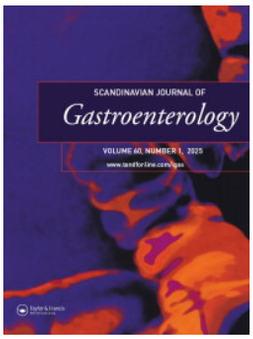


Scandinavian Journal of Gastroenterology

ISSN: (Print) (Online) Journal homepage: www.tandfonline.com/journals/igas20

Suboptimal adherence to a gluten-free diet in adults with both type 1 diabetes and celiac disease using urinary gluten immunogenic peptide measurement

Kristine Vaage Hatlen, Therese Margrethe Lysell Lensnes, Christine Henriksen, Tore Julsrud Berg, Ingrid Nermoen & Knut Erik Aslaksen Lundin

To cite this article: Kristine Vaage Hatlen, Therese Margrethe Lysell Lensnes, Christine Henriksen, Tore Julsrud Berg, Ingrid Nermoen & Knut Erik Aslaksen Lundin (2025) Suboptimal adherence to a gluten-free diet in adults with both type 1 diabetes and celiac disease using urinary gluten immunogenic peptide measurement, Scandinavian Journal of Gastroenterology, 60:1, 28-36, DOI: 10.1080/00365521.2024.2442688

To link to this article: https://doi.org/10.1080/00365521.2024.2442688

SCANDINAVIAN JOURNAL OF GASTROENTEROLOGY
2025, VOL. 60, NO. 1, 28–36
https://doi.org/10.1080/00365521.2024.2442688

Taylor & Francis
Taylor & Francis Group

RESEARCH ARTICLE

OPEN ACCESS Check for updates

Suboptimal adherence to a gluten-free diet in adults with both type 1 diabetes and celiac disease using urinary gluten immunogenic peptide measurement

Kristine Vaage Hatlen[a], Therese Margrethe Lysell Lensnes[b], Christine Henriksen[b], Tore Julsrud Berg[a,c], Ingrid Nermoen[a,d] and Knut Erik Aslaksen Lundin[e,f]

[a]Institute of Clinical Medicine, University of Oslo, Oslo, Norway; [b]Department of Nutrition, Institute of Basic Medical Sciences, University of Oslo, Oslo, Norway; [c]Department of Endocrinology, Oslo University Hospital, Oslo, Norway; [d]Department of Endocrinology, Akershus University Hospital, Lørenskog, Norway; [e]Norwegian Coeliac Disease Research Centre, Institute of Clinical Medicine, University of Oslo, Oslo, Norway; [f]Department of Gastroenterology, Oslo University Hospital Rikshospitalet, Oslo, Norway

ABSTRACT

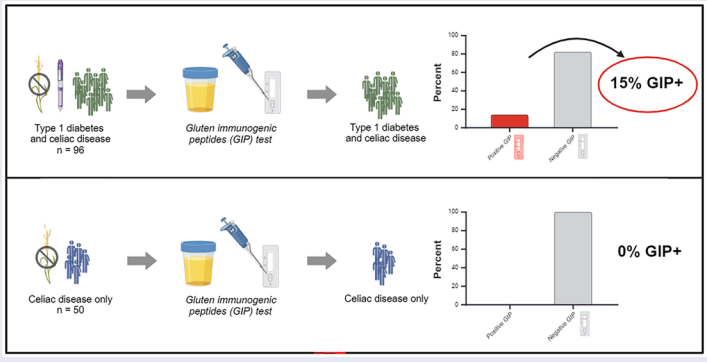
Objectives: Concurrent type 1 diabetes (T1D) and celiac disease (CeD) pose challenges in insulin dosage adjustments and gluten-free dietary adherence. Urine testing for gluten immunogenic peptides (GIP) is a new method to detect gluten exposure within the last 3–12 h. Our aims were to compare gluten-free dietary adherence between T1D+CeD and CeD individuals and evaluate urinary GIP testing in an outpatient setting.

Materials and methods: This observational cross-sectional study included three adult groups: (1) T1D and CeD, (2) CeD only, and (3) T1D only. T1D participants were recruited from outpatient clinics, the CeD group via social media. One urine sample (12 pm–7 pm) was analyzed using a qualitative immunographic GIP test. CeD participants completed 'Celiac Dietary Adherence Test' (CDAT) and 'Celiac Symptom Index' (CSI) questionnaires. IgA anti-transglutaminase 2 (IgA-TG2) and IgG anti-deamidated gliadin (IgG-DGP) serology were also analyzed.

Results: 197 participants, mean (SD) age 43 (15) years, were included. Female percentages were: CeD: 90%, T1D+CeD: 64%, and T1D: 47%. Positive urinary GIP was found in 15% (14/96) of T1D+CeD and 0% (0/50) of CeD ($p=0.002$). As expected, most T1D only participants had positive urinary GIP (86%, 44/51). CDAT and CSI scores did not differ between T1D+CeD and CeD groups. Positive IgA-TG2 and/or IgG-DGP levels were found in 12% of T1D+CeD and 6% of CeD participants ($p=0.38$).

Conclusions: A single GIP urine test revealed higher gluten exposure in T1D+CeD versus CeD only, questioning dietary adherence in this population. Urinary GIP tests can be useful for clinical follow-up.

GRAPHICAL ABSTRACT



Created with BioRender.com

Abbreviations: T1D: (type 1 diabetes); CeD: (celiac disease); GIP: (gluten immunogenic peptides); CDAT: (Celiac Dietary Adherence Test); CSI: (Celiac Symptom Index); IgA-TG2: (IgA anti-transglutaminase 2); IgG-DGP: (IgG anti-deamidated gliadin); AUH: (Akershus University Hospital); OUH: (Oslo University Hospital); NDC: (Norwegian Diabetes Center); CV: (coefficient of variation); HbA1c: (hemoglobin A1c)

ARTICLE HISTORY

Received 13 October 2024
Revised 2 December 2024
Accepted 10 December 2024

KEYWORDS

Diabetes mellitus, type 1; celiac disease; diet, gluten-free; treatment adherence and compliance; point-of-care testing; urine

CONTACT Kristine Vaage Hatlen k.v.hatlen@medisin.uio.no Institute of Clinical Medicine, University of Oslo, P.O.Box 1171 Blindern, 0318 Oslo, Norway
Supplemental data for this article can be accessed online at https://doi.org/10.1080/00365521.2024.2442688

Introduction

Patients with type 1 diabetes (T1D) have an increased risk of celiac disease (CeD), with a CeD prevalence of 4–10% compared to 1–2% in the general population [1–4]. Treatment requires discipline to adjust insulin dosages correctly and adhere to a gluten-free diet. Gluten-free products often have a high glycemic index, which can make it harder to avoid postprandial hyperglycemia [5]. Thus, adhering strictly to a gluten-free diet can be particularly difficult for individuals with T1D. Some patients with T1D do not have CeD symptoms at the time of CeD diagnosis but are identified by screening tests [6]. The lack of symptoms following gluten consumption increases the likelihood of accidental gluten consumption and may decrease the motivation to adopt a lifelong gluten-free diet.

Untreated CeD is associated with osteoporosis, malnutrition, increased risk of malignant diseases and increased overall mortality [7]. Patients with T1D also have decreased bone health [8], as well as increased morbidity and mortality, especially due to cardiovascular diseases [9]. An additional risk in individuals diagnosed with both T1D and CeD was shown in a Swedish national register study where they found a 2.8-fold higher mortality rate in individuals with T1D + CeD, with CeD for at least 15 years, compared to T1D only [10]. Furthermore, studies have shown an elevated risk of vascular complications in individuals with both CeD and T1D [11]. This calls for proper follow-up of patients with T1D + CeD.

So far the only treatment of CeD is a lifelong gluten-free diet [2]. Clinical follow-up is centered towards assessment of adherence to a gluten-free diet. Methods to assess adherence include structured follow-up by a dietitian, standardized questionnaires, IgA transglutaminase 2 (IgA-TG2) and IgG deamidated gliadin (IgG-DGP) serology or duodenal biopsy [12]. Duodenal biopsy is commonly considered to be the gold standard to assess adherence and mucosal healing [13]. Observational studies have shown beneficial effects of follow-up biopsies, and guidelines recommend shared decision-making between the patient and the physician on performing them [14]. However, endoscopy with biopsies is an invasive and resource-demanding procedure that patients often wish to avoid [12]. IgA-TG2 and IgG-DGP are serology tests primarily used for diagnostics. Levels are typically reduced within a year after the initiation of a gluten-free diet [2,15]. Persistent positive serology levels have high specificity for intestinal mucosal damage caused by non-adherence, but is hampered by low sensitivity [16].

Measurement of gluten immunogenic peptides (GIP) in urine or feces has been developed as an objective marker to assess adherence to a gluten-free diet [17]. This method detects gluten peptides from ingested gluten directly in urine during the timeframe of 3–12 h post digestion [18], with inter-individual variability ranging from 2–49 h post digestion [19]. Fecal GIP tests can detect ingested gluten 2–4 days after consumption, with positive test results possible up to 7 days post digestion [19,20]. The minimum gluten intake required to detect GIP varies among studies. However, generally, a gluten intake of at least 25 mg may result in a positive urinary GIP test, while a minimum of 50 mg is needed for a positive fecal test [21,22].

The aim of this cross-sectional study was to assess adherence to a gluten-free diet in individuals with both CeD and T1D, compared to a group with CeD only. We also aimed to study the utility of the GIP urine test for CeD patients with concurrent T1D in an outpatient setting. Furthermore, we included a study group of individuals with T1D without CeD in order to assess the feasibility of the GIP urine test in clinical practice, and to confirm predominantly positive test results in this population.

Materials and methods

Study design and participants

The present study is observational, with a cross-sectional design. It was conducted from October 2021 through January 2023 at the following study sites located in the greater Oslo area in Norway: Akershus University Hospital (AUH), Oslo University Hospital (OUH) and the Norwegian Diabetes Center (NDC).

Participants were recruited into three study groups:

1. Type 1 diabetes and celiac disease (T1D + CeD)
2. Celiac disease only (CeD)
3. Type 1 diabetes only (T1D)

T1D + CeD participants were recruited from three diabetes outpatient clinics. In the CeD group, certain participants were recruited from the outpatient clinic at the Department of Gastroenterology, OUH. In line with guidelines, we do not offer long-term follow-up of CeD at secondary care level, but expect this do be done in general practice [2]. Therefore, we also used social media (Facebook) for recruitment of long-term treated CeD patients. Moreover, participation in the study was open for all eligible patients and communicated on the hospital's web-page [23]. CeD diagnosis followed established guidelines with national modifications [2]. The T1D group was recruited from the diabetes outpatient clinic at AUH concurrently with their regular appointments at secondary care health service. All participants were 18 years or older, fluent in Norwegian, and CeD participants had been diagnosed with CeD for at least 12 months. Inclusion criteria did not require participants to confirm strict adherence to a gluten-free diet, as we aimed to study total compliance in the groups, including both intended and non-intended gluten intake. Exclusion criteria included ongoing urinary tract infection and use of gluten digestive enzymes.

Measurements

The urine samples were analysed for GIP using iVYCHECK GIP Urine test (product reference KT-6411) from Biomedal. This is a qualitative test based on a lateral flow immunochromatographic assay method, designed to detect the presence of GIP in urine, using the anti-gliadin 33-mer G12 antibody [22]. The test is capable of detecting the intake of 2 g of gluten, but it may also yield positive results after consuming 50 mg of gluten in some individuals [18]. These quantities of gluten, when consumed regularly, may lead to intestinal changes [24]. Validation performed by the manufacturer states 98% repeatability and 98% reproducibility. A single GIP urine test

was analysed per participant, carefully following the manufacturer's instructions. Urine samples were taken between 12 pm and 7 pm. For study visits before 12 pm participants were asked to bring a urine sample taken during the same timeframe the day before, stored in a refrigerator.

Blood samples were analysed as routine samples at the respective hospital laboratories. The analyses included the measurements of IgA-TG2, IgG-DGP, and HbA1c levels. In addition, LDL cholesterol and creatinine levels were measured in patients with T1D. The laboratories use different instruments for analyses of IgA-TG2 and IgG-DGP. AUH uses Phadia 2500 E (Thermo Fisher Scientific) with a coefficient of variation (CV) of 13.1% for IgA-TG2 and 15.7% for IgG-DGP. Fürst laboratory (used by NDC) uses Phadia 5000 E (Thermo Fisher Scientific) with a CV of 9.7% for IgA-TG2 and 13.5% for IgG-DGP. OUH uses the instrument Freedom EVOlyzer 150/8 (Tecan) with a CV of 8.2% for IgA-TG2 and 8.0% for IgG-DGP. AUH and Fürst have the same reference levels, valid for both IgA-TG2 and IgG-DGP: <7 U/mL is considered negative, levels between 7 and 10 U/mL are indeterminate, and levels >10 U/mL are positive. Test results from AUH and Fürst were dichotomized using the cut-off >10 U/mL for positive tests. In OUH the reference level for IgA-TG2 is <4 U/mL, and the reference level for IgG-DGP is <20 Units.

Participants in the T1D + CeD and the CeD groups completed the Norwegian versions of two standardized questionnaires: Celiac Dietary Adherence Test (CDAT) and Celiac Symptom Index (CSI) [25–28]. CDAT evaluates adherence to a gluten-free diet using seven Likert-scale questions that assess behaviours associated with non-adherence. Scores range from seven to 35, with lower scores indicating better adherence. Scores <13 indicates excellent or very good adherence, while scores >17 indicates fair to poor adherence. Scores between 13 and 17 are considered intermediate [28]. In most studies, a cut-off of <13 is used to distinguish between good and inadequate adherence [12]. CSI assesses CeD-specific health with 16 Likert-scale questions. Total scores range from 16 to 80, with lower scores indicating better quality of life. Scores ≤30 are associated with high quality of life, while scores >44 indicate relatively poor quality of life. Scores between 31 and 44 are considered intermediate [25].

Study visit protocol

Each participant attended a single study visit, providing a urine sample and measures of blood pressure, height, and weight. Blood samples were taken for hemoglobin A1c (HbA1c), IgA-TG2 and IgG-DGP, if not already taken within three months before or after the study visit. Clinical data were registered from electronic systematic patient records. Participants in the CeD group and in the T1D + CeD group completed a web-based questionnaire including CDAT and CSI. The questionnaire was completed before receiving the urine test results. The primary invitation letter did not disclose the specific substance being tested in the urine sample nor the purpose of assessment of the patient's compliance. However, during study visits participants received detailed information clarifying that the test was aimed at detecting gluten intake, prior to signing a consent form. None of the participants declined enrollment after receiving this information. Participants with positive GIP urine tests were offered a dietetic consultation.

Outcome variables

The primary outcome variable was the urinary GIP results. Secondary outcomes included the CDAT and CSI questionnaire scores, in addition to the serology results for IgA-TG2 and IgG-DGP.

Sample size estimation

Estimation of sample size was conducted prior to inclusion for these two study groups: (1) T1D + CeD and (2) CeD only. To our knowledge, no data had been published on the proportion of positive GIP tests in a population with both CeD and T1D [17]. Assuming 10% positive GIP tests in the T1D + CeD group versus 1% in the CeD only group (power 0.8, $p < 0.05$), a total of 80 participants would be needed in each group to identify a potential difference between the groups. The assumption of a low proportion of positive urinary GIP tests in the CeD group was based on the absence of positive tests in a recent study in Norway [27]. We also expected better dietary compliance than in previous studies on complicated patients referred to tertiary centers [22]. To account for dropouts in data collection, the aim was to include 90 participants in each group. We did not calculate the sample size for the T1D group, as the results from this group were not intended to factor into the calculation of the primary outcome.

Statistics

The data are presented as mean (standard deviation, SD), median (interquartile ranges, IQR) or number (%). Categorical data were tested by Fisher exact test or Chi square test according to expected values in cells. Distribution of continuous data was assessed by descriptive statistics. Independent samples t-test or one-way ANOVA test was used for continuous variables with parametric distribution, whereas Mann Whitney U test or Kruskal Wallis test was used for non-parametric continuous data. Significance level was set at $p < 0.05$.

Missing data were assumed randomly distributed and excluded from the analyses. To account for different reference values for IgG-TG2 and IgA-DGP, we categorized the sample values into a binary variable, classifying them as elevated or non-elevated levels for either one or both antibodies.

Statistical analyses were conducted in Stata 17 (StataCorp LLC, Texas, United States).

Ethics

The study was approved by the Regional Committee for Medical and Health Research Ethics, REK no 213486. Study participants provided signed informed consents.

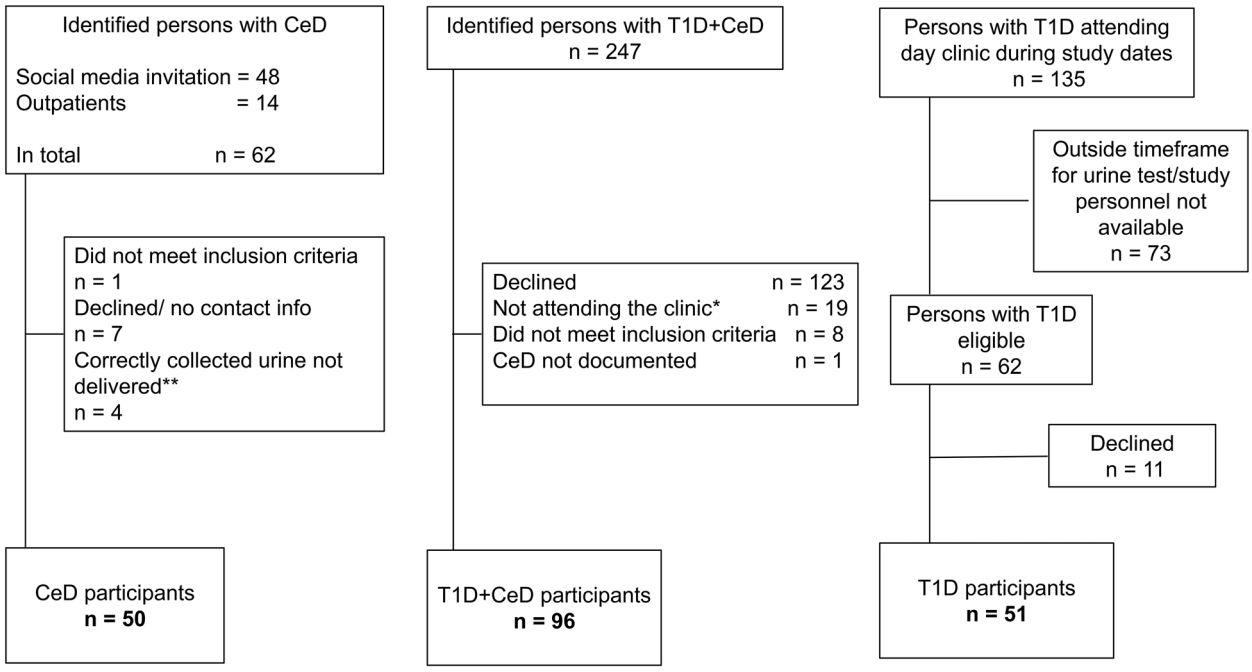


Figure 1. Flowchart of study participants.
CeD: Celiac disease, T1D: Type 1 diabetes.
* Incorrect registration or not followed up at the outpatient clinic.
** Urine not delivered, or urine incorrectly collected as morning urine.

Table 1. Participant characteristics.

	Celiac disease ($n=50$)	Type 1 diabetes ($n=51$)	Type 1 diabetes and celiac disease ($n=96$)	p-value all groups	p-value T1D+CeD vs CeD	p-value T1D+CeD vs T1D
Female	45 [90]	24 [47]	61 [64]	<.001	0.001	0.05
Age (y)	41.6 (12.8)	45.6 (16.5)	42.7 (15.7)	0.39	0.66	0.30
BMI (kg/m^2)	26.0 (4.9)	26.6 (4.8)	25.8 (4.5)	0.56	0.76	0.28
CeD duration > 10 y	22 [44]		60 [63]		0.03	
Symptoms at CeD diagnosis					0.001	
Yes	46 [92]		59 [63]			
Uncertain	1 [2]		9 [10]			
Symptoms after gluten exposure	48 [96]		77 [80]		0.01	
T1D duration, y		16.1 (13.2)	23.8 (14.7)			0.002
SBP, mmHg	117 (12)	133 (18)	126 (15)	<.001	<.001	0.02
DBP, mmHg	73 (8)	82 (9)	76 (10)	<.001	0.13	<.001
HbA1c (mmol/mol)	33 (31–35)	64 (52–72)	56 (49–63)	<.001	<.001	0.03
CeD serology > ULN	3 [6]	0 [0]	11 [12]		0.38	
LDL cholesterol (mmol/l)		2.8 (0.9)	2.6 (0.7)			0.09
eGFR (ml/min/1.73 m^2)		94.5 (80–108)	103 (86–114)			0.31

Data presented as mean (SD), median (IQR) or number (n) [%].
Abbreviations: CeD: Celiac Disease, T1D: Type 1 Diabetes, y: years, BMI: body mass index, SBP: systolic blood pressure, DBP: diastolic blood pressure, ULN: upper limit of normal, SD: standard deviation, IQR: interquartile range.

Results

Details of the recruitment process are illustrated in the flowchart, Figure 1 (supplemental material 1). A total of 96 participants were recruited for the T1D+CeD group, 50 participants for the CeD group, and 51 participants for the T1D group.

Participant characteristics are presented in Table 1.

Mean age (SD) was 43 (15) years. In the CeD group, 90% of the participants were female, compared to 47% in the T1D group and 64% in the T1D+CeD group ($p<0.001$). The proportion of participants with a CeD duration of more than 10 years was higher in the T1D+CeD group compared to the CeD group (63% vs 22%, $p=0.03$). Furthermore, the T1D+CeD group had more participants without symptoms after self-reported gluten exposure compared to the CeD group (20% vs 4%, $p=0.01$), and a larger proportion had no symptoms at the time of CeD diagnosis compared to the CeD group (27% vs 6%, $p=0.001$). Serum levels of IgA-TG2 and IgG-DGP were measured in 95% of the participants in the T1D+CeD group and in 98% of the participants in the CeD group. Twelve% of the T1D+CeD group had one or both serology tests above the upper limit of normal compared to 6% in the CeD group ($p=0.38$) (Table 1).

In the T1D+CeD group 14/96 (14.6%) participants had a positive GIP urine test, while none in the CeD group tested positive ($p=0.002$), Figure 2. In the T1D group, seven out of 51 participants (13.7%) had a negative GIP test despite expected

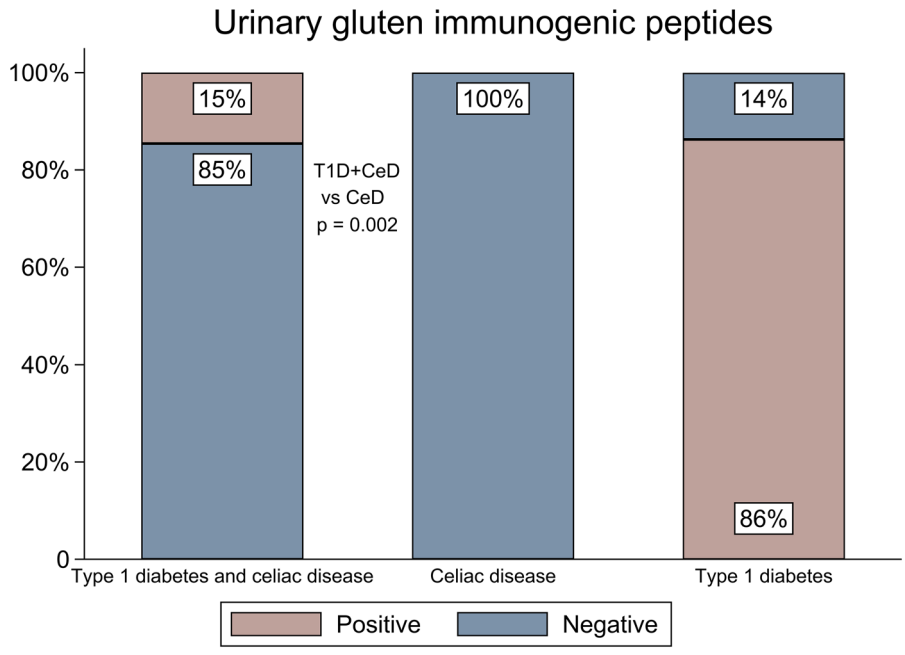


Figure 2. GIP results.
Proportions of positive and negative urinary gluten immunogenic peptide results in participants with type 1 diabetes and celiac disease (n = 96) versus celiac disease only (n = 50). Results for participants with type 1 diabetes only (n = 51) are shown, but not compared in analysis, because of expected positive results.
CeD: Celiac disease, T1D: Type 1 diabetes.

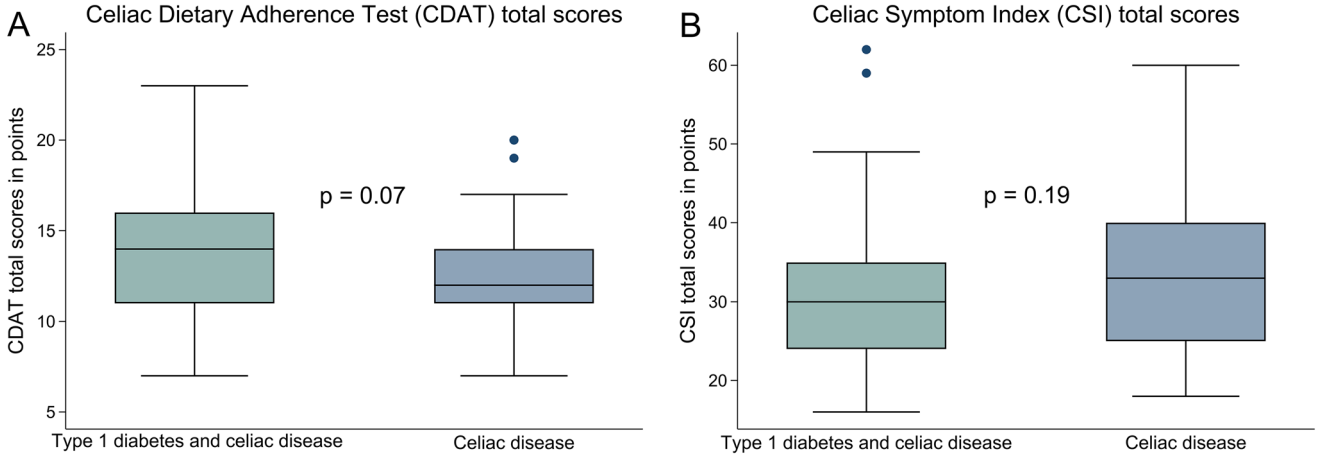


Figure 3. CDAT and CSI results.
Box plots showing the distributions of (A) Celiac dietary adherence test (CDAT) total scores and (B) Celiac Symptom Index (CSI) total scores in participants with type 1 diabetes and celiac disease ($n = 95$) versus celiac disease only ($n = 50$). Total score range for CDAT: 7–35 points, for CSI: 16–80 points.

positive tests due to regular gluten consumption (Figure 2). Out of the 14 T1D+CeD participants who tested positive for GIP, five were already aware of their gluten consumption. The source of gluten intake was identified for six additional patients during the study visit, or after a consultation with a dietician. In the T1D group, two of the seven participants with negative GIP urine test had not eaten since the day before, and one participant followed a low-carbohydrate diet with no known gluten intake within the 24 h prior to the test.

Within the T1D+CeD group, 13 out of the 14 participants who tested positive for urinary GIP had available serology results. Of these, 38% (five participants) tested positive for IgA-TG2 and/or IgG-DGP. Among the 82 T1D+CeD participants with negative urinary GIP, 78 had available serology results. Fewer of these, 8% (six participants), tested positive for IgA-TG2 and/or IgG-DGP, which was significantly lower than in GIP positive participants ($p = 0.002$).

Median CDAT total score (IQR) in the T1D+CeD group was 14 (11–16) points, and 12 (11–14) points in the CeD group ($p = 0.07$) (Figure 3A). In the T1D+CeD group, 41% scored <13 points indicating good or excellent adherence to a gluten free diet. In comparison, 58% of the CeD group scored <13 points ($p = 0.05$). Although these differences did not reach statistical significance, we observed a trend towards better compliance in the CeD group.

Mean CSI total score (SD) was 30.5 (0.9) points in the T1D+CeD group and 32.6 (1.4) points in the CeD group, ($p = 0.19$) (Figure 3B). In the T1D+CeD group 56% had CSI

total scores of ≤30 p, indicating a high quality of life, compared to 46% in the CeD group ($p = 0.26$).

Participants with positive GIP results had no significant differences in CSI (cutoff ≤ vs >30 p) or CDAT scores (cutoff < vs ≥13 p) when compared to participants with negative GIP results within the T1D + CeD group (supplemental material 2). Nine out of 14 individuals with elevated serology levels (in the CeD group and T1D group combined) had CDAT scores ≤ 17 (intermediate to good adherence), and four of them even had CDAT scores < 13 (excellent or very good adherence).

HbA1c in the T1D + CeD group did not differ between participants with positive GIP urine test versus participants with negative GIP urine test ($p = 0.69$). In the T1D + CeD group, the median HbA1c was 56 mmol/mol (IQR 49–63), which was lower than the median HbA1c of 64 mmol/mol (IQR 52–72) in the T1D group ($p = 0.03$).

Supplemental material 3 provides details on the numbers of missing values.

Discussion

This cross-sectional study reveals that non-compliance to a gluten-free diet is disturbingly frequent among patients with both T1D and CeD. We observed a 15% rate of positive urinary GIP tests in the T1D + CeD group, compared to none in the CeD group. Our study represents the first evaluation of urinary GIP testing in patients with a dual diagnosis. In the T1D group (with no imperative for a gluten-free diet) GIP positive results occurred in 86% of participants. There were no significant differences found between the CeD group and the T1D + CeD group in terms of CSI scores, CDAT scores, or serology for IgA-TG2 and IgG-DGP. However, within the T1D + CeD group a higher proportion of GIP positive participants had positive IgA-TG2 and/or IgG-DGP compared to GIP negative participants. This finding is highly relevant, as positive serology levels correlate with mucosal damage [2,16]. IgA-TG2 and IgG-DGP serology have low sensitivity in detecting episodes of dietary transgressions but may instead become elevated after repeated gluten intake over weeks, and have high specificity for gluten intake in CeD patients [2]. On the other hand, a single urinary GIP test is only capable of detecting recent gluten intake.

The urinary GIP positivity rate of 15% in the T1D + CeD group is considered both high and clinically relevant, as it represents a conservative estimate of individuals who habitually or occasionally consume gluten. In the same group, the occurrence of positive IgA-TG2 and/or IgG-DGP was found to be 12%. Given the serology's limited sensitivity to detect gluten exposure in patients with CeD, the serology results suggest a substantial proportion of individuals in the T1D + CeD group with poor adherence to a gluten-free diet, consistent with the GIP urine results.

The higher incidence of GIP positive tests in the double diagnosed group was in line with our assumptions. The limited timeframe for gluten detection in urine means only a certain proportion of individuals with habitual or occasional gluten intake would test positive in a random sample.

Results from the CDAT questionnaire, a subjective method for assessing dietary adherence, showed no significant difference between GIP positive and GIP negative participants. Interestingly, a lack of correlation between CDAT scores and urinary GIP results was recently observed in a small study of pediatric patients [29]. In our study, elevated IgA-TG2/IgG-DGP levels were found in a notable proportion of individuals whose CDAT scores indicated adequate adherence. These findings suggests that objective assessment methods, such as serology and urinary GIP tests, may provide valuable supplementary information beyond self-reported dietary compliance. Although differences were observed in serology and CDAT results between the T1D + CeD and CeD groups, these differences were not statistically significant, possibly due to a low statistical power. Individuals with positive serology and those showing non-adherence based on CDAT scores were present in both GIP positive and GIP negative individuals. This emphasizes that using multiple assessment methods to monitor adherence to a gluten-free diet can yield complementary information. Regarding the urinary GIP test, evidence indicates that the results when performing multiple tests per person correlates with mucosal damage [17].

Interestingly, HbA1c differed between the T1D + CeD group and the T1D group, with higher HbA1c in the latter (Table 1). This aligns with the findings in a study on patients with T1D aged 16–25 years [30]. However, the available evidence on the influence of CeD on HbA1c levels for T1D patients remains inconsistent [3,11]. Variability in study findings may result from differences in adherence to a gluten-free diet and varying choices of gluten-free foods among participants. Non-adherence may impact HbA1c levels via malabsorbtion-related hypoglycemia and subsequent glucose fluctuations. Additionally, the immunological process causing mucosal damage might further influence glucose levels. Gluten-free foods range from processed items high in carbohydrates, including wheat starch, to naturally gluten-free, low-carb options, and individual food choices affect glucose levels [5]. These factors highlight the complexity in assessing HbA1c levels across studies without evaluating the gluten-free diet content and compliance.

Rates of positive GIP urine tests vary across studies, probably influenced by sampling strategy. It can also be expected that disclosing that urine is used for detecting gluten exposure may lead to a more strict adherence by the patients. Most studies include multiple urine tests per participant, reporting rates of participants with at least one positive sample, ranging from 25% to 89% [17,22]. The overall positive test rates for all urine tests in these studies, across different individuals, range from 6% to 42%. However, Lombardo et al. [31] used a single urine test, reporting an 11% positivity rate among adult CeD participants. As in our study, participants were unaware of the purpose of the urine test, which reduced pleasing bias and contributed to more reliable results. The variability in morning urine testing is another important consideration, as several studies do not specify the sampling timeframe [22]. Morning urine testing may not detect gluten consumed the previous day [27]. Therefore, in our study, we used 12 pm–7 pm sampling. Variation in recruitment strategies, such as recruiting from specialized clinics or through patient organizations, may introduce selection bias. The differing recruitment strategies used in our study may have influenced the observed results in the CeD group.

Studies assessing adherence to a gluten-free diet in individuals with T1D+CeD are limited but support our finding of increased gluten exposure in this group. Söderström et al. [32] observed dietary adherence in children with T1D+CeD using IgA-TG2 results measured more than two years after CeD diagnosis. They found as much as 32% of the participants with at least one positive serology level. In a web-based survey by Kivelä et al. [33] adult T1D+CeD participants showed poorer dietary adherence compared to participants without T1D.

Our findings suggest lower adherence to a gluten-free diet in the T1D+CeD group compared to the CeD group. More participants with T1D+CeD lacked symptoms after gluten intake, which may impact compliance. Gluten-free products low in fibre and high in carbohydrates can pose a challenge in determining rapid-acting insulin dosages, which may reduce motivation to maintain a gluten-free diet [5]. Furthermore, the increased cost of of gluten-free products, combined with the additional expenses related to T1D, may present economic barriers to dietary adherence [34].

We recommend increased follow-up for patients with both T1D and CeD to ensure adherence to a gluten-free diet. GIP urine tests in such follow-up could be beneficial. Repeated urinary tests can be employed either on a regular basis or in a targeted manner to assess adherence when compliance is suspected to be low [18,22]. The implementation of GIP urine tests should be relatively simple, as T1D patients are accustomed to providing urine samples, and the GIP urine tests are easily and quickly analysed. Urinary GIP tests could also be helpful in self-monitoring to assess whether gastrointestinal symptoms are caused by gluten intake or diabetes related conditions, like ketoacidosis or gastroparesis. Healthcare professionals responsible for the follow-up of T1D patients should be aware of the unique challenges posed by a dual diagnosis and take these into account when discussing treatment plans and dietary choices.

Future studies should try to answer whether urinary and/or fecal GIP testing, along with follow-up after GIP positivity, may improve adherence to a gluten-free diet.

Strengths in this study include the use of real-life data, a purposely set timeframe for urine tests, and the fact that participants were unaware of the purpose of the urine test until attendance. To our knowledge this is the first study on GIP tests in double diagnosed individuals with T1D+CeD.

Limitations in this study include the lack of mucosal healing status assessment through endoscopy with biopsies and structured dietitian evaluations. Both could have provided comprehensive information on gluten-free dietary compliance. Other limitations include potential selection bias due to varying recruitment strategies and the absence of multiple GIP urine tests per participant. Conducting multiple urinary GIP tests per participant would likely result in a higher proportion of participants with at least one positive result [19,35–37]. This approach could distinguish individuals with repeated positive tests from those with mostly negative results, identifying those in greatest need of compliance support. However, the advantage of using a single urinary GIP test in the study is that multiple tests might influence dietary behavior once individuals are informed about the testing. Choosing urinary GIP tests instead of fecal GIP tests could be considered a limitation. Fecal GIP tests can detect gluten intake from several days prior, providing more comprehensive information. In contrast, urinary GIP tests cover a shorter timeframe but are significantly easier for patients to collect. This ease of use likely facilitates broader recruitment and may reduce dropout rates among patients who struggle with compliance. A single positive urinary GIP result may indicate incidental gluten contamination of food in a CeD patient with high dietary compliance [19]. However, in our study, such instances were identified during subsequent dietetic consultations. Our experience suggests that a positive urinary GIP test serves as a starting point for evaluating the diet and addressing any misunderstandings or the need for further education on a gluten-free diet.

Conclusions

Urinary GIP tests showed that a high proportion of patients with T1D+CeD was exposed to gluten, while no gluten exposure was discovered for CeD patients. These results highlight the importance of improved CeD follow-up in patients with concurrent T1D. Repeated urinary GIP tests would be useful in such follow-up to effectively detect gluten intake.

Acknowledgements

We would like to thank the patients who participated in this study, and we are thankful for the contribution of Åshild Stavik, Stine Rosenqvist Lund, and the staff at the Endoscopy Unit, Department of Transplantation Medicine, OUH Rikshospitalet, for their assistance in participant recruitment. We are also grateful for the collaboration of the Norwegian Diabetes Center, which generously provided us with facilities and assistance in inviting participants from their outpatient clinic.

Disclosure statement

No potential conflict of interest was reported by the authors.

Funding

The work was supported by grants from the Norwegian Society of Internal Medicine. Funding was also provided through the first author's research fellowship at the University of Oslo. The study has no industry funding.

ORCID

Kristine Vaage Hatlen http://orcid.org/0009-0002-6140-735X
Therese Margrethe Lysell Lensnes http://orcid.org/0009-0006-0994-3840
Christine Henriksen http://orcid.org/0000-0002-8079-8467
Tore Julsrud Berg http://orcid.org/0000-0003-4406-2396
Ingrid Nermoen http://orcid.org/0000-0001-6643-8169
Knut Erik Aslaksen Lundin http://orcid.org/0000-0003-1713-5545

References

[1] Nederstigt C, Uitbeijerse BS, Janssen LGM, et al. Associated auto-immune disease in type 1 diabetes patients: a systematic review and meta-analysis. Eur J Endocrinol. 2019;180(2):135–144. doi: 10.1530/eje-18-0515.

[2] Al-Toma A, Volta U, Auricchio R, et al. European Society for the Study of Coeliac Disease (ESsCD) guideline for coeliac disease and other gluten-related disorders. United European Gastroenterol J. 2019;7(5):583–613. doi:10.1177/2050640619844125.
[3] Samuelsson J, Bertilsson R, Bülow E, et al. Autoimmune comorbidity in type 1 diabetes and its association with metabolic control and mortality risk in young people: a population-based study. Diabetologia. 2024;67(4):679–689. doi:10.1007/s00125-024-06086-8.
[4] Lukina P, Andersen IL, Eggen PT, et al. Coeliac disease in the Trøndelag Health Study (HUNT), Norway, a population-based cohort of coeliac disease patients. BMJ Open. 2024;14(1):e077131. [published Online First: 20240109] doi:10.1136/bmjopen-2023-077131.
[5] Myhrstad MCW, Slydahl M, Hellmann M, et al. Nutritional quality and costs of gluten-free products: a case-control study of food products on the Norwegian marked. Food Nutr Res. 2021;65:1–10. doi:10.29219/fnr.v65.6121.
[6] Moravej H, Zamanfar D, Aghamahdi F, et al. Optimal frequency to screen celiac disease amongst patients with type 1 diabetes mellitus: a multicenter study. Prim Care Diabetes. 2021;15(6):1100–1103. doi:10.1016/j.pcd.2021.08.011.
[7] Lebwohl B, Sanders DS, Green PHR. Coeliac disease. Lancet. 2018;391(10115):70–81. doi:10.1016/S0140-6736(17)31796-8.
[8] Shah VN, Carpenter RD, Ferguson VL, et al. Bone health in type 1 diabetes. Curr Opin Endocrinol Diabetes Obes. 2018;25(4):231–236. [published Online First: 2018/05/26] doi:10.1097/med.0000000000000421.
[9] Harding JL, Pavkov ME, Magliano DJ, et al. Global trends in diabetes complications: a review of current evidence. Diabetologia. 2019;62(1):3–16. [published Online First: 20180831] doi:10.1007/s00125-018-4711-2.
[10] Mollazadegan K, Sanders DS, Ludvigsson J, et al. Long-term coeliac disease influences risk of death in patients with type 1 diabetes. J Intern Med. 2013;274(3):273–280. [published Online First: 2013/05/25] doi:10.1111/joim.12092.
[11] Eland I, Klieverik L, Mansour AA, et al. Gluten-free diet in co-existent celiac disease and type 1 diabetes mellitus: is it detrimental or beneficial to glycemic control, vascular complications, and quality of life? Nutrients. 2022;15(1):199. [published Online First: 2023/01/09] doi:10.3390/nu15010199.
[12] Wieser H, Ruiz-Carnicer Á, Segura V, et al. Challenges of monitoring the gluten-free diet adherence in the management and follow-up of patients with celiac disease. Nutrients. 2021;13(7):2274. doi:10.3390/nu13072274.
[13] Moreno M, Rodríguez-Herrera A, Sousa C, et al. Biomarkers to monitor gluten-free diet compliance in celiac patients. Nutrients. 2017;9(1):46. doi:10.3390/nu9010046.
[14] Rubio-Tapia A, Hill ID, Semrad C, et al. American College of Gastroenterology guidelines update: diagnosis and management of celiac disease. Am J Gastroenterol. 2023;118(1):59–76. [published Online First: 20220921] doi:10.14309/ajg.0000000000002075.
[15] Risnes LF, Reims HM, Doyle RM, et al. Gluten-free diet induces rapid changes in phenotype and survival properties of gluten-specific T cells in celiac disease. Gastroenterology. 2024;167(2):250–263. [published Online First: 20240328] doi:10.1053/j.gastro.2024.03.027.
[16] Silvester JA, Kurada S, Szwajcer A, et al. Tests for serum transglutaminase and endomysial antibodies do not detect most patients with celiac disease and persistent villous atrophy on gluten-free diets: a meta-analysis. Gastroenterology. 2017;153(3):689–701.e1. doi:10.1053/j.gastro.2017.05.015.
[17] Coto L, Mendia I, Sousa C, et al. Determination of gluten immunogenic peptides for the management of the treatment adherence of celiac disease: a systematic review. World J Gastroenterol. 2021;27(37):6306–6321. [published Online First: 2021/10/30] doi:10.3748/wjg.v27.i37.6306.
[18] Coto L, Sousa C, Cebolla A. Dynamics and considerations in the determination of the excretion of gluten immunogenic peptides in urine: individual variability at low gluten intake. Nutrients. 2021;13(8):2624. [published Online First: 2021/08/28] doi:10.3390/nu13082624.
[19] Silvester JA, Comino I, Rigaux LN, et al. Exposure sources, amounts and time course of gluten ingestion and excretion in patients with coeliac disease on a gluten-free diet. Aliment Pharmacol Ther. 2020;52(9):1469–1479. [published Online First: 2020/09/28] doi:10.1111/apt.16075.
[20] Costa AF, Sugai E, Temprano MP, et al. Gluten immunogenic peptide excretion detects dietary transgressions in treated celiac disease patients. World J Gastroenterol. 2019;25(11):1409–1420. [published Online First: 2019/03/29] doi:10.3748/wjg.v25.i11.1409.
[21] Russell AK, Lucas EC, Henneken LM, et al. Stool gluten peptide detection is superior to urinary analysis, coeliac serology, dietary adherence scores and symptoms in the detection of intermittent gluten exposure in coeliac disease: a randomised, placebo-controlled, low-dose gluten challenge study. Nutrients. 2024;16(2):279. [published Online First: 20240117] doi:10.3390/nu16020279.
[22] Monachesi C, Catassi G, Catassi C. The use of urine peptidomics to define dietary gluten peptides from patients with celiac disease and the clinical relevance. Expert Rev Proteomics. 2023;20(11):281–290. [published Online First: 20231019] doi:10.1080/14789450.2023.2270775.
[23] Lundin K. Oslo University Hospital. [updated 19.07.2024]. Available from: https://www.oslo-universitetssykehus.no/kliniske-studier/oppfolging-av-coliakipasienter-med-og-uten-diabetes-type-1/.
[24] Catassi C, Fabiani E, Iacono G, et al. A prospective, double-blind, placebo-controlled trial to establish a safe gluten threshold for patients with celiac disease. Am J Clin Nutr. 2007;85(1):160–166. doi:10.1093/ajcn/85.1.160.
[25] Leffler DA, Dennis M, Edwards George J, et al. A validated disease-specific symptom index for adults with celiac disease. Clin Gastroenterol Hepatol. 2009;7(12):1328–1334.e3. doi:10.1016/j.cgh.2009.07.031.
[26] van Megen F, Skodje GI, Stendahl M, et al. High disease burden in treated celiac patients - a web-based survey. Scand J Gastroenterol. 2021;56(8):882–888. doi:10.1080/00365521.2021.1930146.
[27] Skodje GI, van Megen F, Stendahl M, et al. Detection of gluten immunogenic peptides and the Celiac Disease Adherence Test to monitor gluten-free diet: a pilot study. Eur J Clin Nutr. 2022;76(6):902–903. doi:10.1038/s41430-021-01054-6.
[28] Leffler DA, Dennis M, Edwards George JB, et al. A simple validated gluten-free diet adherence survey for adults with celiac disease. Clin Gastroenterol Hepatol. 2009;7(5):530–536.e2. doi:10.1016/j.cgh.2008.12.032.
[29] Mello C, da Silva GAP, Lins MTC, et al. Gluten-free diet adherence in pediatric celiac patients: evaluating CDAT questionnaire and test for gluten detection in urine. J Pediatr Gastroenterol Nutr. 2024;78(6):1310–1316. doi:10.1002/jpn3.12180.
[30] James S, Perry L, Lowe J, et al. Coexisiting type 1 diabetes and celiac disease is associated with lower Hba1c when compared to type 1 diabetes alone: data from the Australasian Diabetes Data Network (ADDN) registry. Acta Diabetol. 2023;60(11):1479. doi:10.1007/s00592-023-02113-z.
[31] Lombardo V, Scricciolo A, Costantino A, et al. Evaluation of a single determination of gluten immunogenic peptides in urine from unaware celiac patients to monitor gluten-free diet adherence. Nutrients. 2023;15(5):1259. doi:10.3390/nu15051259.
[32] Söderström H, Rehn J, Cervin M, et al. Compliance to a gluten-free diet in swedish children with type 1 diabetes and celiac disease. Nutrients. 2021;13(12):4444. doi:10.3390/nu13124444.
[33] Kivelä L, Eurén A, Repo M, et al. Coexisting type 1 diabetes, persistent symptoms, and financial issues associate with poorer adherence to a gluten-free diet in celiac disease after transition from pediatrics to adult care. Front Nutr. 2022;9:883220. doi:10.3389/fnut.2022.883220.
[34] Villafuerte-Galvez J, Vanga RR, Dennis M, et al. Factors governing long-term adherence to a gluten-free diet in adult patients with coeliac disease. Aliment Pharmacol Ther. 2015;42(6):753–760. doi:10.1111/apt.13319.
[35] Ruiz-Carnicer Á, Garzón-Benavides M, Fombuena B, et al. Negative predictive value of the repeated absence of gluten immunogenic peptides in the urine of treated celiac patients in predicting muco-

sal healing: new proposals for follow-up in celiac disease. Am J Clin Nutr. 2020;112(5):1240–1251. [published Online First: 2020/07/22] doi:10.1093/ajcn/nqaa188.

[36] Stefanolo JP, Tálamo M, Dodds S, et al. Real-world gluten exposure in patients with celiac disease on gluten-free diets, determined from gliadin immunogenic peptides in urine and fecal samples. Clin Gastroenterol Hepatol. 2021;19(3):484–491.e1. [published Online First: 2020/03/29] doi:10.1016/j.cgh.2020.03.038.

[37] Garzón-Benavides M, Ruiz-Carnicer Á, Segura V, et al. Clinical utility of urinary gluten immunogenic peptides in the follow-up of patients with coeliac disease. Aliment Pharmacol Ther. 2023;57(9):993–1003. doi:10.1111/apt.17417.