests. We found no statistically significant correlation between the severity of the atopic dermatitis and the IgE levels against cow's milk.
- Elimination diets: a therapeutic elimination diet (longer than 2 weeks) had been established in Primary Care without an actual diagnostic confirmation (no oral food challenge or diagnostic elimination diet) in 28% (7 patients). No statistically

significant correlation was found between this establishment and the IgE levels against cow's milk. A diagnostic elimination diet was established in the specialized exam room in 8% (2 patients), and was negative in all cases (no improvement was found).

- Oral food challenge: the sensitization detected in the mentioned 48% of patients was followed by an oral food challenge in 83'33% of cases (66'66% in the exam room and 16'66% at home, depending on the risk level), and the results were negative in 90% (9 of the 10 patients). The reason not to perform it was previous tolerance.

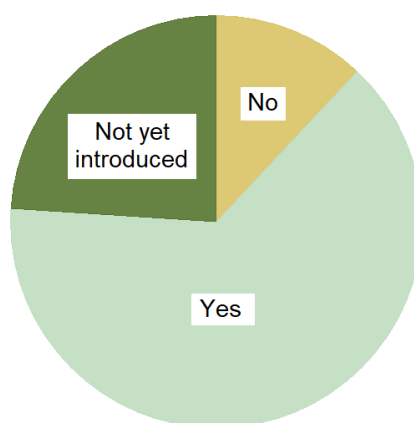


Figure 11. Patients' tolerance to cow's milk.

#### 4.2.4. Other sensitizations and allergies

Aside from hen egg white and cow's milk, information was gathered about other allergens and depicted in **Figure 12**.

- Nuts and peanuts: data was collected about the most common types of nuts (almond, hazelnut, walnut, pistachio, cashew) and peanuts, and it was found that 40% (10 patients) had clinical symptoms upon ingestion (food allergy). Besides, 20% (5 patients) were only sensitized (had tolerance or had not yet eaten nuts).

- Airborne allergens: 76% of patients (19 patients) had symptoms of allergy to airborne allergens (asthma or allergic rhinoconjunctivitis), and 16% (4 patients) were sensitized to dust mites or grass pollen but had no symptoms.
- Other foods: 40% of patients (10 patients) had other types of food allergies and 16% (4 patients) had other types of food sensitizations, mainly to fruits, legumes, fish and shellfish.

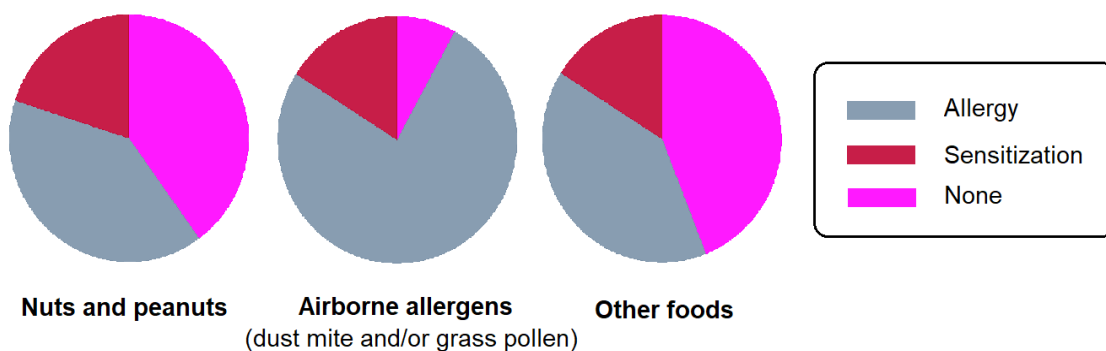


Figure 12. Proportion of other allergies and sensitizations in the sample.

Therefore, excluding the common egg white and cow's milk, we found that 88% (22 patients) had another type of allergy, 8% (2 patients) had another type of sensitization without allergy, and 4% (1 patient) had none.

No statistically significant correlation was found between any of these other allergies or sensitizations and the atopic dermatitis severity or the IgE levels against egg white.

### 4.3. SURVEY

We obtained 67 responses, compiled in **Table 2**. Option *b* and *d* were selected by 37'3% each (25 pediatricians each) and the remaining 25'4% (17 pediatricians) opted for option *b*, as none selected option *a*. The replying professionals were 40'3% from Araba (the majority selecting option *d*), 40'3% from Bizkaia (the majority selecting option *b*) and the remaining 19'4% from Gipuzkoa.

**Table 2. Survey results.** The survey was conducted through Google Forms in February 2021, and the options selected by the replying professionals were classified by the province of origin.

		<i>Option a</i>	<i>Option b</i>	<i>Option c</i>	<i>Option d</i>	Total
Pediatrician's origin	Araba	0	7	7	13	27
	Bizkaia	0	13	5	9	27
	Gipuzkoa	0	5	5	3	13
Total		0	25	17	25	67

## 5. DISCUSSION

### 5.1. LIMITATIONS

First of all, we ought to acknowledge our study's small number of patients, which gives us an idea of the real clinical practice but does not aim at being representative of all population. Besides, the fact that we excluded those patients with diagnosed allergies at referral may skew our view of the sensitizations' management, as those patients may have other sensitizations without allergy, but we hypothesise that their management would be at least as conservative as in cases with only sensitization.

### 5.2. GENERAL FACTS

The results of our study show that patients are usually referred to the specialist when they are about 14 months of age, a very young age but a time in which many foods have already been introduced into the diet.

We expected patients with severe atopic dermatitis to be the most referred kind, as severity is linked to the prevalence of food allergies<sup>4,14</sup>, but all severity groups of our study had roughly the same size. This may be linked to overreferral, but may also be skewed by the fact that those patients with a clear food allergy at the moment of referral were excluded from our sample selection, and by the fact that each group had few individuals (4 to 6 patients each).

### **5.3. IS THERE OVERREFERRAL AND OVERTREATMENT IN PRIMARY CARE?**

As we know, the two situations that justify a diagnostic process are evidence of an immediate reaction after food ingestion and moderate to severe atopic dermatitis after optimal skin care. In our case, the patients' reason for referral was suspicion of food sensitization (diagnostic process request). This referral was justified by evidence of an immediate reaction in 24% (6 patients), and of the remaining 76% (19 patients) who were referred solely for their atopic dermatitis only 63% (12 patients) had moderate to severe atopic dermatitis.

This leaves us with a proportion of 28% (7 patients) whose referral was not justified. Moreover, 48% (12 patients) had had an unjustified IgE screening (with its known high clinical false-positive rates<sup>2,4</sup>) and 40% (10 patients) had had an unjustified therapeutic elimination diet established before referral (with its known potential risks<sup>2,3,4</sup>). These two findings suggest that there is overreferral and overtreatment in pediatric food allergy and sensitization.

This data may be explained by the fact that 62'7% (42 professionals) of the surveyed pediatricians would refer an egg-tolerating patient to the allergy specialist solely based on an egg sensitization and mild-moderate atopic dermatitis. Moreover, 37'3% (25 professionals) would also establish an elimination diet longer than 2 weeks (with its possible loss of tolerance<sup>4</sup>); this percentage drops to 25'9% if we solely analyze the answers coming from OSI Araba. This last fact does not match with the significant proportion of unjustified referrals, IgE screenings and therapeutic elimination diets observed in our sample, and may be related to the possible fact that the replying professionals were not the same as those referring the patients, as it could be hypothesised that those who managed in an unjustified way would possibly have doubts about food allergy and would not answer the survey. Nevertheless, we gladly report that none of replying pediatricians would diagnose a food allergy without confirmation neither would establish a therapeutic elimination diet for that reason.

In this sense, this potential overreferral and overtreatment could be explained by the complexity of allergy diagnosis and the general overestimation of food allergy

prevalence<sup>4</sup>, and hastened by the frequent lack of quality time in Primary Care, which understandably may lead to the management thought to be the most prudent.

It is also relevant to remark that no statistically significant correlation was found between this establishment and the specific IgE levels against the eliminated food, and therefore we can state that in our sample the elimination diet establishment did not appear to rely on the detected specific IgE level.

#### **5.4. WHAT DOES THE SPECIFIC IgE LEVEL PREDICT?**

Scientific studies tell us that specific IgE levels only predict the likelihood of symptom onset, but do not predict actual food allergy or its severity<sup>2,3,7,9,12,13</sup>. This means that high specific IgE levels do not equal severe allergy to that food, and therefore they should not directly lead to a therapeutic elimination diet skipping an oral food challenge (or diagnostic elimination diet, in some cases). Instead, the diagnostic algorithm (Graphic 1) ought to be followed and a sensitization should always be confirmed before establishing any definitive dietary restriction<sup>1,4,9</sup>.

In our study we observed that this shortcut of the algorithm was often taken (40% of patients had had an unjustified therapeutic elimination diet established), leading to the mentioned potential risks.

Likewise, we believe important to remark that most of the determined specific IgE levels were positive but low (see Table 2), being in the uncertainty between the clearly negative and the PPV  $\geq 95\%$ , as it has been determined to be the most frequent case<sup>14</sup>.

We found no statistically significant correlation between the severity of the atopic dermatitis and the IgE levels against egg white or cow's milk, despite it has been stated that the severity of the atopic dermatitis appears to be directly related to the prevalence of food sensitization and allergy<sup>4,14</sup>. This finding may be explained by the small number of patients in our study, especially when divided into severity groups (for example, we only had 4 patients with severe atopic dermatitis).

## **5.5. WHEN DO WE PERFORM THE ORAL FOOD CHALLENGE?**

We are glad to report that most of sensitizations were confirmed in the specialised service (by an oral food challenge or home introduction): 93'70% with egg white and 83'33% with cow's milk. Those not confirmed by an oral food challenge were previously tolerant or had had a clear immediate reaction to the food.

The oral food challenges for egg white were carried out after a mean of 23 months from the first specialised consultation, waiting for the specific IgE levels to drop from a median of 2'75 to 1'33 kU/L, and they were all (100%) negative. As for cow's milk, nearly all (90%) oral food challenges were negative. This may mean that we are waiting longer than necessary to perform oral food challenges in atopic sensitized patients with no previous allergic symptoms. We hypothesised this may be related to the fact that we are nowadays more prone to performing oral food challenges than we were years back, but we found no statistically significant correlation between the current age of the patients and the waiting time for the oral food challenge. Again, we acknowledge the limitation of the small number of patients and also the studied time lapse: a year (from 1<sup>st</sup> March 2020 to 28<sup>th</sup> February 2021), in which we found patients first referred from 2007 to 2018, but surely not all of them. A more detailed study would be necessary for this hypothesis to be appropriately tested.

## **5.6. IMPORTANCE OF OTHER ALLERGIES**

Besides the frequent egg and milk allergies and sensitizations, we found that 88% (22 patients) had another type of allergy, especially to airborne allergens (76%) with their known cross-reactivity<sup>1,9</sup>, which has been linked to the numerous sensitizations atopic patients tend to have<sup>4,14</sup>. This finding agrees with the fact that 60% of food allergies are linked with an inhalant allergy<sup>9</sup>, and also with the atopic march (progression of allergic disorders from early atopic dermatitis to food allergy or sensitization and respiratory symptoms)<sup>4</sup>.



## 6. CONCLUSION

Food allergy is an increasing health problem, especially among children with atopic dermatitis. Its diagnosis can be challenging, but it is vital to differentiate food allergy from food sensitization (specific IgE antibodies without clinical relevance), as the first requires a strict therapeutic elimination diet and the latter enables and actually recommends regular consumption. As both food allergy and sensitizations are common in atopic children, detected sensitizations should always be confirmed by an appropriate diagnostic test (usually an oral food challenge). Likewise, sensitizations alone should not be an indication for therapeutic elimination diets, despite being often viewed as safe and prudent in doubtful cases, as those diets imply potential risks such as loss of tolerance, nutritional deficiencies and patient and parent preoccupation.

Summarizing, our study views our population sample's allergic characteristics in line with the general population worldwide studies reflect. As for the management of food sensitization, our study suggests that oral food challenges could be performed sooner in children with atopic dermatitis and food sensitizations, as nearly all (96'67%) of our oral food challenges were negative. Besides, food allergy in sensitized pediatric patients with atopic dermatitis may be overdiagnosed, overreferred and overtreated in Araba University Hospital's Primary Care. This could be due to the following facts:

- Food allergy is an increasing healthcare problem<sup>1,2,3,4</sup>.
- Children with atopic dermatitis are at higher risk of food allergy than average<sup>14</sup>, and its perception seems to be overestimated by the general population<sup>4</sup>.
- Children with atopic dermatitis are usually sensitized to several food and airborne allergens<sup>4,14</sup>, but that does not necessarily (and actually often does not) mean actual food allergy<sup>2,3,7,9,12,13</sup>.
- IgE detection tests are often requested without a clinical justification and they have a high clinical false-positive rate<sup>2,4</sup>, which can and actually does lead to overreferral to specialised attention and to therapeutic elimination diets without

proper confirmation (oral food challenge or diagnostic elimination diet), with the potential risks elimination diets imply<sup>2,4</sup>.

- Referral and elimination diets are perceived to be a prudent choice when managing food allergies and sensitizations in Primary Care, possibly due to their diagnostic complexity, despite the potential risks of elimination diets<sup>2,4</sup>.

As a result, we sent our simplified conclusions to local pediatricians working in Primary Care because we believe it useful to clearly inform them about the basic food allergy diagnosis interpretation and referral criteria, in order to reduce unnecessary and even dangerous elimination diets primarily, but also to reduce overdiagnosis (consequently reducing patient and parental worry and health costs) and to ease the allergy diagnostic process in Primary Care.

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