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No difference in health-related quality of life, after a food challenge with cashew nut in children participating in a clinical trial.

J.P.M. van der Valk ¹, R. Gerth van Wijk ¹, BMJ Flokstra-de Blok², J.L. van der Velde³, H. de Groot⁴, H.J. Wichers⁵, A.E.J. Dubois³, N.W. de Jong¹

- 1) *Department Of Internal Medicine, Allergology, Erasmus MC, Rotterdam, the Netherlands*
- 2) *Department of General Practice, University of Groningen, University Medical Centre Groningen, the Netherlands*
- 3) *Department of Pediatric Pulmonology and Pediatric Allergology, University Medical Centre Groningen, GRIAC Research Institute, University of Groningen the Netherlands*
- 4) *Department of Pediatric Allergology, Diaconessenhuis Voorburg, RdGG, Delft, the Netherlands.*
- 5) *Wageningen UR Food & Biobased Research, the Netherlands*

Corresponding author mail id: j.p.m.vandervalk@erasmusmc.nl

Keywords

Cashew nut allergy, DBPCFC, Food allergy quality of life, anaphylaxis

Abbreviations

CF	Child Form
DBPCFC	Double-blind placebo-controlled
FAIM	Food Allergy Independent Measure
FAQLQ	Food Allergy Quality of Life Questionnaire

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HRQL	Health-Related Quality of Life
OFC	Oral Food Challenge
PF	Parents Form
TF	Teenager Form

Abstract

Background

Previous studies showed that Health-Related Quality of Life (HRQL) significantly improved after the food challenge, with greater improvements in HRQL after a negative outcome than a positive outcome. It is currently unknown whether this also occurs in patients undergoing DBPCFCs with cashew nut in the context of a clinical trial.

Methods

Quality of life was studied in children enrolled in a cashew nut study using food allergy quality of life questionnaires (FAQLQs). Children, teenagers and parents of the children completed the questionnaires before the challenge test and 6 months after the DBPCFC with cashew nut. The difference in the change in HRQL between the children with a positive and negative DBPCFC outcome was studied by Mann-Whitney U test.

Results

In total 112 children (67 boys, median age 9 yrs.) were included. The children, teenagers and parents of the children completed in total 143 sets of questionnaires. There were no significant differences in baseline total and domain scores compared to the follow-up scores in the FAQLQ-CF, -TF and -PF. In children, the delta FAIM score in the negative DBPCFC tested group was significantly better than the delta FAIM score in the positive challenged group ($p=0.026$). There were no significant differences in the changes in the scores of the FAQLQ-CF and

FAQLQ-PF in the children with a positive challenge outcome, compared to the children with a negative challenge result. However, there was a significant difference in the change in score between the latter groups in the domain 'accidental exposure' of the FAQLQ-TF ($p=0.049$).

Conclusion

This study showed no difference in change of HRQL scores after a DBPCFC with cashew nut in children participating in a clinical trial. The utility of HRQL as an outcome for clinical trials in food allergy may be limited if participant baseline HRQL is relatively unimpaired.

Introduction

Food allergy is a growing problem in the Western world, especially in children [1]. A food allergy may have an impact on the quality of life in children and their parents [2]. The fear of severe reactions and the need of strict avoidance of allergenic foods may contribute to this impact on quality of life. Previous studies, with different allergenic foods, demonstrated that Health-Related Quality of Life (HRQL) for patients with a suspected food allergy significantly improved after a double-blind placebo-controlled food challenge (DBPCFC). Greater improvements in HRQL scores were demonstrated in children with a suspected allergy for peanut, nut, milk, egg, wheat, soy and sesame after a negative DBPCFC test outcome (i.e. allergy refuted/passed test) than a positive DBPCFC test outcome (i.e. allergy confirmed/failed test) [3]. This study included only patients who had sought medical care for their food allergy. In another study, HRQL of patients seeking medical care was compared to food allergic individuals from the general population [4]. HRQL was found to be significantly more impaired in patients seeking medical attention for their food allergy than food allergic individuals in the general population, because this last patient group is probably less afraid of an allergic reaction and have fewer problems with dietary restrictions. Currently, there is little information on the utility of HRQL as an outcome in the

setting of diagnostic clinical trials on specific food allergies. The primary aim of this study was to assess the difference in the effect on HRQL before and 6 months after a DBPCFC in children participating in a clinical trial on cashew nut allergy.

Methods

Participants and procedure

Children (2-17 years of age) participating in the study '*Improvement of Diagnostic methods for Allergy assessment*' with cashew nut allergy in children as a show case (trial number NTR3572) were asked to participate in the evaluation of quality of life [5]. Consecutive patients were invited. All patients underwent DBPCFC with cashew nut with an eight-step incremental dose regime of validated and standardized food challenge materials [6]. The DBPCFC test was discontinued and considered positive when 1) objective symptoms occurred, or 2) when subjective symptoms re-occurred twice after the same dose of challenge material had been administered, three times consecutively [7], or 3) when subjective symptoms persisted for more than one hour. If the child developed the same symptoms with the same severity on the placebo as on the verum day, the DBPCFC test was considered as undetermined and the child was not included in the analysis.

The children were divided into two groups, patients with a positive and patients with a negative DBPCFC outcome. Anaphylaxis was defined according to the EAACI Guidelines for Food Allergy and Anaphylaxis [8].

The validated Food Allergy Quality of Life Questionnaires (FAQLQ) and Food Allergy Independent Measure (FAIM) questionnaire were used and completed by the patient (8-17 years) and/or parents (0-12 years) before the challenge test and 6 months after the DBPCFC [9]. The FAIM questionnaire was used in this study to measure the longitudinal and cross-sectional

validity of the FAQLQs. Only patients who completed both questionnaires in the study period from April 2012 to August 2015 and filled out more than 80% of the questions were included.

Medical ethical approval for this study was obtained (ethics committee Erasmus MC, Rotterdam, 2012-125). All participants signed informed consent (parents of children (2 -12 years old) and parents and children (≥ 12 years old)). The study is registered in the Dutch Trial register (trial number NTR3572).

Food allergy health related quality of life questionnaires (FAQLQ)

The FAQLQ used in this study is a disease specific instrument that evaluates the impact of food allergy on patients' HRQL. For this study, the FAQLQ child form (FAQLQ-CF) for children between 8 and 12 years of age, the teenager form (FAQLQ-TF) for children between 13-17 years of age and the parent form (FAQLQ-PF) for parents of children between 0 and 12 years of age were used. The FAQLQ-CF contains 24 items and 4 domains (allergen avoidance, risk of accidental exposure, emotional impact and dietary restrictions). The FAQLQ-TF contains 23 items and 3 domains (allergen avoidance and dietary restrictions, risk of accidental exposure and emotional impact). The FAQLQ-PF contains 14 items for children 0 -3 years of age, 26 items for children 4- 6 years of age and 30 items for children 7-12 years of age; and for all-ages, 3 domains (emotional impact, food anxiety and social and dietary limitations)[2,9,10]. The questionnaire items are scored on a seven point scale ranging from 1 to 7. The answer options for children (8-12 years of age) are illustrated with smileys and are simple to use. The FAIM questionnaire is a disease specific instrument that measures self-perceived severity of food allergy [11]. The FAIM consists of 4 expectations of outcome questions on the chance of accidental exposure, severe reactions, dying due to the food allergy and effectiveness of self-treatment and 2 questions on extent of disease. The FAIM questionnaire items are also scored on a seven-point scale ranging from 1 to 7.

Statistical analysis

The total FAQLQ score was calculated by adding up the scores, and consequently dividing this score by the number of answered questions at each time point. The domain scores were calculated in the same manner. The FAQLQ mean total score and mean domain scores were measured at baseline (before DBPCFC) and follow-up (6 months after DBPCFC). The FAIM mean total score was also measured at baseline and follow-up. The statistical significance between the two measurement points (before and after DBPCFC) was calculated by using the paired t-test with 95% confidence intervals and p-values (>0.05). The changes in FAQLQ scores (follow-up score after the DBPCFC test minus baseline score before DBPCFC test) were calculated for the relevant FAQLQ (all domains) and for the FAIM. The statistical significance between the two groups (patients with a positive and a negative DBPCFC outcome) was calculated by using the Mann-Whitney U test. Multiple linear regressions, correcting for the possibly influencing factors on the change of FAQLQ overtime (dependent variable), was also used to study possible improvement in HRQL. Possible influencing factors (independent variables) used in the multiple linear regression were: age, centre of inclusion (Erasmus Medical Centre Rotterdam, Reinier de Graaf Hospital, University Medical Centre Groningen), atopic features as hay fever, asthma and eczema, history of cashew nut allergy, multiple reported food allergies, anaphylaxis during DBPCFC, baseline score and outcome of the DBPCFC with cashew nut (positive (allergy confirmed)/ negative (allergy refuted) and the dose eliciting a reaction during the challenge with cashew nut. Pearson correlation coefficients were calculated for measuring validity between the baseline, follow-up and change in FAQLQ (CF, TF and PF) scores and FAIM scores. All analyses were done with SPSS software, 20th edition.

Results

Patients and clinical characteristics

In total 112 patients (67 boys, 60%) with a median age of 9.0 years (range 2-17 years) were included. 6 children with an undetermined challenge test were excluded from the analysis. The questionnaires were completed before the challenge test and 6 months after the DBPCFC with cashew nut, and in total 143 pairs of questionnaires were completed from April 2012 to August 2015. Of these 143 pairs of questionnaires, 84 parents' forms 33 child forms and 26 teenager forms were obtained. Of all 112 children, 74 children (66 %) had a history of cashew nut allergy and 39 children (34%) had never eaten cashew nut before the challenge test. Positive challenge tests were observed in 85 children (76%), negative tests in 27 children (24%). Most positively tested children had gastro-intestinal symptoms (nausea, vomiting, abdominal pain and diarrhoea) followed by oral allergy symptoms, skin symptoms (redness and itch), angioedema and urticaria. In total 34% (29/85) of the children with a positive DBPCFC to cashew nut had an anaphylactic reaction [8]. The children with an anaphylactic reaction most commonly experienced a combination of skin and gastro-intestinal symptoms (n=22) followed by respiratory, gastro-intestinal and skin symptoms (N=5) and respiratory and skin symptoms only (N=2). Concerning atopic features, 34 (30%) had asthma, 44 (39%) had eczema and 55 (49%) had hay fever. All children were sensitised in either SPT (median 2.97 [0-15.16] HEP-index area) or specific IgE (sIgE) (median 3.42 [0- $\geq$ 100] kU/L).

In order to exclude selection bias, we compared the patient characteristics and diagnostic results between the participating children (n=112) and the non-participating children from the IDEAL study (n= 61) (Mann Whitney U test and chi square test). There was no significant difference in gender (p=0.92), age (p=0.74) symptoms according to asthma (p=0.91), eczema (p=0.68), and hay fever (p=0.65), history of cashew nut allergy (p= 0.12), sIgE to cashew nut (p= 0.29), SPT cashew nut (p= 0.63) and DBPCFC outcome (p=0.15).

Initial Health- Related Quality of Life

The mean baseline scores for the FAQLQ-CF, FAQLQ-TF and FAQLQ-PF of 3.32, 3.50 and 2.37 respectively, were measured.

Change in Health-Related Quality of Life after a challenge test with cashew nut

The mean baseline scores for the FAQLQ-CF, FAQLQ-TF and FAQLQ-PF were 3.32, 3.50 and 2.37, respectively. The mean baseline score and the mean follow-up score were compared for the FAQLQ-CF, FAQLQ-TF and FAQLQ-PF and its separate domains. There were no significant differences in baseline total and domain scores compared to the follow-up scores in the FAQLQ-CF and FAQLQ-TF and FAQLQ-PF. However, there was a small but, significant increase measured in FAIM score compared with the follow-up score for children as well as a significant decrease in FAIM score compared with the follow-up score for teenagers ($p=0.025$ and $p=0.006$ respectively) (Table 1).

Change in Health-Related Quality of Life after a challenge test with cashew nut in children with a positive and negative challenge outcome (delta scores)

The mean changes in scores (delta scores) were measured for the FAQLQ-CF, FAQLQ-TF and FAQLQ-PF and the separate domains and the group of children with a positive challenge outcome were compared with the group of children with a negative challenge outcome. There were no significant differences in the changes in the scores of the FAQLQ-CF and FAQLQ-PF in the children with a positive challenge outcome compared to the children with a negative challenge result. However, there was a significant difference in the change in score in the domain 'accidental exposure' of the FAQLQ-TF ($p=0.049$). The change in scores for the FAQLQ-TF in total and the other two domains showed no difference between the groups with a positive vs. a

negative outcome. The same applies for the change in the FAIM scores of parents and teenagers.

In children, the delta FAIM score in the negative DBPCFC tested group was significantly better than the delta score in the group with positive challenge outcomes ($p=0.026$). (Table 2)

Possibly influencing factors on Health Related Quality of Life changes

The association of factors that could have influenced the lack of improvement in HRQL were studied using multiple regression analysis in an associative model. Age, centre of recruitment, atopic features as hay fever, asthma and eczema, history of cashew nut allergy, number of reported food allergies, anaphylaxis during DBPCFC, outcome of the DBPCFC with cashew nut, the dose eliciting a reaction during the challenge, were not associated with impairment in HRQL.

A higher FAQLQ baseline score (lower HRQL) significantly influenced improvement of HRQL for the child and the teenager group ($p=0.003$ and $p=0.015$, respectively) and a higher FAQLQ baseline score for parents of the children, was almost significantly associated with improvement of HRQL ($p=0.056$).

The possible influence of symptoms caused by (accidental) cashew intake after the challenge in the 6 months before the FAQLQ's were administered, were also evaluated. In the group of children with a positive challenge, there were no reported symptoms due to accidental exposure during this period of 6 months. In the group of children with a negative challenge, we measured introduction rate and reactions during introduction [12]. Only 3 children experienced mild symptoms during introduction, which did not allow analysis as a possible influencing factor on FAQLQ score.

Longitudinal and cross-sectional validity of Food Allergy of Life Questionnaires

We calculated a significant cross-sectional correlation between the baseline FAQLQ children, teenagers and parents of the children scores and the baseline FAIM scores. The Pearson correlation coefficients thus obtained were 0.48 ($p = 0.005$) for the FAQLQ-CF, 0.73 ($p = 0.000$) for the FAQLQ-TF, and 0.67 ($p = 0.000$) for the FAQLQ-PF. The follow-up score (after 6 months) also showed a significant correlation for the FAQLQ-CF, -TF and PF of 0.58 ($p = 0.000$), 0.74 ($p = 0.000$) and 0.73 ($p = 0.000$), respectively. The correlation between the change in the FAQLQ score (follow-up score minus baseline score) and the change in the FAIM score were correlated for the FAQLQ-TF (0.43, $p = 0.025$) and FAQLQ-PF (0.54, $p = 0.000$), but not for the FAQLQ-CF (0.27, $p = 0.124$).

Discussion

Previous studies with other allergenic foods showed that HRQL significantly improved after the food challenge, with greater improvements in HRQL after a negative outcome than a positive outcome [3, 13]. Our study participants apparently did not experience substantial improvement of food allergy-related quality of life after a cashew nut challenge. However, there was a significant difference in delta score in the FAIM between the children in the group with a positive challenge outcome and those with a negative challenge outcome ($p = 0.026$). We could not find this difference in the teenagers or the parent group. Apparently, a negative challenge outcome improves the self-perceived severity of food allergy in young children. Perhaps young children are more focused on the tested foods than teens and adults, who may be more broadly concerned about their food allergies. This could result in a greater impact of a negative test outcome in younger children. This is also suggested by the observation that introduction of foods into the diet after a negative food challenge, is more successful in younger children than

older children or adults [14]. This may be cause and/or consequence of greater improvement in perceived severity of food allergy in these patients seen in our results.

A possible cause for the lack of improvement in HRQL in this study is the relatively low baseline scores, which corresponded to the relatively benign perception of participants of the severity of their food allergy as measured with the FAIM. Although these were not as low as in the general population, baseline scores in the present study were lower than in several other HRQL studies where patients and not researchers initiated participant contact.

In a study also performed in Dutch children, van der Velde et al. found higher mean baseline scores for the child forms (3.80) and teenager forms (3.89) compared to our study with 3.32 for the child forms and 3.50 for the teenager forms [3]. Thus there was less room for improvement of HRQL in our study compared to the above mentioned study. This is also reflected in the fact that FAQLQ and FAIM scores changed very little in both the challenge positive and even in the challenge negative participants.

Impairment of HRQL may also depend on the food causing the allergy. For example, it is demonstrated that parents of children with milk or egg allergy have a significantly poorer quality of life than parents of children with peanut or tree nut allergy [15]. An explanation for this may be the ease to avoid cashew nut from the diet compared to avoidance of other allergens. The risk of accidental exposure is relatively low as it is seldom a hidden allergen. It is known that the numbers of allergic reactions caused by hidden allergens differ extremely per allergen [16].

Consequently, the dietary impact of cashew nut allergy on the HRQL might be lower than that of, for example, peanut allergy.

Moreover, a previous study by our group demonstrated a low introduction rate of cashew nuts after a negative DBPCFC of 43.3%, probably due to a low perceived need on the part of parents to do so. If the outcome of the DBPCFC does not change the diet of the children, and/or fear

for accidental exposure does not drive the need for accurate diagnosis, then a part of the beneficial effect of the challenge test might be lacking [12].

Possibly, the long-time (6 months) between the challenge with cashew nut and administration of the second questionnaire in our study might also be a reason for the unchanged HRQL in our children. A study by Soller et al. demonstrated an improvement of HRQL after a food challenge test for both allergic and non-allergic patients, however, this effect appeared to wane between 2 and 6 months after the challenge test [17].

The FAIM questionnaire was used to measure the validity of the FAQLQs. The Pearson correlations were significant for the baseline and follow-up scores and established the cross-sectional validity of the FAQLQs for children, teenagers and the parents of the children. The change in FAQLQ scores (follow-up minus baseline score) was significantly correlated with the change in FAIM scores for teenagers and parents of children, but not for children. The latter finding is in contrast to the previous study by Van der Velde et al. [3]. However, their study showed a significant change (improvement) in HRQL after a DBPCFC. Therefore, it is likely that longitudinal validity could not be demonstrated because there was insufficient change in FAIM or FAQLQ scores in this study.

Conclusion

This study in participants of cashew nut allergy showed no difference in the change of HRQL after a positive vs. a negative DBPCFC test outcome. There was no significant change in HRQL after challenge testing, probably because participants did not experience a significant impairment (low baseline score) of their HRQL. Aside from the relative ease with which cashew nut may be

avoided, this study was investigator initiated and not patient initiated. This may have contributed to the relatively good quality of life seen in the study subjects at the start of the study.

Researchers in food allergy should thus be aware that participants recruited to a study may have relatively good initial HRQL and that this may jeopardize efforts to demonstrate improvements in HRQL due to the study intervention.

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Conflict of interest

The authors confirm no conflict of interest

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Table1. Food quality of life before and after the DBPCFC test

FAQLQ Form		Base-line Score (mean)	Follow-up score (mean)	Delta Score (mean)	Statistical Significance (P- value)
Child Form N= 33	FAQLQ				
	Domain 1	3.06	3.57	0.51	0.102
	Domain 2	3.50	3.79	0.29	0.340
	Domain 3	3.93	3.75	-0.18	0.437
	Domain 4	3.44	3.43	-0.01	0.970
	Total	3.32	3.49	0.17	0.491
	FAIM	2.86	3.27	0.41	0.025
Teenager Form N= 26	FAQLQ				
	Domain 1	3.45	3.24	-0.21	0.392
	Domain 2	3.31	3.14	-0.17	0.591
	Domain 3	3.73	3.26	-0.47	0.086
	Total	3.50	3.22	0.28	0.286
	FAIM	3.26	2.89	-0.37	0.006
Parents Form N= 84	FAQLQ				
	Domain 1	2.15	2.24	0.09	0.302
	Domain 2	2.79	2.80	0.01	0.961
	Domain 3	2.28	2.35	0.07	0.532
	Total	2.37	2.43	0.06	0.538
	FAIM	3.17	3.01	-0.16	0.113

FAQLQ= Food Allergy Quality of Life Questionnaire, FAIM= Food Allergy Independent Measure

Table 2. Food quality of life before and after DBPCFC test with cashew nut in children with a positive and negative challenge outcome

FAQLQ Form		Delta score * Positive DBPCFC tested group	Delta score* Negative DBPCFC tested group	Statistical significance (P- value)**
Child Form		N= 24	N=9	
	FAQLQ			
	Domain 1	0.53	0.44	0.777
	Domain 2	0.33	0.18	0.935
	Domain 3	0.14	-0.41	0.777
	Domain 4	-0.27	0.56	0.292
	Total	0.19	0.10	0.840
	FAIM	0.68	-0.32	0.026
Teenager Form		N =21	N=5	
	FAQLQ			
	Domain 1	-0.43	-0.90	0.215
	Domain 2	0.15	-1.49	0.049
	Domain 3	-0.26	-1.31	0.090
	Total	-0.06	-1.18	0.085
	FAIM	-0.32	-0.60	0.252
Parents Form		N=62	N=22	
	FAQLQ			
	Domain 1	0.16	-0.11	0.196
	Domain 2	0.08	-0.19	0.113
	Domain 3	0.08	0.03	0.541
	Total	0.11	-0.10	0.176
	FAIM	-0.07	-0.41	0.066

FAQLQ= Food Allergy Quality of Life Questionnaire, FAIM= Food Allergy Independent Measure, DBPCFC= Double-Blind Placebo-Controlled Food Challenge

* Follow-up score minus baseline score

** Statistical difference between the delta score of the positive and negative tested group

Child form: 1 domain: allergen avoidance, domain 2: risk accidental exposure, domain 3: emotional impact, domain 4: dietary restriction

Teenager form: domain 1: allergen avoidance, domain 2: risk accidental exposure, domain 3: emotional impact

Parents form: domain 1: emotional impact, domain 2: food anxiety, domain 3: social and dietary limitations