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REVIEW ARTICLE

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Practical protocol of the food allergy committee of the seicap on open oral food challenges to nuts

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Abstract
Food allergy is rising rapidly among children, and allergy to nuts is one of the most prevalent allergies among them. The category "nuts and seeds" include several plant foods from different botanical families, very different from each other. It is not uncommon to detect co-sensitization to different nuts. However, true co-allergy is less frequent. Up to 80% of patients with positive skin prick tests or specific IgE without true history of reaction who avoid certain nuts, might tolerate them in an Oral Food Challenge (OFC). Although molecular diagnostic techniques help to improve nut allergy diagnosis, OFC still remains the gold standard. For this reason, after reviewing the current bibliography and the recommendations of different allergy societies on standardization of open OFC, the Food Allergy Committee of the Spanish Society of Pediatric Allergy, Asthma and Clinical Immunology (SEICAP) food allergy working group proposed a unified protocol to undertake these OFC, which include preliminary

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recommendations, unification of total dose, number of doses and interval between doses. Additionally, this group offers an interactive table to facilitate calculation of doses specific to each nut under study.

Introduction

What we commonly refer to as nuts and seeds is a heterogeneous group of plant foods which includes a range of botanical families. The name comes from the custom of consuming them after a drying process; it does not refer to a concrete botanical or taxonomic entity. Most nuts share important similarities in allergenic terms and in the forms of consumption. The present study refers only to the following nuts: almonds, cashews, hazelnuts, peanuts, walnuts, pumpkin seeds, sunflower seeds, pistachio, pine nuts, sesame seeds, and chestnuts.

The prevalence of food allergy is on the rise, with cumulative incidences reaching 11% of all children under four years of age.[1] Nuts are among the most frequently implicated foods, with approximately 2% prevalence rate in some countries.[2] Although the prevalence of nuts allergy in Spain has not been clearly established, walnuts (7.7%), peanuts (7.2%), and hazelnuts (6%) are known to be the nuts with the highest sensitization rates.[3] In Europe, these data have been corroborated by different studies with small regional variations, attributable to different consumption habits, the ages of the included patients[4,5] and other potential factors. Nuts can often cause serious anaphylactic reactions and may be associated to other food allergies – all of which often has a detrimental impact on families' and patients' quality of life.[6]

Diagnosing nut allergy in children can be a tough challenge for pediatric allergologists. Co-sensitization to a range of nuts is common, though true co-allergy is less frequent.[2] that is, a positive skin prick test or specific IgE might not be clinically relevant.[7] Indeed, 80% of patients avoiding nuts due to positive skin tests or specific IgE were without a history of previous reaction (i.e., detected in the context of atopic dermatitis or another nut allergy) and tolerate them at food challenge.[8] Molecular diagnostic techniques[2,9] have helped improve nut allergy diagnosis by recognizing co-sensitization/co-allergy patterns[10] and the influence of concomitant pollen allergy in test results. Nonetheless, OFC remains the gold standard in the allergy diagnosis.

OFC's involve the planned and incremental administration of a substance suspected to cause the allergic reaction, with a view to confirming or discarding the diagnosis of an allergy, or to assess the acquisition of tolerance over time. It is the definitive test for diagnosing food allergy. There are many publications and position statements on the way to perform an OFC,[11,12,13] which include the indications, contra-indications, requirements, precautions, methods of administration, types of OFCs, dosage, masking, interpretation of the results, and required treatments. A review of all these aspects falls beyond the scope of the present protocol, which intends to serve as a clinical guide on open OFCs with nuts, placing emphasis on the safety precautions required due to the potential risk of serious allergic reactions.

On performing OFC with nuts, it must be taken into account that the food processing methods like roasting can induce changes in the allergenic properties of the food as a result of multiple non-enzymatic biochemical reactions that can modify allergenicity.[14,15] For example, heat processing reduces the allergenicity of the PR-10 proteins in hazelnuts and almonds, but not of the Lipid Transfer Proteins (LTPs) and storage proteins.[16] In contrast, grilling or roasting peanuts increases their allergenicity, while boiling them in water reduces it.[17] The patient's clinical history, the type of processing involved (boiled, roasted, or raw), and the information provided by the molecular diagnosis may indicate the type of processing required by the nuts with which OFC is performed. Processed nuts could be tolerated by patients that only recognize PR-10 proteins, in contrast to nuts that are consumed raw. As a general rule in patients sensitized to proteins other than PR-10, OFC can be performed indistinctly with raw or roasted nuts.

Since there is a risk of allergic reactions (including anaphylaxis) when performing OFC, such tests must always be performed by professionals trained in the diagnosis and treatment of such reactions, including the resuscitation equipment at hand. It is essential for the patient or legal guardian to understand and authorize the test by signing an informed consent before the OFC is carried out.

Recommendations

1. Following the recommendations of a majority of the allergy societies on the standardization of OFC, it is advisable for the total challenge dose to be 0.15-0.3 g of protein/kg body weight, without exceeding 3 g of protein or 10 g of the whole food. Distribution is made into 5 doses of 0.03 – 0.1 – 0.3 – 1 and 2 g of protein at 20 minute intervals, though this may be increased according to the latency period stated in the clinical history of the patient. The final cumulative amount is 3.43 g of protein. Although some protocols recommend a final dose of 3 g of protein, with a cumulative dose of 4.44 g, this committee considers that such a dose would be excessive in the pediatric population and exceeds the usual serving size at these ages.

   Table 1 includes the protein weight proportion for each nut or seed, and the amount of actual food linked to each dose of the OFC.[18]
2. Whole pieces of nuts should not be used in OFC in infants under three years of age due to the risk of suffocation. They may be replaced by an equivalent in crushed or ground form, or by a cooking presentation containing them.[19]

Table 1 Weight and units of nuts corresponding to the different protein doses in each step of the oral food challenge test.

		Nut weight for each amount of protein						Nut units for each amount of protein				
		1st dose	2nd dose	3rd dose	4th dose	5th dose		1st dose	2nd dose	3rd dose	4th dose	5th dose
	% of prot	0.03 gr prot	0.1 grprot	0,3 grprot	1 gr prot	2 gr prot	Weight of one nut in gr	0.03 grprot	0.1 gr prot	0,3 gr prot	1 gr prot	2 gr prot
Walnuts	14,00	0,21	0,71	2	7	14	6,00	0,04	0,12	0,36	1,19	2,38
Almonds	19,00	0,16	0,53	2	5	11	1,00	0,16	0,53	1,58	5,26	10,53
Cashews	17,50	0,17	0,57	2	6	11	2,00	0,09	0,29	0,86	2,86	5,71
Peanuts	25,00	0,12	0,40	1	4	8	1,00	0,12	0,40	1,20	4,00	8,00
Hazelnuts	12,00	0,25	0,83	3	8	17	1,00	0,25	0,83	2,50	8,33	16,67
Pistachio	18,00	0,17	0,56	2	6	11	1,00	0,17	0,56	1,67	5,56	11,11
Pine nuts	14,00	0,21	0,71	2	7	14	0,20	1,07	3,57	10,71	35,71	71,43
Sunflower seeds	20,80	0,14	0,48	1	5	10	0,08	1,80	6,01	18,03	60,10	120,19
Sesame	19,00	0,16	0,53	2	5	11						
Pumpkin seeds	30,00	0,10	0,33	1	3	7	0,24	0,42	1,39	4,17	13,89	27,78
Chestnuts	3,00	1,00	3,33	10	33	67	14,00	0,07	0,24	0,71	2,38	476

Interactive table is available at https://www.seicap.es/: changing the weight of the piece of nut varies the resulting quantities.

Table 2 Number of pieces of nuts in each step of the oral food challenge test.

	1st dose	2nd dose	3rd dose	4th dose	5th dose	Total
Almonds	½	1	2½	4½	9	17.5
Cashews	⅓	½	1¼	2½	5	10
Hazelnuts	½	1	3	7	15	26.5
Peanuts	½	1	2	3½	7	14
Chestnuts	¼	½	1	2	5	8¾
Walnuts	⅛	¼	½	1	2	4
Pumpkin seeds	1	2	4	10	28	45
Sunflower seeds	2	6	18	60	120	206
Pistachio	½	1	2	5	11	19.5
Pine nuts	1	3	11	36	72	123
Sesame	0.2 g	0.5 g	2 g	5 g	11 g	19 g

3. When possible, it would be advisable to measure (using a precision balance) the amount of nuts administered in each OFC dose, particularly in the context of a scientific research study. It is not always practical or necessary to control the dose precisely in routine clinical practice. We can use the doses reflected in Table 2, taking into account that these are approximate data, since they may vary with the different sizes and weights of each piece of nut.
4. In some cases, the starting dose should be lower than that reflected in Table 2, for instance when there is a history of a previous reaction to a very small amount with very severe symptoms, or when the allergy tests results are high.[20,21,22] In such cases, if OFC is indicated, the starting dose should be lower.
5. If OFC is performed with small-size nuts such as sunflower seeds or pine nuts, where it is difficult to quantify the final intake in pieces, we can accept the recommended amount to be the equivalent number of pieces of nuts that can be "contained in the fist of the child".
6. In the case of sesame seeds, since the number of pieces cannot be counted in practical terms, it is advisable to use a balance to calculate the OFC dose.
7. In patients where the pre-test probability (based on the clinical history and allergological study) of a positive OFC with a given nut is very low, we can perform the test with 2–4 nuts at the same time, in order to reduce the number of challenges needed to assess allergy or tolerance.[23]
8. As a general rule, an OFC should be considered positive in the presence of an objective sign of reaction.[24]

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