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What is the Role of Measuring Urinary Gluten Immunogenic Peptides in Clinical Practice in Patients with Coeliac Disease?

Suneil A. Raju[1,2], Katerina E Ingham[1,2], Olivia Green[1,2], Calvin M Johnson[1,2], Mohamed G Shiha[1,2], Nicoletta Nandi[1,2], Nick Trott[1,2], Hugo A Penny[1,2], Marios Hadjivassiliou[3], Graeme Wild[4], David S. Sanders[1,2]

1) Academic Unit of Gastroenterology, Sheffield Teaching Hospitals National Health Service Foundation Trust, Sheffield;
2) Division of Clinical Medicine, School of Medicine and Population Health, University of Sheffield, Sheffield;
3) Department of Neurology, Royal Hallamshire Hospital, Sheffield Teaching Hospitals National Health Service Foundation Trust, Sheffield;
4) Immunology Department, Sheffield Teaching Hospitals National Health Service Foundation Trust, Sheffield, United Kingdom

Address for correspondence:
Suneil A. Raju
Academic Unit of Gastroenterology, Sheffield Teaching Hospitals National Health Service Foundation Trust, Sheffield
suneilraju@gmail.com

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ABSTRACT

Background & Aims: In coeliac disease, the clinical role of the urinary gluten immunogenic peptide is unclear. It has been suggested it can be a non-invasive marker of villous atrophy. Therefore, we present the largest cross-sectional clinical data in patients with coeliac disease to establish the diagnostic accuracy of the urinary gluten immunogenic peptide in identifying villous atrophy.

Methods: Patients providing urinary gluten immunogenic peptide were identified between September 2018 and August 2023 at the National Health Service (NHS) England National Centre for Non-Responsive and Refractory CD. In our retrospective study, the results of the urinary gluten immunogenic peptide test collected within 7 days, self-reported adherence to a gluten free diet reported within 3 months, serology collected within 7 days (immunoglobulin A - tissue transglutaminase and endomysial antibody) and histology at the time of endoscopy were compared in individuals with coeliac disease who were either asymptomatic and undergoing remission biopsies (group 1), non-responsive coeliac disease (group 2) and refractory coeliac disease on immunosuppressive therapy (group 3). Associations between dichotomous variables were calculated using chi-squared test.

Results: In group 1 the sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV) for detecting villous atrophy were 42.9%, 83.3.%, 64.3% and 67.6% respectively. In group 2 the sensitivity, specificity, PPV and NPV for detecting villous atrophy were 36.2%, 79.0%, 39.5% and 76.6% respectively. In group 3 the sensitivity, specificity, PPV and NPV for detecting villous atrophy were 56.3%, 70.6%, 73.0% and 53.3%. More patients on immunosuppression had a positive urinary gluten immunogenic peptide than those not on immunosuppression (43.3% vs 24.1%, p<0.001).

Conclusions: The urinary gluten immunogenic peptide does not have a role in identifying villous atrophy. Therefore, to assess for villous atrophy an upper gastrointestinal endoscopy is still required.

Key words: coeliac disease – monitoring - gluten immunogenic peptide - villous atrophy - dietary adherence.

Abbreviations: AUC: area under curve; CD: coeliac disease; CDAT: CD adherence test; EMA: anti-endomyseal antibody; GFD: gluten free diet; GIP: gluten immunogenic peptides; IgA: immunoglubuline A; NPV: negative predictive value; NRCD: non-responsive CD; OSG: oesophagogastroduodenoscopy; PPV: positive predictive value; RCD: refractory CD; tTG: tissue transglutaminase; u-GIP: urinary GIP; VA: villous atrophy.

INTRODUCTION

Coeliac disease (CD) is a common autoimmune enteropathy resulting from the ingestion of gluten in genetically predisposed individuals that affects around 1% of the population. The diagnosis of CD is confirmed by demonstrating villous atrophy (VA) in the duodenal mucosa with positive coeliac serology [immunoglobulin-A (IgA) tissue transglutaminase (tTG) and anti-endomyseal antibody (EMA)] taken at the same time whilst on a normal (gluten containing diet) or after a gluten challenge [1-4]. Patients have a wide range of gastrointestinal ssymptoms; however, it is increasingly recognised that patients may also have extra-intestinal symptoms and in 3-10% of cases be asymptomatic [1, 5, 6]. Once CD is diagnosed, the only recognised treatment is a strict, lifelong gluten free diet (GFD) with the goal being resolution of symptoms and mucosal healing [1].

Despite adhering to a gluten free diet, up to 30% of patients do not report symptom improvement. Given the ubiquitous nature of gluten, the most common cause of persistent

symptoms is ongoing gluten exposure [7, 8]. However, continued gluten exposure can be difficult to objectively confirm. Dietetic assessment and adherence questionnaires are subjective and dependent on patient recall. IgA- tTG has until recently been the only objective marker of adherence [9].

The correlation between serological markers and persisting VA is poor. A meta-analysis of 26 studies showed that both IgA-tTG and IgA-EMA have poor sensitivities for persistent VA (50%; 95%CI: 41-60% and 45%; 95%CI: 34-57% respectively). Despite the poor sensitivity, a positive IgA-tTG did have good specificity for persistent VA (83%, 95%CI: 79-87%) [9]. Similarly, the use of dietary questionnaires such as the CD adherence test (CDAT) and Biagi score have yielded poor sensitivities (55.6% and 55.2% respectively) for persistent VA [1, 10].

Persistent VA in CD is associated with a greater risk of mortality (HR=2.93, 95%CI: 1.433-6.02) and complications (HR=9.53, 95%CI: 4.77-19.04) such as enteropathy-associated T-cell lymphoma, refractory coeliac disease (RCD) and coeliac crisis [11]. Patients with RCD have ongoing VA and are broadly divided into type 1 (characterised by phenotypically normal intra-epithelial lymphocytes) and type 2 (characterised by aberrant intraepithelial lymphocytes) [12]. Persistent VA as seen in RCD may be treated with immunosuppression [13]. The gold standard method to assess for VA is an oesophagogastroduodenoscopy (OGD) to acquire duodenal biopsies that can be graded by the Marsh-Oberhuber criteria [14]. However, OGD may be poorly tolerated by patients due to the significant discomfort experienced and therefore less invasive methods of assessment are required [15].

Gluten immunogenic peptides (GIP) are recently identified proteins that are resistant to digestion and therefore excreted in both urine and faeces. Measuring excreted GIP is a novel, non-invasive marker allowing for the detection of gluten ingestion. Early data suggested good correlation between urinary GIP (u-GIP) and persistent VA (Spearman's correlation r=0.75) and therefore it was suggested it could be used as a clinical tool to detect VA [16]. However, the clinical value of u-GIP in identifying VA in clinical practise remains unclear (sensitivity 23-94%) [16-20]. Our aim was to define the clinical role of the u-GIP by establishing its accuracy in identifying VA in patients with known coeliac disease. A secondary aim was to compare the results of the u-GIP to other clinical markers of adherence to a GFD.

METHODS

In this retrospective study, patients attending the National Health Service (NHS) England National Centre for Non-Responsive and Refractory CD (Sheffield Teaching Hospitals NHS Foundation Trust, UK) between September 2018 and August 2023 were identified. Data were collected after assessment from a clinician with a special interest in CD from case notes, endoscopy reports and referral letters on the individuals' symptoms, serology (IgA-tTG and IgA-EMA), histology of duodenal biopsies, if they self-reported adherence to a gluten free diet, u-GIP positivity and medication history.

Patients

As a specialist centre for coeliac disease, referrals from across the UK are accepted. This includes patients with non-responsive coeliac disease (NRCD) and RCD. As patients included were diagnosed prior to their referral, appropriate paediatric and adult guidelines were used based on their age at diagnosis using clinical and serological investigations with or without histological confirmation [1, 21]. At the time of referral, all patients were older than 18 years of age and had been diagnosed with CD over two years prior.

The patients were divided into three groups. Group 1 consisted of patients who were asymptomatic and undergoing a remission biopsy. Group 2 consisted of all patients who were symptomatic and assessed for ongoing VA. None of the patients in Group 2 were on any immunosuppressive medications. Group 3 consisted of all patients categorized as having RCD type 1 and were on either steroids (prednisolone or budesonide) and/or immunosuppression (azathioprine, mycophenalate, 6-mercaptopurine). The purpose of this further biopsy was to establish if histological remission had been achieved.

Serology

IgA-tTG titres were measured using the ELiA Celikey kit (Thermo Fisher, Freiburg, Germany) and IgA-EMA by immunofluorescence on primate oesophagus sections (Binding Site, Birmingham, UK). Signs of malabsorption included low iron, vitamin B12 and folic acid with or without anaemia.

Biopsies and Histology

Quadrantic biopsies were taken in D2 and two biopsies from the duodenal bulb. Specimens were preserved in formalin and embedded in paraffin wax. Specimens were then sliced into 3μm sections and stained using haematoxylin and eosin. Biopsies were then assessed by an experienced histopathologist with an interest in CD. Grading was completed using the Marsh-Oberhuber criteria [14].

Urinary GIP

Urine samples were processed by iVYDAL GIP urine immunochromatographic point of care test (Biomedal; Seville, Spain). For testing, 70 μL of urine was mixed with 30 μL of conditioning solution and added to the sample zone on the test cassette. If present, GIPs in the sample interacted with A1 and G12 monoclonal antibodies on the test strip, producing a red line in the test zone that can be manually read as per the manufacturer's instructions [13, 22].

Statistics

Data handling was completed using Microsoft Excel (2016) and analysis in IBM SPSS V27.0. Associations between dichotomous variables was calculated using chi-squared test and agreement using kappa correlation coefficients. The accuracy of the u-GIP for identifying VA was graded as excellent (90-100), good (80-90), fair (70-80), poor (60-70) and a fail (<60) based on the area under the curve (AUC) [23].

RESULTS

In group 1 (patients with no symptoms and not on immunosuppression) there were 31 individuals (61.3% female, median age=48.7 years, IQR: 33.2-62.4 years). In total, 98 u-GIP

samples were taken (23.5% positive) at different time points. The sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV) for detecting VA of a u-GIP taken within 1 week of their gastroscopy was 42.9%, 83.3.%, 64.3% and 67.6% respectively. In total, 61.3% of patients reported adherence to a GFD.

In group 2 (patients with non-responsive coeliac disease and not on immunosuppression) there were 127 patients (72.4% female, median 47.9 years, IQR: 33.8-61.4 years). In total, 342 u-GIP samples were taken (24.3% positive) at different time points. The sensitivity, specificity, PPV and NPV for detecting VA of a u-GIP within 1 week of their gastroscopy was 34.7%, 79.5%, 39.5%, and 75.9% respectively. In total, 63.8% of patients reported adherence to a GFD. When the IgA-tTG was negative, 21.8% of cases had a positive u-GIP. When the u-GIP was negative 4.2% of IgA-tTG results were positive. Where the u-GIP was positive within 1 week of their OGD, 88.9% of patients reported adherence to a GFD and of them, 43.8% had VA. Conversely, when the u-GIP was negative within 1 week of their OGD, 26.3% of patients reported eating gluten, of which 11.8% had VA. Patients were investigated due to gastrointestinal symptoms (88.8%), extra-intestinal symptoms (25.9%), or evidence of malabsorption (20.7%). There was no significant difference in patients who reported adhering to a GFD when grouped by their symptoms.

Group 3 consisted of 46 patients (63.0% female, median age 57.4 years IQR: 48.7-68.4 years) with coeliac disease who provided 201 urine samples whilst on steroids (budesonide or prednisolone) or immunosuppression (azathioprine, mycophenolate, 6-mercaptopurine). Of the samples provided, 82 were within one week of their OGD. For patients in group 3 the sensitivity, specificity, PPV and NPV of the u-GIP taken within 1 week of their OGD for detecting VA was 56.3%, 70.6%, 73.0% and 53.3% respectively. In total, 58.7% of patients reported adherence to a GFD. When the u-GIP was positive (n=37) within 1 week of their OGD, 78.1% of patients reported adherence to a GFD and of them, 60% had VA. Conversely, when the u-GIP was negative (n=45) within 1 week of their OGD, one patient reported eating gluten and had VA. In group 3, where a patient had a negative IgA-tTG (n=56), 33.9% had a positive u-GIP and where IgA-tTG was positive (n=17), 17.6% had a negative u-GIP. More patients on immunosuppressive medications (group 3) had a positive u-GIP than patients not on immunosuppressive medications (group 1 and 2 combined) (43.3% vs 24.1%, p<0.001). Patients were investigated due to persisting gastrointestinal symptoms (60.9%), extra-intestinal symptoms (13.0%), or signs of malabsorption (26.1%). Whilst on treatment 23.9% were asymptomatic and were assessed for remission.

Figure 1 shows the ROC curve for the diagnosis accuracy of u-GIP, IgA-tTG and self reported adherence to GFD in patients with known CD.

Timing of Urinary Gluten Immunogenic Peptide Sampling

To examine the effect of timing of sample collection on accuracy for predicting VA all samples in group 1 and 2 (patients with coeliac disease not on immunosuppression) were assessed. Samples from patients in group 3 were not included in the analysis due to the potential effect of immunosuppression on VA. The time of u-GIP sampling effected the diagnostic accuracy for identifying VA (Table I). The accuracy was lower if the u-GIP was taken prior to their OGD than when it was taken after (AUC=0.506, 95%CI: 0.397-0.705 versus AUC=0.627, 95%CI: 0.478-0.776). Weekday u-GIP results better detected VA than weekend results (AUC=0.682, 95%CI: 0.472-0.891 versus AUC=0.573, 95%CI:0.361-0.786). However, based on the AUC, the highest accuracy score was only fair. Similar to u-GIP, both IgA-tTG and self-reported adherence to a GFD had poor accuracy for identifying VA (Table I).

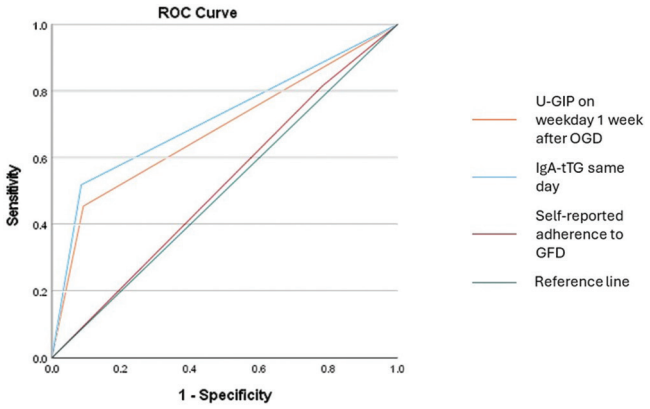

Fig. 1. Receiver operator characteristic (ROC) curve for the diagnostic accuracy of urinary gluten immunogenic peptide (u-GIP), immunoglobulin A-tissue transglutaminase (IgA-tTG) and self-reported adherence to a gluten free diet (GFD) in patients with known coeliac disease.

DISCUSSION

We present the largest clinical data on the use of the u-GIP test in clinical practice of patients with non-responsive coeliac disease and refractory coeliac disease on medication. Both a single and triple u-GIP test had a poor diagnostic accuracy for identifying VA. This may vary based on the time of sampling. However, the u-GIP did identify a large number of patients who despite reporting adherence to a GFD were exposed to gluten. This was more commonly seen in patients on immunosuppression for refractory CD type 1 (43.3% vs 24.3%, p<0.001).

The optimal timing for the u-GIP testing is unclear [24]. We found the diagnostic accuracy of the u-GIP was lower when taken prior to or on the same day as their OGD procedure. Urinary-GIP peaks between 4-17 hours and is undetectable 16-34 hours after gluten ingestion, therefore it stands to reason that patients fasting for their OGD will be more likely have a negative result [16, 25, 26]. This observation may also be in part due to the Hawthorne effect; patients know their OGD was undertaken to assess for villous atrophy caused by gluten ingestion and so modify their behaviour.

Previous studies have suggested a role for multiple u-GIPs on different days. A study of 77 patients found urine samples collected at the weekend before their OGD were positive more often than on the same day as their OGD (30-36% vs 21%, p<0.001) [27]. Whilst this could be due to higher

Table I. The diagnostic accuracy for identifying villous atrophy of u-GIP (urinary gluten immunogenic peptides), IgA-tTG (immunoglobulin A- tissue transglutaminase), self-reported adherence to a gluten free diet at different time points

Time taken in relation to OGD	N	Sensitivity	Specificity	PPV	NPV	AUC	95% CI
Timing of u-GIP							
1 – 7 days before	71	20.0	90.2	44.4	74.2	0.506	0.397-0.705
Same day	89	46.4	68.9	40.6	73.7	0.576	0.446-0.706
1 – 7 days after	67	40.9	84.4	56.3	74.5	0.627	0.478-0.776
Weekday versus weekend u-GIP							
Weekday 1-7 days after	33	45.5	90.9	71.4	76.9	0.682	0.472-0.891
Weekend 1-7 days after	34	36.4	78.3	44.4	72.0	0.573	0.361-0.786
IgA-tTG							
Within 1 week	212	36.5	94.6	74.2	77.9	0.656	0.568-0.743
Self-reported adherence to a gluten free diet							
Within 3 months	105	81.5	21.8	26.5	77.3	0.516	0.391-0.642
Combined u-GIP and IgA-tTG							
1 – 7 days before	63	5.9	97.8	50.0	73.8	0.519	0.354-0.683
Same day	86	29.6	94.9	72.7	74.7	0.623	0.487-0.759
1 – 7 days after	63	31.6	100.0	100.0	77.2	0.658	0.498-0.820
Three u-GIP samples							
1 – 7 days before	27	57.1	75	44.4	83.3	0.537	0.208-0.866
1 – 7 days after	22	28.6	80	40	70.6	0.655	0.338-0.972

OGD: oesophagogastroduodenoscopy.

dietary transgressions at the weekend, the results could also be explained by the reduced gluten ingestion on the day of OGD as patients are fasted. For this reason, our study excluded u-GIPs taken on the day of the OGD and found an increase in the diagnostic yield of the u-GIP. Another possible explanation for better diagnostic accuracy at identifying VA from weekday samples may be due to the greater effect of consistent dietary transgressions on five days of the week compared to two. The reason for more gluten ingestion on weekdays is difficult to ascertain, but may be due to individuals having less time on weekdays to prepare their meals as they may be at work or having less access to cheap gluten free foods [28].

Early reports suggested high reliability for the u-GIP test in monitoring a GFD [16, 22]. However, a recent randomised, double-blind study in 25 healthy medical doctors who underwent six single-dose gluten challenges (0, 10, 50, 100, 500 and 1000 mg) suggested the u-GIP may be less accurate than initially thought [29]. Despite a three day washout period with no gluten prior to the gluten challenge, 34% of participants still had positive u-GIPs. Furthermore, 25% of negative u-GIP results followed gluten challenges of 500-1,000mg. Interestingly, 33% of patients had positive u-GIPs in a secondary study where 5 or 10 mg of gluten was ingested despite these levels being classed as trace levels found in commercially available gluten free foods [29]. Therefore, the high sensitivity and current inaccuracies in testing of the u-GIP risks patients becoming unnecessarily restrictive in their diet. Patients with high levels of vigilance towards food have a lower quality of life and may reduce social activities such as eating out [30]. Care must therefore be taken if using the u-GIP as a monitoring tool for gluten ingestion in adult patients with CD in order to avoid hypervigilance.

In our study, there was no association between patients who reported adherence to a GFD and their symptoms. Despite reporting adherence to a GFD, more than three quarters of patients had a positive u-GIP. The clinical significance of this is difficult to establish. A study of 1,378 patients with CD found that 8% were eating weekly or monthly gluten. However, 57% of them did not exhibit histological changes suggesting a degree of tolerance towards gluten [31].

More patients on immunosuppressive medications had a positive u-GIP than patients on neither group of medications (43.3% vs 24.3%, $p<0.001$). This may reflect that a number of patients with RCD type 1 are people who eat gluten, but have negative IgA-tTG. In group 3, when the IgA-tTG was negative, in 33.9% of cases there was a positive u-GIP. This could allow for a reassessment of the initial diagnosis made.

There are limitations to this work. Firstly, the observational nature meant we were unable to assess how much gluten patients ate prior to their OGD and therefore cannot draw causation between ingested gluten and persisting VA. Secondly, patients returned different numbers of urine samples and at different times. To minimise the risk of bias, all sample timings were recorded in relation to their OGD. Also, as this study was completed in the NHS England National Centre for Non-Responsive and Refractory CD, a national centre for CD, it is difficult to extrapolate these results to other settings.

Further study is required to establish the role of u-GIP in clinical practice. The sensitivity to ingested gluten of the u-GIP test is unclear and merits further research. Despite this, a study of 30 adults in Italy with CD were provided 5 u-GIP point of care tests to perform when symptomatic or concerned of gluten exposure [32]. In this study patients were able to assess their adherence to a GFD and seek reassurance from the test.

However, this study lacked long term follow-up. The burden of coeliac disease and following a strict GFD may lead to anxiety and depression. One study of 7,648 individuals diagnosed with CD found that mucosal healing was associated with a subsequent diagnosis of anxiety (HR=1.49, 95%CI: 1.12-1.96) or depression (HR=1.39, 95%CI: 1.05-1.82) compared to those with persistent VA[33]. The use of a clinical tool that allows instant monitoring may increase the risk of hypervigilance and thus negatively affect quality of life.

CONCLUSIONS

In conclusion, u-GIP can be used as an objective marker to assess gluten ingestion; however, it does not identify villous atrophy in patients with CD. In clinical practice, the u-GIP should not be used to assess for villous atrophy and an OGD is required for this purpose. It may have a role in identifying gluten ingestion and is best taken on a weekday when they are not attending for an OGD appointment. Our study is the largest clinical study showing that u-GIP can be used to identify advertent or inadvertent gluten ingestion. Our data suggest there may be a role for the u-GIP in the follow up of patients with CD but the results must be interpreted with caution. Further study is needed to determine the role of this in specific settings such as for home testing or in dietetic clinics to assess gluten free diet adherence.

Conflicts of interest: None to declare.

Authors' contribution: S.A.R. and D.S.S. conceptualised and designed the study with comments from all authors. Data was collected by S.A.R., K.E.I., O.G., C.M.J., G.W. and collated by S.A.R.. Data analysis and interpretation was completed by S.A.R., M.H.S., N.N., M.H., N.T. and H.A.P.. Writing of the manuscript was completed by S.A.R. and edited initially by D.S.S. and then all authors. The final version was approved by all authors. D.S.S. is the guarantor.

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