

ORIGINAL RESEARCH—CLINICAL

Association in Clinical Practice Between Gluten Intake and Gluten Immunogenic Peptides in Celiac Children

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BACKGROUND AND AIMS: The dietary compliance and its assessment in celiac disease (CD) patients on a strict gluten-free diet (GFD) remain a challenge. Two relatively new, validated methods have been proposed to detect occasional gluten ingestion: standardized dietary questionnaire and determination of urinary gluten immunogenic peptides (GIPs). Our aim was to prospectively assess dietary compliance via these methods and compare their results with those of tissue transglutaminase antibodies (tTGA). **METHODS:** This was a prospective single-center study. Consecutive CD patients (aged 1–18 years) on a GFD scheduled for regular consultation between March and August 2019 were invited. In addition to standard care, a completed dietary questionnaire and urine sample for GIP were collected. Pearson's chi-square test, Fisher's exact test, and Mann-Whitney U test were performed. **RESULTS:** Of the 156 eligible children, 110 provided informed consent. Completed dietary questionnaire, GIP, and tTGA results were available from 86 children (median age 12.8 years, median GFD duration 30 months, 65% female). Adherence to the GFD evaluated by GIP, dietary questionnaire, and anti-tTGA was 94.2%, 75.6% and 94.2%, respectively. No association was found between the tTGA results and the detection of GIP, as well as between the tTGA results and the dietary questionnaires scores ($P = .5$ and $.312$, respectively). The participants perceived both the questionnaire and the measurement of GIP as reassuring with regard to correct implementation of the GFD. **CONCLUSION:** All the 3 methods have limitations to monitor dietary compliance. The comparison of their performance shows that the best single method is the use of the validated dietary questionnaire, which should therefore be implemented in the regular care for children with CD. The most effective combination of dietary questionnaire and urinary GIP determination should be used in specific clinical situations.

Keywords: Gluten Immunogenic Peptides; Dietary Adherence; Gluten-Free Diet; Celiac Disease

Introduction

The only effective treatment for celiac disease (CD) is a strict life-long gluten-free diet (GFD), which usually improves symptoms, restores small bowel histology, and avoids long-term complications.^{1,2} Nevertheless, dietary adherence is a challenge because of dietary restrictions,

poor labeling regulations, sociocultural restrictions, decreased quality of life and limited availability, and high costs of gluten-free alternatives.^{3–5} Dietary compliance in children with CD has been estimated as 25%–50%.^{1,5,6} The golden standard to assess mucosal healing (ie, endoscopy and small bowel biopsies) is an invasive procedure that is not performed during regular check-ups. Usually, compliance with the GFD is evaluated by dietary interview with a dietician and/or by serum determination of immunoglobulin A against tissue transglutaminase (tTGA).^{4,7} However, both methods have limitations, as tTGA testing is insufficiently sensitive for detecting occasional dietary transgressions, and dietary evaluation by a trained dietician is time consuming and not always available in clinical settings and dependent on patient reporting.^{5,8,9}

Other methods to determine gluten ingestion by CD children are a standardized dietary questionnaire reflecting a regular interview by a specialized dietician and the measurement of gluten immunogenic peptides (GIPs) in urine or stool.^{5,6,10,11} GIP are small fragments of gluten resistant to gastrointestinal digestion, causing the immunotoxic T-cells reaction in CD patients. A fraction of the GIP makes it into the circulation and is excreted in urine, being detectable after 4–6 hours and remains detectable for up to 24–36 hours.¹¹ The test is highly sensitive with a limit of detection of ≥ 50 mg of ingested gluten, taking into account that the maximal gluten ingestion during a strict GFD should not exceed 10–20 mg/d.¹²

The aim of this study was to prospectively compare the performance of 3 methods to assess dietary compliance in clinical practice during the follow-up of CD children: via validated dietary questionnaire, GIP in urine, and tTGA determination in serum.

Abbreviations used in this paper: CD, celiac disease; DQ, dietary questionnaire; ESPGHAN, European Society for Pediatric Gastroenterology Hepatology and Nutrition; GFD, gluten-free diet; GIP, gluten immunogenic peptides; LUMC, Leiden University Medical Centre; tTGA, antitissue transglutaminase antibodies.

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2772-5723

<https://doi.org/10.1016/j.gastha.2022.04.015>

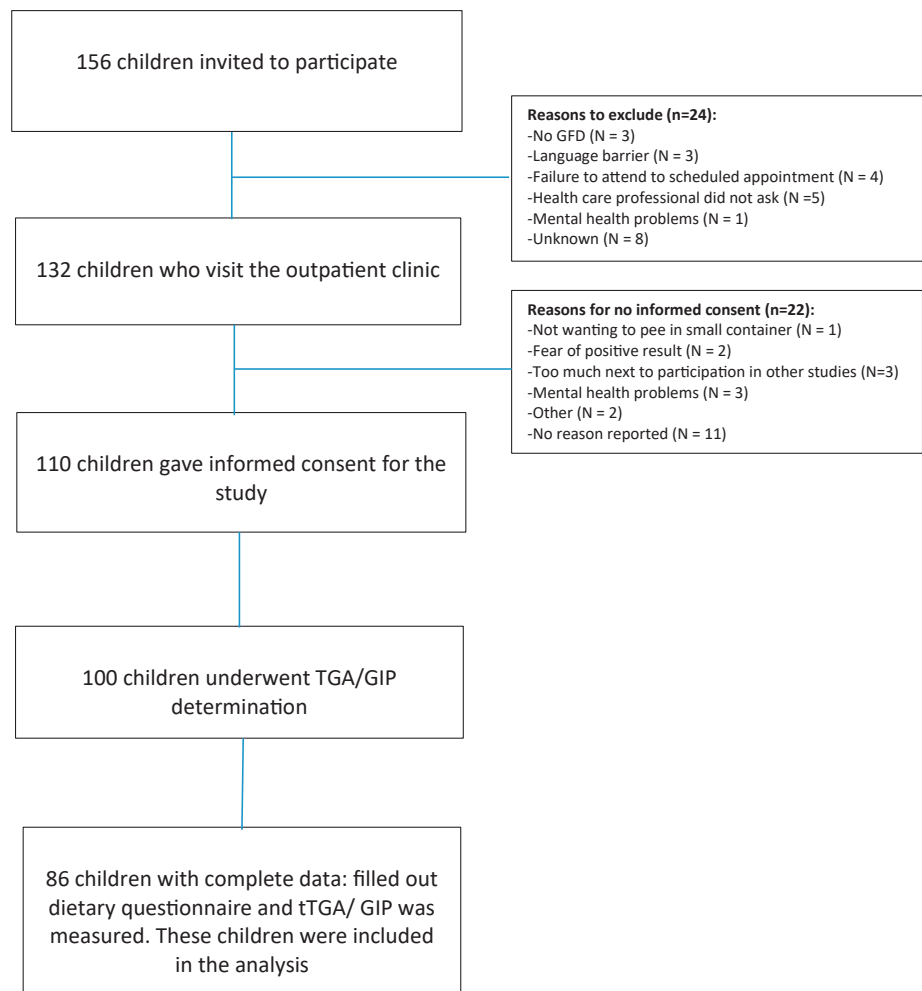


Figure. Flowchart of the eligible children with celiac disease (CD), including the reasons for exclusion and no informed consent.

Methods

Study Population

For this prospective single-center implementation study, consecutive patients with CD (1–18 years) attending the celiac outpatient clinic of the Leiden University Medical Center (LUMC) for a regular follow-up visit were recruited between March 2019 and August 2019. Inclusion criteria were CD diagnosed according to the guidelines of the European Society for Pediatric Gastroenterology Hepatology and Nutrition, following a GFD, parents/child having sufficient knowledge of the Dutch language, and written informed consent.¹³ Consent was provided by parent/legal guardians and also by children ≥ 12 years old. Patient characteristics were collected from the electronic medical record. All authors had access to the study data and reviewed and approved the final manuscript.

Procedure

Invitation to participate in the study was sent by letter to (parents of) the children 2–3 weeks before their appointment at the outpatient clinic. It was explained that participation included providing a urine sample for the detection of GIP collected on the day of the consultation. In addition, (parents of) children were asked to complete the Dutch version of the validated dietary questionnaire on the compliance with the GFD

[5; Annex 1]. The questionnaire addresses several domains, including compliance with and knowledge of the GFD and the attitude toward the diet. Each answer corresponds with a point score, which were not visible for the (parents of) the children, providing a score between 0 and 84, which corresponds to 1. Strict GFD (0–2 points); 2. GFD with important errors (3–20 points); and 3. GFD not followed (21–84 points; [Supplementary Material](#)).⁵

Furthermore, the children received the standard care for CD, including tTGA determination (ThermoFisher, Germany; ImmunoCAP250; cut-off of normality 7 U/mL).

GIP in urine was determined at the clinical chemistry laboratory of the LUMC, blinded for clinical information and tTGA results, using the iVYCHECK GIP Urine kit (Biomedal, Spain), following the manufacturer's instructions. The results were expressed as ng GIP per 1 mL of urine, with the limit of detection being 2.2 ng GIP/mL (>50 mg of ingested gluten).

If dietary adherence was considered as insufficient by raised tGA titers, positive GIP, or dietary questionnaire, a referral to a dietician was offered.

Statistical Analysis

A Shapiro-Wilk test was used to test for the normality of the data. Where applicable, Pearson's chi-square test, Fisher's exact test, or Mann-Whitney U test was used for evaluating baseline

Table 1. Characteristics of the 110 Children Who Gave Informed Consent for the Study and the Children Who Declined Informed Consent (n = 22)

Characteristic	Participating CD children (N = 110)	Declined informed consent (N = 22)	P value
Age (y), median	12.8	11.1	.128
Age groups, n (%)			
0–4 y	16 (14%)	4 (18.2%)	.06
5–12 y	61 (56%)	6 (27.3%)	.13
≥13 y	33 (30%)	12 (54.5%)	.03
Female, n (%)	71 (64.5%)	13 (59.1%)	.1
Age at diagnosis of CD (y), median	4	7.1	.158
Duration of GFD (mo), median	30	74	.24
0–24, n (%)	35 (32%)	6 (27.2%)	.31
25–48, n (%)	21 (19%)	3 (13.6%)	.83
≥49, n (%)	54 (49%)	13 (59.1%)	.68
Positive family history of CD, n (%)	55 (50%) ^a	7 (31.8%)	.318
Filled in dietary questionnaires, n (%)	95 (86.3%)	–	
Score dietary questionnaire, mean (range)	1.77 (0–14)	–	
Anti-tTG measured, median (range)	8.9 (0–104)	7.7 (0.1–44)	.655
Elevated anti-tTG ^b , n (% of measured anti-tTG)	22 (20%)	5 (22.7%)	.922
GIP measured in urine, n (%)	100 (90.1%)	–	
GIP present, n (% of measured GIP)	5 (4.5%)	–	
GIP levels (ng/mL), median (range) ^c	8.74 (7.88–14.27)	–	

Bold values indicate statistical significance ($P < .05$).

CD, celiac disease; GFD, gluten-free diet; GIP, gluten immunogenic peptides; tTG, antitissue transglutaminase type 2 antibodies.

^aFamily history was unknown in 4 children.

^bCut-off of normality >7 U/mL.

^cMedian concentration from positive tests only.

characteristics. Furthermore, these tests were used to estimate the strength of association between the outcomes reported in the dietary questionnaire, GIP, and tTGA levels. A 2-tailed probability of $P < .05$ was considered statistically significant. Statistical analyses were performed using SPSS 25.0.

Ethical Considerations

The study was approved by the Medical Ethics Committee of Leiden-Den Haag-Delft (P18.241).

Results

The flowchart of the eligible children for the study is presented in Figure. In total, 156 children were eligible for participation, and (the parents of) 110 gave informed consent (70.5%); median age: 12.8 years, 71 females (64.5%). Characteristics of the children who gave informed consent and of the children who refused participation were similar, except for age >13 years because these children refused participation significantly more ($P = .03$; Table 1). In total, 86 children had complete data (filled out dietary questionnaire and measured tTGA and GIP) and were included in the analyses (Figure).

Twenty-one children (24.4%) had elevated tTGA levels (median age 11.0 years [range 2–15], median duration GFD

22.9 months [range 3–135]). Of them, 16 had a decreasing trend in antibody titers from the start of their GFD, with 10 children following the diet for <1 year. Increased tTGA results were observed in 5 children, 4 of which were older than 11 years of age, with a median duration of GFD of 35 months (range 23–138). The children with elevated tTGA (n = 21) followed a GFD significantly shorter than those with negative antibodies (median duration 22.9 vs 69.3 months; $P = .02$), although the median age of both groups was similar ($P = .937$).

Five children (5.8%; 4 females; median age 8 years [range: 4–16]) had detectable urinary GIP with a median level of 8.74 ng/mL (7.88–14.27). Their characteristics were similar in terms of age, median duration of the GFD, age at diagnosis, and gender to the ones of the GIP negative children ($P = .382$, $P = .293$, $P = .996$, and $P = .068$, respectively; data not shown).

Only the parents of a 7-year-old girl with positive GIP and rising tTGA, who followed the GFD for 36 months, agreed to have a consultation with the dietician. The parents of the other 4 children reported “not seeing an added value in an appointment with a dietician” as they already knew what caused the positive GIP test, including “gluten contamination or a small mistake at a new school,” “probable mistake in hand hygiene,” “probable mistake at grandparents or school,” and “occasional intentional gluten consumption.”

Table 2. Comparison of the Patient Characteristics Following a Strict Gluten-Free Diet or Reporting Dietary Errors According to the Dietary Questionnaires

Score dietary questionnaire	Strict GFD ^a N = 65 (%)	GFD with important errors ^b N = 21 (%)	P value
Median age, y	9.23	11.3	.974
Age groups (y)			.097
0–4	9 (13.8)	1 (4.7)	.08
5–12	43 (66.2)	10 (47.6)	.01
≥13	13 (20.0)	10 (47.6)	.01
Median age at diagnosis (y)	4.97	5.29	.398
Female	43 (68.3)	14 (60.9)	.932
Symptoms after unintentional gluten intake	51 (81.0)	18 (78.2)	.313
Positive family history for CD	34 (54.0)	9 (39.1)	.467
Only one person following a GFD at home	37 (58.7)	8 (34.7)	.374
Other dietary restrictions	6 (9.5)	1 (4.3)	.184
Median duration of GFD in months (range)	38.7 (2–184)	64.4 (4–193)	.533

Bold values indicate statistical significance ($P < .05$).

CD, celiac disease; DQ, dietary questionnaire; GFD, gluten-free diet.

^aStrict GFD is defined as score between 0 and 2.

^bScores between 3 and 20 on dietary questionnaire on adherence to the gluten-free diet.⁵

On the dietary questionnaire, 21 children (24.4%) reported important errors (median age 11.3 years [range 2–17]; median duration GFD 64.4 months [range 4–193]). The most frequent errors were “consuming food with a label may contain traces of gluten or wheat” ($n = 42$), “consuming food with a label “prepared in an environment where gluten/wheat is processed” ($n = 29$), and “consuming naturally gluten-free flour with no gluten-free label or logo” ($n = 16$). The characteristics of the children who reported strictly complied with the GFD ($n = 65$) were similar to those reporting dietary errors ($n = 21$; [Table 2](#)).

In total, 80 (93.0%) children and/or their parents stated that they had enough knowledge of the GFD. The 6 children/parents reporting insufficient knowledge, followed the GFD significantly shorter than the others (14 months vs 59 months; $P = .008$). Two of these children had a positive urinary GIP and scored important errors on the dietary questionnaire.

The absence of association between the tTGA results and the detection of urinary GIP as well as between the tTGA results and the ones from the dietary questionnaires is presented in [Table 3](#) ($P = .5$ and $.312$, respectively). Likewise, no significant association was found between the

scores of the dietary questionnaire and the measurement of GIP in the urine ($P = .08$; [Table 4](#)).

Discussion

To the best of our knowledge, this is the first study comparing 2 relatively new methods to detect (un)intentional noncompliance with the GFD in children with CD, namely, a validated dietary questionnaire reflecting a regular dietary interview as performed by an experienced dietician and the measurement of urinary GIP. Our results did not show an association between the results of tTGA and the dietary questionnaire, tTGA, and GIP or the dietary questionnaire and urinary GIP.

By using the dietary questionnaire, we found that 24.4% of our population was not fully compliant to the GFD vs 5.8% as assessed by urinary GIP. Elevated but decreasing tTGA was found in 16 of 21 children (76%) who followed the GFD for a relatively short time of 22.9 months, which is in agreement with the time frame in which normalization of tTGA usually occurs.^{7,14,15} Also, 5 children showed an increase/stagnation in their tTGA titers (5.8%), but only one

Table 3. Association Between tTGA and GIP Results and Between tTGA and Dietary Questionnaire (DQ) Scores in 86 Children

tTGA, n (%)	GIP, n (%)		P value	Score DQ			P value
	Positive N = 5	Negative N = 81		Strict GFD N = 65	Errors GFD N = 21	Nonadherence	
Elevated 21 (24)	2 (9)	19 (91)	.5	17 (81)	4 (19)	0	.312
Normal 65 (76)	3 (5)	62 (95)		48 (74)	17(26)	0	

Table 4. Association of GIP Results and Dietary Questionnaire (DQ) Scores in 86 Children

GIP	Score DQ		P value
	Strict GFD ^a N = 65	Errors GFD ^b N = 21	
Positive (N = 5)	3	2	.08
Negative (N = 81)	62	19	

DQ, dietary questionnaire; GFD, gluten-free diet; GIP, gluten immunogenic peptides; tTGA, antitissue transglutaminase antibodies.

^aStrict GFD is defined as score between 0 and 2.

^bImportant errors between 3 and 20.

of them had positive GIP. Our results therefore show that the dietary questionnaire is the best single method to detect occasional gluten intake. The discrepancy between the dietary compliance assessed by the questionnaire and the results of tTGA in our study confirms the lack of sensitivity of CD serology to detect occasional transgressions as shown in previous studies.^{6,10,16–19} Nevertheless, 3 of 5 children with detectable GIP in their urine did not report dietary transgressions in their questionnaire. This suggests that the combination of the dietary questionnaire and urinary GIP is the most effective method to detect occasional/inadvertent gluten intake. To calculate the diagnostic performance of the evaluated methods in terms of sensitivity, specificity, positive predictive value, and negative predictive value is not possible by lacking of a gold standard to assess dietary compliance.

The noncompliance with the GFD of almost 25% found in our study using the questionnaire agrees with the previously reported noncompliance of 25%–50%,⁵ indicating that our population is representative of children with CD. However, the number of patients with detectable GIP in their urine in our study (5.8%) is surprisingly low compared with other studies performed on CD children in other countries. A systematic review of the literature reported fecal GIP detection in 25% of the children.¹ Four prospective studies among children (2 combined with adults) assessing diet adherence by fecal/urinary GIP showed noncompliance in 45%, 29.8%, 16%, and 14.5% of patients.^{8,16,20,21} This discrepancy may be explained by the difference in methodology. Our population received information 2 weeks before the consultation describing the aim of the study and the purpose of the use of the urine for the detection of excreted gluten peptides. This may have established a time frame in which the children could re-evaluate and improve their compliance with the diet. Also, urinary GIP as assessed in this study is only detectable for 36 hours after gluten ingestion, in comparison to 4–7 days in the feces as used in other studies,^{8,20,21} and we may have missed dietary transgressions made before this time

frame. Another possible limitation of our study is the relatively small number of participating children, although it is comparable to (or even higher) sample sizes from previous studies performed of children.^{8,11,16,21}

Most of the previous studies on GIP in feces and/or urine did not describe the manner in which the included patients were informed.^{11,16,22} It is possible that recruitment of patients on short notice could have led to a higher number of positive GIP in those studies, as the 16% reported by 1 study in which the participants were not specifically aware of the GIP measurement.⁸ Nevertheless, if urinary GIP determination is implemented in the regular consultations in the long term, the CD patients would become aware of it. As such, sending study information before the consultation in our study is comparable with the possible implementation of GIP in the standard of care for CD children.

Another possible explanation of the low frequency of positive GIP in our study may be the high number of children aged >13 years who refused participation in the age category with the highest percentage of noncompliance to the GFD.¹⁶ A possible reason for declined consent may have been the fear of the exposure of potential noncompliance with the diet through a positive GIP result.

In addition to detect errors in the GFD, urinary GIP determinations may also be used to guarantee or reassure (parents of) patients that the GFD is correctly adhered to. This was also reported in the interviews that were taken by a randomly selected number of children and/or parents after terminating the study. The majority of (parents of) the patients believed that the test had an added value, especially in children who remained symptomatic or who were still familiarizing themselves with the diet (results not shown).

Our results show that from the 3 evaluated methods, the dietary questionnaire is the best single one to detect noncompliance with the GFD compared with the other methods, and we, therefore, propose it for assessing diet adherence during the regular follow-up of CD children. In addition, the validated dietary questionnaire also identifies sources of noncompliance, facilitating self-correction by the patient. With the increasing use of eHealth, partly due to the COVID pandemic, completing and processing the questionnaire will become easier and the implementation in standard health care more accessible and less time consuming.

The combination of the dietary questionnaire and urinary GIP test is the most effective method in detecting (un)intentional gluten transgressions. This combination may be implemented in specific clinical settings to rule out (un)intentional gluten consumption or gluten cross-contamination, namely, in children (1) with recently diagnosed with CD as they familiarize themselves with the GFD, (2) reporting symptoms with normal tTGA and no errors in the dietary questionnaire, (3) with (persistent) elevated or very slow normalization of tTGA levels despite no errors in the dietary questionnaire, and (4) with suspected intentional gluten intake.

Code Availability

Custom codes are available on request to the corresponding author.

Supplementary Materials

Supplementary data associated with this article can be found, in the online version, at <https://doi.org/10.1016/j.gastha.2022.04.015>.

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Received December 21, 2021. Accepted April 22, 2022.

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Conflicts of Interest:

The authors disclose no conflicts.

Funding:

No funds were received for the study. Biomedal provided 100 GIP test strips and the reader.

Ethical Statement:

The corresponding author, on behalf of all authors, jointly and severally, certifies that their institution has approved the protocol for any investigation involving humans or animals and that all experimentation was conducted in conformity with ethical and humane principles of research.

Data Transparency Statement:

Available on request to the corresponding author. The study protocol is included as a data supplement available.