

INVITED REVIEW

Quality of life measures for food allergy

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Experimental
Allergy

Summary

Food allergy has become an emerging health problem in Western societies. Although food allergy is characterized by a relatively low mortality and an almost continual absence of physical symptoms, food allergic patients are continually confronted with the possibility of potentially severe reactions and the necessity of dietary vigilance. Health-related quality of life (HRQL) may be the only meaningful outcome measure available for food allergy measuring this continuous burden. HRQL may be measured with generic or disease-specific instruments. Generic instruments may be relatively unresponsive to differences or changes in health status, whereas disease-specific instruments are generally more sensitive for relatively subtle problems related to a particular illness. Recently, a number of disease-specific questionnaires have become available to measure the HRQL of food allergic patients. An important area for further research is the interpretation of the outcome of HRQL measures. In this respect, the minimal clinically important difference (MCID) is of special interest. In combination with the numbers needed to treat (NNT), this may give an ultimate insight into the clinical relevance of an intervention. Since there is still no cure for food allergy, the only available treatment is strict avoidance of the culprit food and provision of emergency treatment. The double-blind placebo-controlled food challenge (DBPCFC) is considered to be the gold standard for diagnosing food allergy. A number of studies have investigated the perceptions of parents whose children underwent a DBPCFC. In contrast to the parental perception, there is much currently still unknown about the effects of undergoing a DBPCFC in the perceptions of patients. In addition to the research on MCID and NNT of food allergy HRQL questionnaires, further research should focus on deriving quality-adjusted life years (QALYs) from food allergy HRQL questionnaires and the application of food allergy HRQL questionnaires at the individual patient level in clinical practice.

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Introduction

The emergence of food allergy in recent decades as an important health problem has resulted in a dramatic increase in scientific research as to the cause, diagnosis, treatment and prevention of this disorder [1]. An important area of activity has been the development of suitable outcome measures which can reflect the severity of the disease as well as changes resulting from diagnostic and/or therapeutic interventions. In the field of allergy, patient-reported outcomes (PROs) have become an important and recommended outcome measure for use in clinical trials [2]. PROs include all health-related reports from patients such as symptom

scores, illness perception or health-related quality of life. However, food allergy is characterized by a relatively low mortality and an almost continual absence of physical symptoms. For this reason, traditional outcome measures such as symptom-medication scores or mortality are insensitive and often inappropriate in this disease [3]. Despite the absence of daily, chronic, physical symptoms, food allergic patients are continually confronted with the possibility of potentially severe or even fatal reactions and the necessity of dietary vigilance which ultimately detracts from their quality of life [4]. Thus, while quality of life is an important outcome measure for any disease, it is perhaps the only meaningful outcome measure available for food allergy [5].

What is quality of life?

Quality of life is a broad concept influenced by multiple factors and integrated at the level of the individual by numerous and complex objective and subjective considerations. A key concept in the study of quality of life as an outcome measure in medicine is health related quality of life (HRQL), which may be regarded as that part of quality of life which is influenced or determined by health and disease [6]. It is essential in both qualitative and quantitative research on quality of life to limit investigation to HRQL, as other areas of quality of life may confound or obscure HRQL outcomes. In qualitative research this is achieved by regularly reinforcing the food allergic context of questions and discussions. In quantitative research this is achieved by the process of validation. Validity is generally considered to be the capacity of an instrument to measure that which one thinks one is measuring. In the case of quality of life, validation attempts to ensure that one is only measuring the part of quality of life influenced by health and disease, or HRQL. This is usually achieved by correlating the responses to items to an independent measure of the disease in question. Such independent measures have traditionally been objective disease parameters which reflect the severity of the illness in question. Since there are no objective disease parameters for food allergy, a suitable independent measure was devised for validation purposes [7] using a method similar to that employed with venom allergy [8, 9]. This independent measure is the food allergy independent measure (FAIM), which captures the patients expectations of the chance and consequences of future encounters with an allergenic food, as well as questions on the subjective extent of food avoidance and social restriction [7].

How may HRQL be measured in food allergy?

Health-related quality of life may be measured in food allergy using qualitative or quantitative methods. Qualitative methods are useful for identifying new areas of interest and forming hypotheses and benefit in this regard from their relatively open structure. Quantitative methods require validated instruments and provide precise outcomes which may be useful as a research tool and/or guide to clinical practice. Instruments suitable for quantitative research may be generic or disease-specific [10]. Generic instruments cover a wide range of basic physical functioning and are suitable for comparing HRQL of patients with different diseases to each other or even comparing HRQL of patients with a disease to healthy controls. The disadvantage of such instruments is they may be relatively unresponsive (or insensitive) to differences or changes in health status. The latter may be overcome by the use of disease-

specific instruments, which are generally more able to pick up relatively subtle problems related to a particular illness. Disease-specific instruments cannot be used to compare HRQL in individuals with different diseases or healthy controls [10]. Because of the lack of daily physical symptoms in food allergy, it was particularly relevant to develop disease-specific instruments for these patients.

Available HRQL measures for food allergy

During the last years, a number of disease-specific questionnaires have become available to measure the HRQL of food allergic patients [11]. Some of these questionnaires were developed for a specific age group and some were developed to be completed by patients themselves or by the parents of food allergic children. However, not all of these questionnaires were thoroughly validated [12].

As part of the EuroPrevall project, a large European multicenter study on food allergy, a series of HRQL questionnaires for food allergic patients of all ages were developed and validated. These questionnaires were named the Food Allergy Quality of Life Questionnaires (FAQLQ). Three of these questionnaires were developed to be completed by the patients themselves and two questionnaires were developed to be completed by the parents of food allergic children:

- FAQLQ – Child Form (CF), completed by children aged 8–12 years [13]
- FAQLQ – Teenager Form (TF), completed by teenagers aged 13–17 years [14]
- FAQLQ – Adult Form (AF), completed by adults 18 years and older [15]
- FAQLQ – Parent Form (PF), completed by parents of children aged 0–12 years [16]
- FAQLQ – Parent Form (PFT), completed by parents of teenagers aged 13–17 years [17]

All these FAQLQs were developed by using the same established methodology [8, 18, 19]. The first step was the item generation in which the food allergic patients were the most important source. This was followed by item reduction using the clinical impact method by which the items were reduced to the most important items as perceived by the patients. Thereafter the questionnaires were cross-sectionally validated by calculating the correlation with the Food Allergy Independent Measure (FAIM). The cross-sectional validation determines whether the questionnaires measure what they are supposed to measure at one point in time. Finally, the longitudinal validity was investigated, which determines the ability of the questionnaires to measure differences over time [20, 21]. The FAQLQs have been translated and validated for use in many European

countries [22] and the USA [16, 23]. These translations were performed following the WHO guidelines [24] which included translation to the target language, back translation to the original language and comparison of the back translation with the original questionnaire. The translation process was followed by cross-cultural validation, which means that for each translation the cross-sectional validity was again investigated in the new language (i.e. correlation between FAQLQ and FAIM).

In addition to the validated HRQL questionnaires developed in the EuroPrevall project, there are several other validated HRQL questionnaires available for food allergic patients. These are the Food Allergy Quality of Life – Parental Burden (FAQL-PB) questionnaire [25] and the Food Allergy Quality of Life – Teen (FAQL-teen) questionnaire [26]. Both questionnaires were developed and validated using a comparable methodology to that used in the development and validation of the FAQLQs. The FAQL-PB is completed by the parents and measures the burden that is incurred and perceived by the parents by having a child with food allergy [25]. The FAQL-teen was developed explicitly for adolescents in the United States [26].

Interpretation of the outcome of HRQL measures

Measuring HRQL in food allergic patients provides insight in the perception of the patient. The outcome of the HRQL measurement is usually expressed as a numeric score, for example a total score and/or domain scores. However, it is not always clear what the clinical significance of such a score is. Similarly, when HRQL is measured before and after an intervention, it is not always clear what the meaning of the change in scores is. A statistically significant difference may not always be perceived by patients as a clinically important difference. Therefore, the concept of minimal clinically important difference (MCID) has been developed. The MCID has been defined as: the smallest difference in score which patients perceive as beneficial and which would mandate, in absence of troublesome side effects and excessive cost, a change in the patient's management [27]. It has been reported that the MCID of HRQL questionnaires with a 7-point scale is usually approximately 0.5 [28]. However, the MCID should be investigated for each individual HRQL questionnaire.

There are different strategies to determine the MCID which may be divided into clinical methods and statistical methods. In contrast to the statistical methods, the clinical methods take the patients' own perceptions into account. The clinical methods asks patients to judge whether they are unchanged, better or worse over a specific period of time (within patients method) or whether they are the same, better or worse compared to

a patient with the same disease (between patients method) by using global rating questions. If patients indicate that they are better or worse, then they are asked to quantify the magnitude of the change or difference on a 7-point scale. A score of 2 or 3 is classified as a small change, a score of 4 or 5 is classified as a moderate change and a score of 6 or 7 is classified as a large change. The mean change score on the target questionnaire of the patients with a score of 2 or 3 on the global rating questions corresponds to the MCID of the target questionnaire [25]. The statistical methods are based on the distribution of the patients' responses to the target questionnaire itself and one example is the standard error of measurement (SEM) [29]. There is emerging evidence for a link between the clinical MCID and the statistical SEM [30, 31]. This may make the calculation of the SEM from the patients' responses to the HRQL questionnaire itself, a usable alternative for determining the MCID by asking patients. The SEM of the FAQLQ-PF has been reported to be 0.45 [20]. The MCID of the FAQLQ-CF, -TF and -AF is currently under investigation and the MCID of the other diseases-specific HRQL questionnaires for food allergic have not yet been reported.

To further elucidate the clinical significance of changes in HRQL scores, such measurements may be used in tandem with estimation of the numbers needed to treat (NNT) [28]. The NNT is the number of patients that need to be treated for one patient to have a clinically important improvement over and above that which the patient would have experienced with the control intervention [32]. NNT has become widely recognized as an intuitively easily understood method for expressing the overall clinical efficacy of an intervention in quantitative terms. Combining the NNT methodology with measurements of HRQL allows estimation of the number of patients that need to be treated in order for one patient to experience a significant improvement in HRQL. This outcome measure is patient reported, quantitative, and grounded with regard to clinical relevance, and is therefore a powerful tool for comparing interventions. An example of this analysis in allergy is its use in a RCT of venom immunotherapy [32]. NNT may be used to compare interventions in food allergy as treatments for this disease become available.

The impact of food allergy on HRQL

The impact of a DBPCFC on food allergy-specific HRQL

Since there is still no cure for food allergy, the only available treatment is strict avoidance of the culprit food and provision of emergency treatment such as an epinephrine auto-injector. In order to identify which

foods should be avoided, an accurate diagnosis is very important. The double-blind placebo-controlled food challenge (DBPCFC) is considered to be the gold standard for diagnosing food allergy. Until recently, however, the effects of undergoing such diagnostic testing on parental perceptions were largely unknown. A number of studies have now been done investigating the perceptions of parents whose children underwent a food challenge [20, 33–36]. In a qualitative study on the mothers' experiences ($n = 6$) following a negative DBPCFC, two themes were identified: 'living with fear of the unknown' and 're-evaluating earlier experiences' [35]. Another study conducted telephone interviews with 46 parents of children who underwent an open food challenge and 54% of them were very satisfied with the food challenge [34]. A questionnaire based survey was performed in 167 parents of children who underwent an open egg challenge. Parental expectations were significantly better in those who underwent a food challenge, irrespective of the outcome of the challenge, than those who had never undergone such a test [33]. In contrast to these studies, a validated questionnaire was used in a study to measure parental anxiety before and after a DBPCFC for peanut or hazelnut. State anxiety of the parents was significantly lower after the DBPCFC of their child, irrespective of the outcome of the challenge [36]. Recently, the first study was published which measured food allergy-specific HRQL before and after DBPCFC. In total, parents of 82 children who underwent a DBPCFC completed the validated FAQLQ-PF. HRQL was significantly improved at 2 and 6 months after the food challenge and the improvement was greater in parents of children who had a negative food challenge (allergy refuted) than those parents of children who had a positive food challenge (allergy confirmed) [20]. In contrast to the parental perception, there is much currently still unknown about the effects of undergoing a DBPCFC in the perceptions of the patients themselves. The impact of DBPCFC on the quality of life of children, adolescents and adults as measured with the FAQLQ-CF, -TF and -AF is currently under investigation. However, preliminary results have also shown that in food allergic adults HRQL is significantly improved 6 months after the DBPCFC irrespective of the outcome of the food challenge. This study also demonstrated that the improvement of HRQL as measured with the FAQLQ-AF was greater in adults who had a negative food challenge (allergy refuted) than those who had a positive food challenge (allergy confirmed) [21].

The impact of food allergy across Europe and the USA

The FAQLQ-AF has been translated to a number of European languages and was completed by food allergic

patients in Iceland ($n = 57$), the Netherlands ($n = 53$), Poland ($n = 71$), France ($n = 40$), Spain ($n = 85$), Italy ($n = 58$) and Greece ($n = 32$). The food allergic adults were recruited through the community survey and outpatient clinic survey of the EuroPrevall study. The FAQLQ-AF was shown to be valid and consistent in these European countries and HRQL scores were comparable between the seven European countries studied [22]. Also, the FAQLQ-CF and FAQLQ-PF have been translated in a number of European countries as part of the EuroPrevall project, but results on validity and outcomes have not yet been published.

In another study, the English translation of the FAQLQ-AF was used in the USA in an online version instead of a conventional paper format. The online version was found to be feasible, consistent and valid in the USA. Interestingly, when comparing the HRQL scores of the American food allergic patients with a sample of Dutch food allergic patients of comparable severity, a greater impairment in HRQL was found for the American food allergic patients. As the American patients reported having been prescribed more epinephrine auto-injectors, prescription of epinephrine auto-injectors and its effect on HRQL may be important targets for further research [23].

Costs and QALYs in food allergy

Health-related quality of life questionnaires measure a part of the costs caused by having food allergy on the subjective well-being and welfare of the patient, also called intangible costs. In addition, food allergy may cause direct costs (e.g. financial costs due to medical treatment) and indirect costs (e.g. time costs or lost working days) [37]. As part of the EuroPrevall project, an economic questionnaire has been developed to measure the economic impact of food allergy [38].

Recently, a few studies have investigated the costs of food allergy. In a nested case-control study in nine European countries, it has been shown that food allergic patients consume twice as much health care as non food allergic individuals [39]. In addition, in the USA the costs of food allergy were estimated to be half a billion dollars in the year 2007 [40]. Finally, when looking at the house-hold level in four European countries, families with food allergic family members have lower direct and indirect costs than house-holds without a food allergic family member [41]. The families with a food allergic member spend less time and money on groceries and food preparing due to the restricted food choices. In addition, social and recreational activities are restricted (i.e. eating out, foreign travel, ordering takeaway food) leading to less expenses compared to families without a food allergic member. In other words, food allergic individuals are not paying for their

disease in terms of money, but in terms of diminished well-being. In order to capture this type of costs, cost-utility analysis would be useful.

Cost-utility analyses can be performed by measuring Quality-Adjusted Life Years (QALYs). QALYs measure the number of healthy years gained by a particular health care intervention. QALYs could be used in cost-utility analysis to calculate the ratio of costs to QALYs gained for a particular health care intervention. An advantage of using QALYs is that health outcomes can be compared across different diseases. Cost-utility analyses are usually based on generic health status measures (e.g. the EQ-5D) [42]. However, generic measures may not be sensitive enough to measure disease-specific problems. Therefore, it would be of value to use a disease-specific HRQL questionnaire for food allergy to calculate utility scores. One possibility is mapping of the disease-specific HRQL questionnaire onto a generic utility index [43, 44]. Another possibility is direct valuation of the disease-specific scores into preferences. It has already been shown that it is feasible to convert data collected with a disease-specific questionnaire for lung cancer into preferences [42]. Further research may focus on the conversion of disease-specific HRQL questionnaires for food allergic patients into QALYs.

Clinical implications of HRQL measures for food allergy

The disease-specific HRQL questionnaires for food allergy that have become available in the last few years have been proven to be valid and reliable and are therefore suitable to use as outcome measure in clinical research. However, these validation and reliability analysis have all been performed at a group level. Therefore, the question arises to what extent these questionnaires can be used at the level of the individual patient to guide treatment in clinical practice. In order to be used at an individual level, the individual validity of the HRQL questionnaires should be investigated. Recently a new method to investigate individual validity has successfully been applied on a disease-specific health status measure in COPD [45].

A first attempt to use a disease-specific HRQL questionnaire with a psychosocial intervention for parents of food allergic children has been described [46]. The authors conclude that the use of the Food Allergy Quality of Life – Parental Burden (FAQL-PB) questionnaire

and expectation of outcome questions may be useful to determine whether families are having difficulty maintaining a balance between anxiety and avoidance strategies. In addition, the HRQL assessment is viewed as a brief therapeutic intervention, since it may reassure parents that their concerns are shared by other parents of food allergic patients [46]. However, further research is needed on the use and validity of disease-specific HRQL questionnaires for food allergic patients at the individual level.

Conclusion

Food allergy is a disorder characterized by low mortality and a preponderance of psychological symptoms, and HRQL is thus the most important outcome measure for this disease. Validated instruments have been devised to measure HRQL for food allergic patients of all ages. These instruments are exceptionally well-suited for measuring differences and/or changes in health status which is clinically meaningful to patients by determination of the minimal clinically important difference (MCID). Using patient data on HRQL obtained in this way, numbers needed to treat (NNT) may be calculated which allows comparison of different treatments. Moreover, NNTs based on HRQL will even allow comparison of treatments for different diseases, and could, together with measures such as quality-adjusted life years (QALYs) provide governments and health care policy makers with a comprehensive analysis of the benefits of health care interventions. In addition to MCID and NNT, further research may focus on unmet needs of food allergic patients, including information needs regarding the presence of allergens, food labelling, as well as factors affecting compliance with proper emergency medication use. Such management strategies could be adapted for individual patients taking into account their specific needs. This will require establishing the validity of food allergy HRQL questionnaires at the individual patient level in clinical practice.

Acknowledgements

Conflict of interest: The authors have no conflict of interest to declare.

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