Enhanced monitoring and screening in pediatric coeliac disease

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CHAPTER 3

Assessment of dietary compliance in coeliac children using a standardized dietary interview

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Abstract

BACKGROUND & AIMS Compliance to a gluten-free diet (GFD) in coeliac disease (CD) is ideally assessed by dietary interviews, albeit time-consuming. Short dietary questionnaires have been developed for adults but not for children. Primary aim was to compare GFD compliance in coeliac children, measured by a short dietary questionnaire against a dietary interview. Secondary aims were correlation between both questionnaires and coeliac antibodies and identifying variables predicting noncompliance.

METHODS Between 2012 and 2014, participants in the eHealth CoelKids study, completed a short dietary questionnaire and standardized dietary interview together with measurement of anti-tissue transglutaminase antibodies (TG2A). Results of the questionnaires were assigned under similar categories. Factors possibly influencing dietary compliance were recorded. Where appropriate, Pearson's Chi-square test for trend, unpaired t-test, Cohen's kappa and one-way ANOVA were used.

RESULTS 151 of 165 participating patients were studied, 66% were female. Mean age was 11.3 years (2-26, SD 5.4), mean age at CD diagnosis was 4.9 years (1-23, SD 4.0). The short questionnaire and dietary interview correlated poorly, detecting problems in dietary adherence in 14% and 52% of the patients, respectively (Cohen's kappa 0.034). Only the short questionnaire correlated with TG2A ($p = 0.003$). Only older age was associated with noncompliance, the mean age of completely nonadherent, adherent but committing errors, and strictly adherent patients were 15.5, 11.5 and 10.1 years, respectively ($p<0.001$).

CONCLUSION Compared to the dietary interview, short dietary questionnaires and TG2A serology failed to detect dietary transgressions in CD children, wherein adolescents were shown to be at highest risk.

Introduction

Coeliac disease (CD) is an immune-mediated systemic disorder elicited by gluten in genetically susceptible individuals and is characterized by anti-tissue transglutaminase type 2 antibodies (TG2A) and enteropathy[1]. In individuals carrying the HLA-DQ2 and/or DQ8 haplotype, the ingestion of gluten (a group of proteins present in cereals such as wheat, barley and rye, can lead to a T cell-initiated inflammatory response, damaging the small bowel mucosa[2]. CD is a common disorder, occurring in approximately 1-3% of the general population[3,4].The disease has a variable clinical presentation, ranging from malabsorption with diarrhea, abdominal distention and weight loss, to nonspecific signs and symptoms such as fatigue, osteoporosis or iron deficiency anemia. CD can be diagnosed by the detection of CD-specific antibodies (usually IgA class tissue transglutaminase antibodies TG2A and anti-endomysium antibodies)[5,6] and small bowel biopsies that show characteristic histological alterations. CD can be successfully treated in most cases with a gluten-free diet (GFD) which restores small bowel histology and improves symptoms. However, this diet may be difficult to follow and may lead to social constraints. It is known that dietary adherence differs among individuals, with noncompliance varying from 25-50%[7-9] among children and adolescents. Despite the absence of a gold standard to assess dietary compliance[10], a dietary evaluation by a trained dietitian is considered the best method[11]. Repeat duodenal biopsies to monitor mucosal recovery is usually not a practical option, especially in children wherein endoscopy to obtain biopsies is done under anesthesia or deep sedation. Serologic testing is not sensitive enough to detect infrequent gluten exposure[12-14]. It has been shown that adults tend to overestimate their level of compliance if they are asked to self-report it[15]. Furthermore, information about the trustworthiness of adherence as reported by parents show a broad range[16]. Food diaries and questionnaires are frequently used in CD research in order to estimated gluten intake. These are, however, mostly used in order to assess the diet's nutritional content[17,18] and have not been validated, except for food questionnaires in infants[19] and children aged 1-4 years[20]. A dietary interview to assess compliance is time-consuming, taking 20-30 minutes per patient, and requires expert personnel. Several short questionnaires have been developed to measure GFD adherence in order to save time and address compliance in a standardized manner. For example, a questionnaire developed in Italy and tested in coeliac adults[13] consists of four questions that take less than a minute to administer. Moreover, it may be filled out even by non-expert personnel or by patients themselves online. To our knowledge, these short questionnaires have never been tested in children, adolescents or young adults.

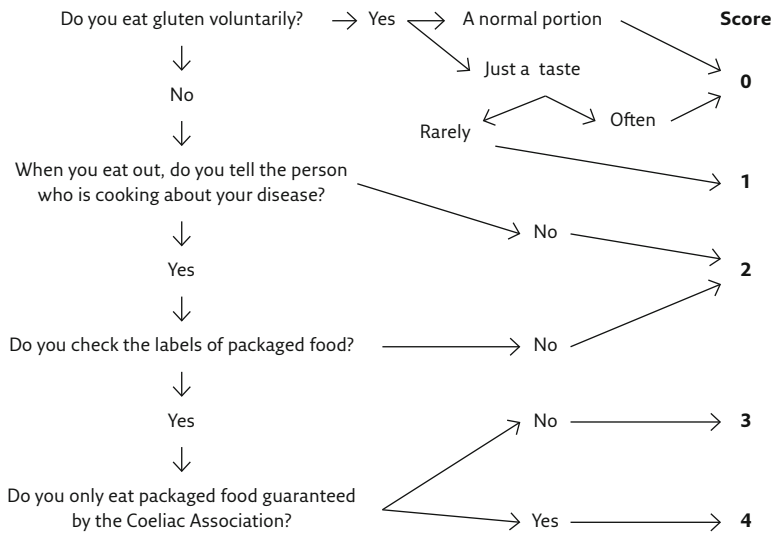
The primary aim of this study was to compare GFD compliance in CD children, adolescents and young adults as measured by a short and standardized dietary questionnaire that has been validated in coeliac adults[13] against a standardized dietary interview.

Secondary aims include 1. the assessment of the correlation between the short dietary questionnaire, standardized dietary interview and coeliac-specific serum antibodies, and, 2. the identification of risk factors for noncompliance with the gluten-free diet.

Materials and methods

For this cross-sectional study, dietary compliance was assessed in coeliac children and young adults participating in the eHealth CoelKids study and who were randomized to receive the usual health care (www.coelkids.nl). Patients were recruited between May 2012 and July 2014. They became eligible if CD was diagnosed according to ESPGHAN criteria[1,21] at least 1 year before enrolment and patients (or their parents) could complete the online questionnaires in Dutch. As part of the CoelKids project, the patients and/or parents were asked to complete two questionnaires about dietary compliance. The first questionnaire consisted of a Dutch adaptation of a short questionnaire validated in Italian CD adults to assess GFD compliance, hereafter referred to as the "short questionnaire"[13] (**Figure 1**) in this article.

Figure 1 *Short diet questionnaire validated in coeliac adults*[13]



'Often': the patient consumes gluten quite frequently that he/she cannot remember when and how many times that has happened. 'Rarely': the patient consumes gluten only occasionally. She/he can remember when and how many times that has happened.

The scores obtained from this questionnaire were divided into three scores: 1 — indicating GFD not followed, 2 — GFD with important errors, 3 — strict GFD. The second questionnaire, hereafter referred to as the "dietary interview questionnaire", consisted of an extensively written patient interview developed by one of the authors (EH) who is an experienced dietitian specializing in CD and GFD. This 26-item questionnaire reflects the patient interview that was verbally conducted during regular face-to-face consultations with the dietitian to evaluate the GFD (**Supplemental material appendix C**). This interview was standardized and converted into a written version for this project. It addresses several domains, including GFD compliance and patient (or parent) knowledge and attitude toward the GFD. For example, they were asked about gluten-free food preparation, the reading of food labels, and the need for extra information/ contact with a dietitian or medical doctor. For optimal comparison, the final scores of the dietary interview questionnaire were grouped into the same three scores obtained from the short questionnaire. In addition, to improve user-friendliness, a comprehensive 11-item version of the dietary interview was also tested (**Supplemental material appendix C**).

The questionnaires were completed after a regular patient (and parent) outpatient visit for CD follow up. The questionnaires were filled out by the parents if the child was younger than 12 years or by the parents and child together if the child was older than 12. Since the visit was a regular medical check for CD, coeliac-specific antibodies in the serum were tested according to (inter-)national CD guidelines[22,23]. The Coelkids study protocol was approved by the Medical Ethical Committee of LUMC and by the respective boards of each participating center and complied with Good Clinical Practice guidelines (registration in the Dutch Trial Register, NTR3688, www.trialregister.nl).

Data management and statistics

The responses to the questionnaires were entered by the participants themselves into a secure web-based data management application (NEN7510 certified). Patient characteristics such as age, age at CD diagnosis and sex were recorded, as was their serum TG2A at the time of questionnaire completion. Pearson's Chi-square test for trend and unpaired t-test and one-way ANOVA were used where appropriate. Cohen's kappa was used to measure inter-rater agreement for the two questionnaires. A two-tailed probability of $p < 0.05$ was considered significant. Analyses were performed with SPSS software (version 20.0, IBM Corp. Armonk, New York).

Results

In total, 151 of 165 children and young adults completed both questionnaires on dietary compliance. Patient characteristics are shown on **Table 1**.

Table 1 *Characteristics of the 151 participating children and young adults with coeliac disease (CD)*

Age (years), median (IQR)	10.2 (7-14)
Age groups, no. (%) 2-6 years 7-10 years 11-15 years >16 years	 27 (18%) 53 (35%) 39 (26%) 32 (21%)
Female, no. (%)	100 (66%)
Age at diagnosis of CD (years), median (IQR)	3.8 (2-7)
Duration of CD (years), median (IQR)	5.3 (3-8)
Anti-tissue transglutaminase type 2 antibodies (TG2A) measured, no. (%)	145 (96%)
TG2A positive*, no. (%), Mean TG2A level if positive, in U/mL (range)	14 (10%) 20.6 (7-56)
Being on another diet in addition to gluten-free diet, no. (%)	9 (6%)
Other family members present with CD, no. (%)	45 (30%)
Expected complaints after eating gluten containing food, no. (%)	39 (26%)

* Cut-off of normality >7 U/ml

The results of the short questionnaire and the dietary interview questionnaire do not correlate with each other since dietary adherence problems (scores 1 and 2) were reported by 52% (n=78) and 14% (n=21) of the patients when using the dietary interview questionnaire and the short questionnaire, respectively (Cohen's kappa 0.034) (**Table 2**).

Table 2 *Inter-rater agreement between the short gluten-free dietary adherence questionnaire and dietary interview, tested in children, adolescents and young adults with coeliac disease, measured by Cohen's kappa.*

Dietary compliance		**Short questionnaire**			
		Score 1 (non- adherent)	**Score 2 (adherent but with errors)**	**Score 3 (strictly adherent)**	**Total**
Standardized interview	**Score 1 (non- adherent)**	11	0	6	17
	Score 2 (adherent but with errors)	3	0	58	61
	Score 3 (strictly adherent)	6	1	66	73
	Total	20	1	130	151

Cohen's kappa 0.034

TG2A were measured in 145 patients wherein 10% of them turned out to be positive. Sex and age at the time of questionnaire completion were similarly distributed among the patients with positive and negative TG2A levels (64% and 66% female, p = 0.87; and 10.6 and 11.0 years, p = 0.79, respectively). However, patients with positive TG2A were significantly older at the time of diagnosis and had been treated with a GFD for a shorter period of time when the questionnaires were filled out (6.5 and 4.3 years, p = 0.017, and 4.1 and 6.8 years, p = 0.042, respectively). Positive TG2A results were mostly seen in children 2-6 years of age as well as among adolescents and young adults >16 years (both groups 15%). As shown in **Table 3**, only the results of the short GFD questionnaire were significantly associated with the presence of a positive TG2A, which was found in 35% (n=6) of the patients with self-reported noncompliance (n=17) versus 6% of the patients who reported good adherence (n=8 out of 127 patients, p=0.003).

Table 3 *Distribution of anti-tissue transglutaminase type 2 serum antibodies (TG2A) levels in 145 coeliac patients according to the results obtained from the gluten-free diet (GFD) adherence questionnaires.*

Short dietary questionnaire†	**Number of patients**	**TG2A positive* patients Number**	**%**	**p-value (Fisher's exact test)**
1 Non adherence	17	6	35	
2 Errors	1	0	0	p = 0.003
3 Good adherence	127	8	6	
Standardized dietary interview†	**Number of patients**	**TG2A positive* patients Number**	**%**	**p-value (Fisher's exact test)**
1 Non adherence	14	3	21	
2 Errors	59	6	10	p = 0.191
3 Good adherence	72	5	7	

* Cut-off normality >7 U/ml

† Score of 1 reflecting non-adherence to a GFD, 2 reflecting adherence to a GFD but with errors that require correction, and 3 reflecting strict adherence to a GFD.

Older age was the only factor significantly associated with noncompliance, with mean ages of 15.5 , 11.5 and 10.1 years for patients who were completely non-adherent to the diet, those who adhered but committed errors, or those who strictly adhered, respectively (p<0.001). Compliance to the GFD diet was best in children younger than 6 years of age, with strict dietary compliance (score 3) in 74% of them, and without any child

in the totally non-adherent group (score 1). Sex, age at CD diagnosis and the presence of other family members with CD did not influence GFD compliance (data not shown), nor did being on another diet in addition to the GFD (data not shown) or the presence of complaints after gluten ingestion.

Since the results of the short questionnaire did not correlate with that of the dietary interview questionnaire, we modified the latter to become more comprehensive and user-friendly. To achieve this, the items of the dietary interview questionnaire were separately weighed using item-total correlation, with regard to their contribution to the score. This resulted in reduction of the total number of items from 26 to 11. For reproducibility and verification, this modified questionnaire was tested in the 158 coeliac children and young adults of the eHealth intervention group of Coelkids, who also completed the short diet questionnaire and the dietary interview questionnaire. Sex, age and disease duration at time of questionnaire completion were similar in the Coelkids intervention and control group: 69 and 66% female, 11.0 and 11.4 years and 6.9 and 6.7 years, respectively. As shown in **Table 4**, there was a moderate correlation between the results of self-reported dietary adherence as assessed by the dietary interview questionnaire and the adapted questionnaire with 11 items (Cohen's kappa 0.56). All patients who reported to be totally non-adherent the GFD by using the dietary interview questionnaire (n=14) also reported as non-compliant upon completing the adapted 11-item questionnaire. However, discrepancies in self-assessed dietary adherence were observed in 24% of the patients (n= 38).

Tabel 4 *Inter-rater agreement between the long gluten-free diet adherence questionnaire, tested in children, adolescents and young adults with coeliac disease, and its modified gluten-free diet score, measured by Cohen's kappa.*

Dietary compliance		**Modified score**			
		Score 1 (non-adherent)	**Score 2 (adherent but with errors)**	**Score 3 (strictly adherent)**	**Total**
Standardized interview	**Score 1 (non- adherent)**	14	0	0	14
	Score 2 (adherent but with errors)	0	35	22	57
	Score 3 (strictly adherent)	0	16	71	87
	Total	14	51	93	158

Cohen's kappa 0.56

Discussion

Although GFD is the only effective therapy for CD, guidelines that assess dietary adherence do not exist for either adults or children. By using a standardized dietary interview questionnaire in this study, we found a high percentage (52%) of children, adolescents and young adults who followed the GFD, but they did so with errors or did not follow the diet at all. In 40% of these coeliac patients, dietary transgressions would have been unnoticed if dietary adherence were only assessed using CD-specific serology and the short dietary adherence questionnaire validated in adults. This short questionnaire has proven to have a good correlation with serum levels of coeliac-specific antibodies in adults[13] and in children during their first year of starting a GFD[24]. Our results however show that patients may have negative TG2A serology, yet do not strictly adhere to the diet when using the long questionnaire derived from the dietary interview. This discrepancy between GFD adherence and results of CD serology has been previously demonstrated, both for EMA and TG2A[9,25,26] and indicates that measurement of CD-specific antibodies is not a sensitive tool to detect problems in dietary adherence[24]. One of the main differences between the short GFD adherence questionnaire and the dietary interview questionnaire is that the latter addresses practical issues possibly leading to errors related to the GFD such as storing gluten-free products at home separate from gluten-containing food, and preparing gluten-free food with separate kitchen utensils. These issues address the actual daily risk of gluten consumption. Despite our efforts, we were unable to reduce the length of the dietary interview questionnaire. However, with the increasing use of electronic patient records and eHealth tools, completing questionnaires before or during a medical consultation should be easily implemented in the health care for children and young adults with CD. In addition, we expect that this will contribute to improvement of care for CD patients by, on the short term empowering them, leading to a better diet adherence, and possibly, on the long-term, by avoiding complications of their disease. If a better dietary assessment will also result in improvement of symptoms can only be investigated in (future) prospective studies.

One of the strengths of this project is the prospective design and the relatively large group of patients included. All participants completed the questionnaires and TG2-serology was available in 96% of them. Our cohort seems representative for CD children and young adults, including the decreased dietary compliance in adolescents; an established fact in CD populations[8,27].

One may argue that since the dietary interview questionnaire was designed with the purpose of this project in mind, without previous validation, it might not accurately demonstrate problems with GFD compliance. The questionnaire, however, was developed by an experienced dietitian who has worked extensively with coeliac patients. It

therefore reflects the patient encounter and contains the same questions asked during this dietetic consultation. Furthermore, completing the standardized dietary questionnaire by patients avoids omissions that may occur during face-to-face consultations, for example, due to insufficient time. A possible limitation could be the fact that we also included CD patients who had been on a GFD for only 1 or 2 years. In our opinion, the first year on a GFD is intense and essential to learn how to adhere to the diet (with regard to shopping, reading etiquettes, contamination etc). Therefore, face-to-face contact seems to be more adequate than questionnaires. One could argue that CD specific serology might not have normalised in the first 1-2 years on a GFD, thus impeding the correlation between serology and the questionnaires. However, it has been shown that TG2A normalisation occurs after 12 months on a GFD in the majority of children[28], therefore limiting this effect.

Recent developments in diet monitoring include a new method of measuring gluten immunogenic peptides in the stool and urine[29,30], which seem to enable direct and quantitative assessment of gluten ingestion. However, its future role needs to be more extensively evaluated because result manipulation by gluten avoidance prior to testing is possible since gluten immunogenic peptide analysis only detects gluten if ingested a few days before testing.

In conclusion, our results show that dietary adherence should be assessed by a dietary interview in combination with specific CD antibodies determination. Available short dietary questionnaires and TG2A serology alone do not detect all errors in GFD adherence in children and young adults. A standardized dietary questionnaire reflecting the regular dietary interview as performed by an experienced dietitian is a good alternative to face-to-face contact.

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