

# A prospective comparative study of five measures of gluten-free diet adherence in adults with coeliac disease

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## Publication data

Submitted 1 August 2007

First decision 22 August 2007

Resubmitted 24 August 2007

Accepted 24 August 2007

## SUMMARY

### Background

Increasing numbers of individuals are now being diagnosed with coeliac disease. The only accepted treatment for coeliac disease is lifelong adherence to a strict gluten-free diet (GFD). Individuals' ability to adhere to the GFD varies, but systematic studies guiding the assessment of adherence are currently lacking.

### Aim

We sought to compare the predictive value of self-report and four serologic tests compared to expert nutritionist evaluation.

### Methods

In all, 154 individual adults with biopsy-proven coeliac disease rated their adherence to the GFD on a Likert scale. Serum antibody titres of IgA anti-tissue transglutaminase, and IgA and IgG anti-deamidated gliadin peptides were determined. Using ANOVA and ROC analyses, results were compared to a standardized evaluation by an expert nutritionist blinded to the participants' self-rated adherence and serology results.

### Results

All serologic measures as well as participant reported adherence were significantly associated with GFD adherence as assessed by expert nutritionist evaluation. However, on ROC analysis no measure performed satisfactorily. The performance of serologic testing, but not self-report, improved with increased time on the GFD.

### Conclusion

Although current serologic tests have very high sensitivities and specificities for the diagnosis of coeliac disease, they cannot replace trained nutritionist evaluation in the assessment of GFD adherence.

*Aliment Pharmacol Ther* 26, 1227–1235

## INTRODUCTION

Coeliac disease (CD) is common throughout a large part of the world and is of increasing significance in gastroenterology practice. The only accepted treatment for CD is lifelong adherence to a gluten-free diet (GFD). Complete gluten withdrawal in individuals diagnosed with classic symptoms has been shown to lead to normalization of standardized mortality rate,<sup>1, 2</sup> as well as improvement in the majority of CD-related complications including osteoporosis/osteopenia,<sup>3</sup> anaemia,<sup>4</sup> risk of malignancy,<sup>1, 5</sup> gastrointestinal symptoms,<sup>4</sup> and in some studies, psychological well-being and quality of life.<sup>6, 7</sup> Unfortunately, maintenance of a GFD entails avoiding the ingestion of even small amounts of products derived from wheat, rye or barley.

Despite the proven benefits it can be exceedingly difficult to completely avoid gluten-containing foods. As a result it is estimated that only 45–80% of patients with CD adhere strictly to a GFD.<sup>8, 9</sup> Many patients with continuing gluten exposure will have persistent or recurrent symptoms of CD, and laboratory and/or pathologic changes consistent with active CD. Individuals with CD who present with ongoing symptoms despite dietary therapy are often found to have ongoing gluten exposure.<sup>10, 11</sup> However, the differential diagnosis is wide and includes refractory CD, intestinal T-cell lymphoma, small intestinal bacterial overgrowth, microscopic colitis, disaccharide intolerance and irritable bowel syndrome (IBS). For this reason, it is crucial for clinicians to accurately gauge a patient's adherence to a GFD. In that way individuals with likely gluten exposure can be evaluated carefully by a trained and experienced coeliac nutritionist, while those who adhere strictly can undergo further testing and treatment as needed.

As the clinical spectrum of CD has widened individuals are increasingly diagnosed with minimal or no symptoms. It is not certain that all individuals with CD including those with silent disease or atypical presentations will benefit from diagnosis and treatment. However, regardless of clinical presentation, a strict GFD is the sole therapy for CD and is effective in healing the mucosal lesion in the majority of cases. Thus, adherence to the GFD is the single most important contributor to disease activity and is often used as a surrogate measure of CD activity both in clinical practice and in research studies. Thus, the lack of a standardized, accurate measure of GFD adherence is a

significant problem both clinically and in research. Despite this clear need, validation of a test to measure GFD adherence has been difficult. Studies of conventional serologic tests have not yielded favourable results.<sup>12–14</sup> In this study, we prospectively examined the predictive value of self-report, of four serologic measures of GFD adherence (IgA anti-tissue transglutaminase (tTG), IgA anti-deamidated gliadin peptides (DGP), IgG anti-DGP, and combined IgA-IgG anti-DGP) against the current gold standard of expert nutritionist evaluation.

## METHODS

Adults (≥18-year-old) with biopsy-confirmed CD for greater than 3 months were enlisted to participate through recruitment posters that were mailed to local New England support groups and advertisements placed in regional CD newsletters and publications frequented by individuals with CD. In addition, eligible patients with CD being treated by the coeliac centre at Beth Israel Deaconess Medical Center (BIDMC), Boston, a tertiary care centre, were invited to participate. There was no exclusion of participants based on ongoing symptoms or laboratory abnormalities in order to avoid selection bias. Participants were asked to complete a three-day food record prior to their main research visit. During that visit participants first self-reported their GFD adherence on a 5 point Likert scale ranging from 'Highly Compliant' to 'I am not following a GFD at this time', had blood drawn for antibody testing and underwent evaluation for GFD adherence by an expert coeliac nutritionist (>5 years of experience working with >500 patients with CD). Of the 154 patients enrolled, two were excluded due to substantial irregularities within their questionnaire responses and three others due to insufficient sample volume for serologic testing.

The nutritional evaluation was done in a standardized fashion by analysis of 3-day food record [or by 24-h food recall when a 3-day food record was not available (20 cases)], a food ingredient quiz (see Appendix S1), and a dynamic clinical interview by an expert nutritionist. Global GFD adherence, taking into account avoidance of cross-contamination, and quantity and frequency of gluten exposure, was recorded on a 6-point Likert scale ranging from 'Excellent adherence' to 'Not currently following a GFD' (see Appendix S1).

Analysis of IgA anti-tTG and anti-DGP was performed by enzyme linked immunosorbent assay

(ELISA) with native tTG purified from human red blood cells (INOVA Diagnostics, Quanta Lite human-tTG IgA, San Diego, CA, USA; sensitivity 97%, specificity 99% in untreated CD<sup>15</sup>) and DGP (INOVA Diagnostics, Quanta Lite IgA DGP; sensitivity 97%, specificity 95%, Quanta Lite IgG DGP; sensitivity 96%, specificity 99%, and QUANTA Lite IgA/IgG composite DGP; sensitivity 97%, specificity 99%, as to recent test series<sup>16</sup>).

Data were entered into a secure database (Access, Microsoft Office, Microsoft Corp. Redmond, WA, USA) and reviewed for errors prior to analysis. Statistical analysis was completed using SPSS for Windows, Rel. 13.0. 2004. Chicago. SPSS Inc (Chicago, IL, USA). Correlations were examined using Student's *t*-test, ANOVA, and ROC analysis. For serologic tests, the analysis was repeated after excluding participants who had been on the GFD for less than 6 months and less than 1 year to exclude the potential compounding effects of residual elevated antibody titres.

This study was approved by the Beth Israel Deaconess Medical Center Committee on Clinical Investigations.

## RESULTS

Demographic characteristics of the study population were not significantly different from those of the overall CD population treated at BIDMC (Table 1). Although females showed marginally greater adherence to the GFD, as assessed by the expert nutritionist, this difference did not reach statistically valid significance ( $P = 0.06$ ). Neither age at participation, age at diagnosis of CD, length of time on GFD, marital status,

educational achievement, or employment status correlated with the level of GFD adherence.

Twenty-seven participants (17.5%) reported no classic symptoms prior to diagnosis with CD and instead were diagnosed with atypical symptoms or laboratory abnormalities alone (Table 2). The level of adherence was not different between this group and the group diagnosed due to typical CD symptoms, mean expert evaluation score of 1.96 vs 1.91, respectively ( $P = 0.835$ ). The presence of additional food intolerances was reported by 38% of participants and was the only factor significantly correlated with greater adherence ( $P = 0.028$ ), and being married was associated with a trend for better adherence ( $P = 0.052$ , Table 3a and 3b). The majority of participants were in clinical remission with 7%, 9%, 13% and 17% reporting frequent abdominal discomfort, diarrhoea, loose stools and severe fatigue, respectively.

In general, adherence rates in the study population were high with 44.2% and 34.4% being rated as 'Excellent' or 'Good' adherers to the GFD, respectively, by the expert nutritionist. Self-reported adherence and each of the serology measures were all highly associated with GFD adherence on ANOVA, yielding  $P < 0.001$  (Table 4 and Figure 1). However, for the serum tests much of this significance was dependent on the very high antibody titres of those few patients ( $n = 7$ ) who were the least adherent, with no serology test distinguishing reliably between excellent, good and fair adherence. This is evident from the ROC curves which for all measures performed poorly with areas under the curve of less than 0.7 for all data and less than 0.8 using the manufactures suggested cutoff value of 20 units when restricted to those on a GFD for more than 12 months. The performance of all serologic tests

Table 1. Characteristics of study population

	Study group ( $n = 154$ )	Overall coeliac population seen at BIDMC ( $n = 601$ )	<i>P</i>
Mean age of diagnosis (years)	44.8 (1–89)	43.7 (1–90)	0.45
% Female	76.6%	71.7%	0.23
Ethnicity			
White	152	598	0.58
Other	2	3	
% Other autoimmune disorder*	30.5% (47)	27.1% (163)	0.42

BIDMC, Beth Israel Deaconess Medical Center.

\* Predominantly thyroid disease > type 1 diabetes mellitus >> Raynaud's phenomenon > inflammatory bowel disease > sarcoidosis > psoriasis.

**Table 2.** Categorization of symptoms preceding the diagnosis of coeliac disease (CD)

Classic symptoms*	Asymptomatic/non-classic symptoms
Diarrhoea	No symptoms
Abdominal pain	Anaemia
Weight loss	Laboratory abnormalities
Fatigue	Osteopenia/osteoporosis
Dermatitis herpetiformis	Constipation
Fatigue/lethargy	Heartburn/GERD
Nausea/vomiting	Myalgias
Bloating/gas	Arthralgias
	Alopecia
	Headaches
	Asthma
	Infertility

GERD, gastro-oesophageal reflux disease.

\* One or more needed to qualify for classic CD presentation.

**Table 3a.** Association of binary demographic factors with gluten-free diet adherence

Factor	Percentage with excellent to good adherence	<i>P</i>
Presence of other food intolerances	87.9%	0.028
Absence of other food intolerances	72.9%	
Female gender	79.7%	0.551
Male gender	75.0%	
Co-morbid autoimmune disorders	78.7%	0.976
No co-morbid autoimmune disorders	78.5%	
Co-morbid psychological disorders	69.2%	0.203
No co-morbid psychological disorders	80.5%	
Classic CD symptoms	79.2%	0.450
No classic CD symptoms	75.9%	
Employed	81.5%	0.177
Not employed	71.7%	
Married	83.5%	0.052
Not married	70.2%	

CD, coeliac disease.

improved after excluding participants on a GFD for less than 6 months or less than 12 months. There was no change, however, in the predictive value of self-report with time on the GFD as measured by the area under the ROC curve (AOC). (Table 5 and Figure 2). For a set sensitivity of 80%, a cutoff value of 17.0 for

IgA anti-DGP yielded a specificity of 58%, a cutoff value of 10.4 for IgG anti-DGP yielded a specificity of 54%, a cutoff value of 15.0 for combined IgA-IgG anti-DGP yielded a specificity of 50%, and a cutoff value of 18.5 for IgA anti-tTG yielded a specificity of 56%.

The use of serology alone for predicting poor adherence with the cutoff value of 20 units suggested by the manufactures yielded positive predictive values (PPV) of 30.6%, 30.6%, 31.0% and 31.4% and negative predictive values (NPV) of 83.2%, 81.7%, 80.5% and 82.1% for IgA tTG, IgA DGP, IgG DGP and IgA/IgG DGP respectively for all participants. Including only participants on the GFD for a minimum of 12 months resulted in PPV of 53.8%, 50.0%, 42.8% and 55.6% and NPV of 84.5%, 86.7%, 82.5% and 83.9% for IgA tTG, IgA DGP, IgG DGP and IgA/IgG DGP respectively, again for the prediction of poor adherence. In comparison, self-report using any response other than 'Highly Compliant', as suggestive of poor compliance resulted in a PPV of 42.9% and NPV 86.5% for all time points and a PPV of 42.1% and NPV 84.8% for participants on a GFD for at least 1 year. Using a composite measure of serology and self-report (serology titre >20 and self-report other than 'Highly Compliant') resulted in PPV of 60.0%, 64.3%, 60.0% and 45.4% and NPV of 87.6%, 88.0%, 87.0% and 87.7% for IgA tTG, IgA DGP, IgG DGP and IgA/IgG DGP, respectively, for all data, and PPV of 80.0%, 80.0%, 100% and 85.7% and NPV of 86.7%, 89.2%, 85.7% and 87.7% for IgA tTG, IgA DGP, IgG DGP and IgA/IgG DGP, respectively, for participants on a GFD for at least 1 year (see Table 6).

## DISCUSSION

Adherence with the GFD has been measured in a number of ways. Patient self-report of believed level of adherence (i.e., visual analogue scales, Likert scales), dietary history, an evaluation conducted by a professional nutritionist well-versed in the intricacies of the GFD, serologic screening tests, and small-bowel biopsy have been used to measure individual levels of adherence with the GFD. Accuracy, invasiveness, time, and cost must be considered when choosing a measure of GFD adherence.

Self-report is a problematic method for measuring adherence to the GFD. Individuals tend to inaccurately report their level of adherence, whether intentionally or unintentionally. In our study, we found that self-report performed similarly to serologic testing when

**Table 3b.** Association of ordinal/continuous demographic factors with gluten-free diet (GFD) adherence

Factor	Mean value for participants with excellent to good adherence	Mean value for participants with fair to poor adherence	P
Educational achievement*	6.6	6.3	0.488
Age	50.11	51.24	0.967
Age at CD diagnosis	44.82	44.70	0.721
Months on GFD	56.21	66.30	0.829

CD, coeliac disease.  
\* Reported on a scale of 1 to 10 where 1 equals completion of 8th grade or less and 10 is a doctorate.

**Table 4.** Spearman's correlation of serologies and self-report to expert evaluation

Test	>3 months on GFD, n = 151		>6 months on GFD, n = 128		≥12 months on GFD, n = 108	
	rho	Significance	rho	Significance	rho	Significance
Self-report	0.403	<0.001	0.375	<0.001	0.346	<0.001
IgG anti-DGP	0.248	0.002	0.293	0.001	0.361	<0.001
IgA anti-DGP	0.193	0.017	0.280	0.001	0.342	<0.001
IgG-IgA anti-DGP	0.210	0.010	0.258	0.003	0.327	0.001
IgA anti-tTG	0.199	0.015	0.243	0.006	0.278	0.004

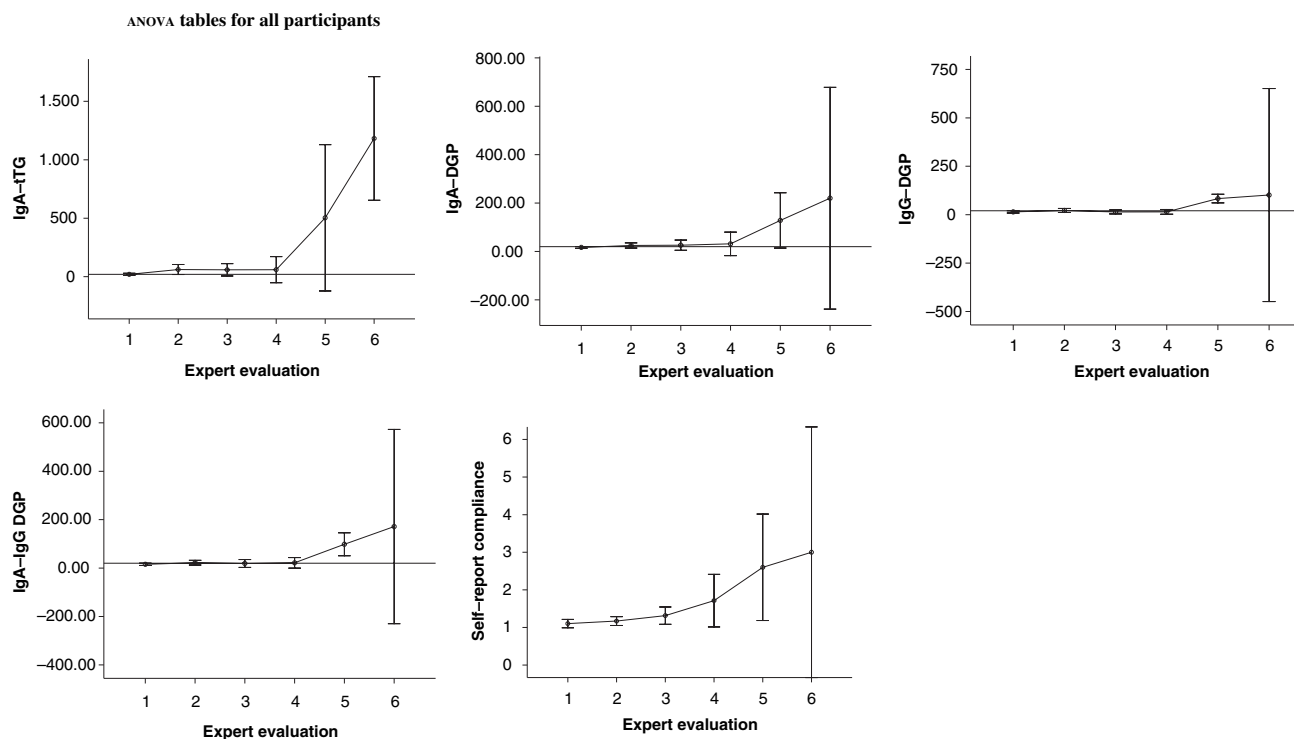
GFD, gluten-free diet; DGP, deamidated gliadin peptides; tTG, transglutaminase.

evaluating all patients on a GFD for more than 3 months. However, when including only individuals who had been on the diet for more than 6 or 12 months, unlike with serologic testing, there was no incremental improvement in performance of self-report, suggesting that when evaluating individuals who have been treated for longer periods of time, self-report is marginally less reliable than serology at determining adherence. Self-report measures do not correlate closely with nutritionist evaluation, serologic screening or small bowel biopsy results. Fera *et al.*<sup>17</sup> found that inter-rater agreement between self-reported GFD adherence and an objective adherence evaluation resulted in worse than chance agreement ( $\kappa = 0.328$ ). For example, 82 of the 100 patients in Fera's study reported that they strictly complied with the GFD, while direct inquiry by an expert in the GFD confirmed a strict GFD for only 49 of the 100 participants.

The reason for the poor performance of self-report is not entirely clear. One possibility is that patients

understanding of the GFD is flawed leading to inaccurate assessment of adherence. In this cohort, most but not all patients included in this study receive primary coeliac care at BIDMC and would have received uniform instruction on following the GFD. However, many patients are seen only infrequently for follow-up after the first year of diagnosis and there may be some 'drift' in understanding of the GFD as individuals forget details or procure information from other sources. Interestingly, although score on a GFD facts quiz correlated more poorly with expert evaluation of adherence than self-report (Spearman's Rho 0.328 and 0.403, respectively), degree of discrepancy between expert evaluation and self-report was associated with score on the GFD quiz (Spearman's Rho 0.328,  $P \leq 0.001$ ), suggesting that diet comprehension does partially explain the discrepancy between expert assessment and self-assessment.

While specific serologic assays, such as IgA or IgG anti-gliadin antibody, IgA anti-endomysial antibody (EMA), or IgA anti-human tTG antibody testing, have



**Figure 1.** ANOVA tables for all participants. Horizontal reference line placed at manufactures recommended cutoff value of 20 units for all serologic tests.

X axis is nutritionist evaluation rated as follows:

- 1—Excellent: Participant eats gluten less than 3 times per year ( $n = 68$ )
- 2—Good: Participant eats gluten 1 time per month ( $n = 53$ )
- 3—Fair: Participant eats gluten 2–3 times per month ( $n = 19$ )
- 4—Poor: Participant eats gluten 1–2 times per week ( $n = 7$ )
- 5—Very Poor: Participant eats gluten greater than 2 times per week ( $n = 5$ )
- 6—Participant does not follow the gluten-free diet ( $n = 2$ )

Self-Report Compliance rated as follows:

- 1—Highly compliant with the gluten-free diet
- 2—Moderately compliant with the gluten-free diet
- 3—Moderately non-compliant with the gluten-free diet
- 4—Highly non-compliant with the gluten-free diet
- 5—I am not following a gluten-free diet at this time.

a high diagnostic accuracy in detecting individuals with untreated CD, their reliability as predictors of adherence is not as robust. More specifically serologic tests are often falsely negative in patients with incomplete adherence.<sup>12</sup> In this study, for example, 53% of subjects with fair to very poor adherence had an IgA anti-tTG or IgA anti-DGP below the normal cutoff value of 20 units, while IgG anti-DGP and IgA/IgG anti-DGP performed even worse with 72% and 66% of individuals with fair to very poor adherence having serologies within the normal range. In terms of predictive value of poor adherence, even the most accurate serologic tests had only a 56% PPV and 87% NPV

after excluding those on a GFD for less than 1 year. Combining self-report and serology improved the PPVs significantly, while preserving acceptable NPVs. However this strategy is limited by the fact that between 7% and 10% of participants had both a serologic titre greater than 20 and reported being other than 'highly compliant'. Further, the high NPV found in this study would be expected to decrease in a more heterogeneous population with lower overall compliance.

The poor sensitivity of serology tests to incomplete GFD adherence is partially due to the fact that different antibodies disappear at different rates after starting

Table 5. ROC results

	AOC > 3 months	AOC > 6 months	AOC ≥ 12 months
Test	<i>n</i> = 150	<i>n</i> = 127	<i>n</i> = 107
Self-report	0.684	0.647	0.661
IgG anti-DGP	0.635	0.676	0.715
IgA anti-DGP	0.661	0.734	0.789
IgG-IgA anti-DGP	0.628	0.674	0.723
IgA anti-tTG	0.647	0.689	0.721

Cutoff level expert evaluation score less than or equal to 2 (excellent or good adherence) vs. 3 or greater (fair to non-adherent).

DGP, deamidated gliadin peptides; tTG, transglutaminase.

the GFD. Anti-gliadin titres reportedly fall more rapidly than EMA or anti-tTG, and IgA titres often normalize with 2–3 months, while IgG titres routinely take longer than 6 months to reach normal levels. Patients with very high antibody titres at diagnosis will take longer to achieve a normal titre regardless of their degree of adherence.<sup>18</sup> Additionally, adapting to CD and the GFD takes time and individuals often do not reach a plateau of comprehension and adherence for weeks to months after diagnosis. These facts are

evidenced in this study by the improved performances of serology testing in subjects who have been on a GFD for longer than 12 months. Thus, for recently diagnosed patients, the first 6 to 12 months can be considered a 'transition' period, during which the trend is more informative than the absolute antibody titre, and assessment of adherence is best done after this time period. To further complicate matters, disorders including giardiasis,<sup>19</sup> refractory CD,<sup>11</sup> small intestinal bacterial overgrowth,<sup>11</sup> and autoimmune hepatitis<sup>20</sup> have been noted to cause persistent elevations in coeliac antibody titres potentially misleading clinicians.<sup>11, 21, 22</sup>

A nutritionist's evaluation to pinpoint and quantify the number and degree of transgressions from the GFD has proven itself an excellent measure of GFD adherence with acceptable cost, non-invasiveness and correlation with histologic changes.<sup>9</sup> However, nutritionist evaluation is time consuming, subject to inter-observer variability and, in many locations, limited by a lack of adequately trained personnel. For this reason, a reliable surrogate measure of GFD adherence has been avidly sought.

In this study, we compared the predictive value of four different serologic tests with high sensitivity and specificity to detect CD, as well as simple self-report

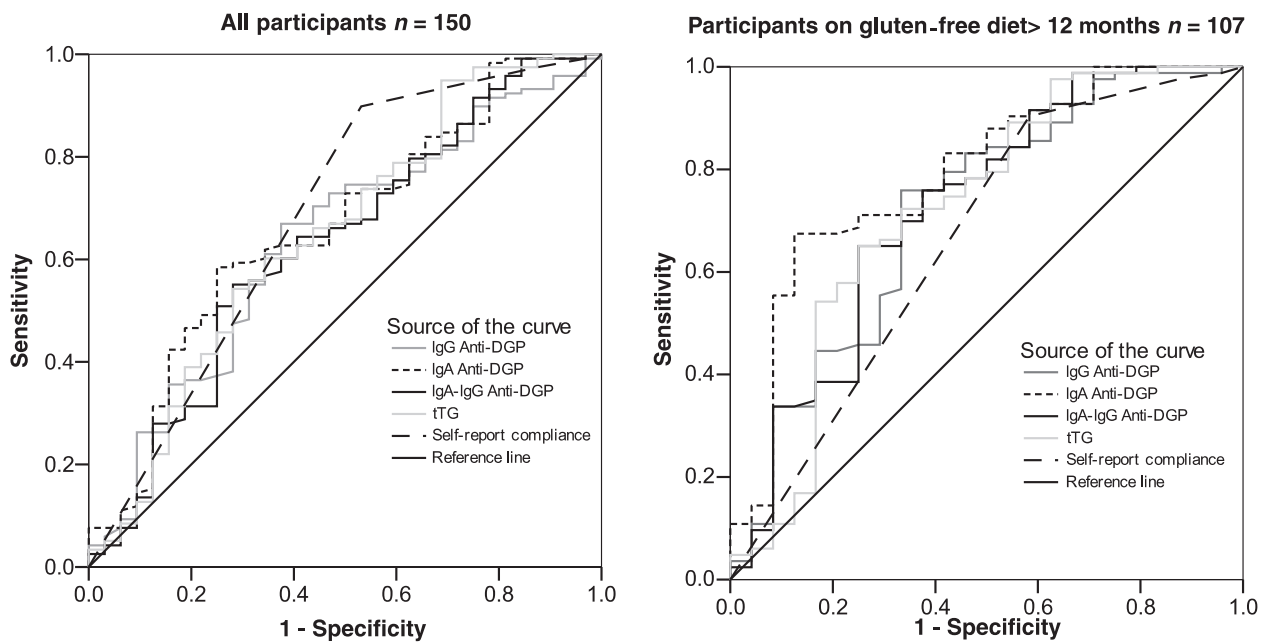


Figure 2. ROC curves for all participants and for  $\geq 12$  months. Cutoff level expert evaluation score less than or equal to 2 (excellent or good adherence) vs. 3 or greater (fair to non-adherent).

**Table 6.** Positive (PPV) and negative predictive values (NPV) for fair to poor gluten-free diet (GFD) adherence

Test	PPV	NPV	PPV GFD $\geq$ 12 months	NPV GFD $\geq$ 12 months
IgA anti-tTG $\geq$ 20 ( $n = 49$ )	30.6%	83.2%	53.8%	84.5%
IgA DGP $\geq$ 20 ( $n = 46$ )	30.6%	81.7%	50.0%	86.7%
IgG DGP $\geq$ 20 ( $n = 29$ )	31.0%	80.5%	42.8%	82.5%
IgA-IgG DGP $\geq$ 20 ( $n = 35$ )	31.4%	82.1%	55.6%	83.9%
Self-report $\neq$ highly adherent ( $n = 28$ )	42.9%	86.5%	42.1%	84.8%
Self-report $\neq$ highly adherent + IgA anti-tTG $\geq$ 20 ( $n = 15$ )	60.0%	87.6%	80.0%	86.7%

DGP, deamidated gliadin peptides; tTG, transglutaminase.

against standardized nutritionist evaluation of GFD adherence. Our hope was that the new generation of deamidated anti-gliadin tests would combine the responsiveness of anti-gliadin testing with the superb sensitivity and specificity of anti-tTG and EMA testing allowing for accurate serologic monitoring of GFD adherence. Unfortunately, our study does not indicate that this is the case. IgA anti-DGP did perform marginally better than anti-tTG in predicting GFD adherence. However, no test provided an accurate measure of the degree of GFD adherence due to their inability to accurately report less frequent or minor transgressions.

Although the anti-tTG data from this study are in line with prior studies of its use in estimating GFD adherence, some limitations are notable. First, adherence was not compared with concurrent histological evaluation, although, as noted above, it is doubtful that biopsy is superior to expert nutritionist evaluation in assessing GFD adherence. Prior studies show only a modest correlation of histology with clinical presentation or assessed dietary adherence.<sup>9, 23</sup> This is not surprising as the degree and extent of histological abnormality at the time of CD diagnosis varies widely despite the fact that most patients consume a gluten-rich diet prior to diagnosis. Furthermore, histologic recovery is variable, does not always correlate with clinical status and, in refractory CD, does not correlate with GFD adherence. Thus, we determined that a standardized assessment by an expert nutritionist was the best available standard of GFD adherence, whereas biopsy histology is the gold standard measure of CD activity.

Our study size was large in comparison to previous studies. However, the data were collected from participants in a limited geographic region. Also, as

is clear from the distribution of adherence levels, the studied population was weighted toward more adherent individuals, and the findings may not apply equally to patients with lesser levels of adherence as may be evident in a primary or secondary care setting.

In conclusion, options for the standardized evaluation of GFD adherence in adults with CD, other than by expert nutritionist assessment, remain unsatisfactory. The inability to easily and accurately gauge GFD adherence is a glaring problem that adversely affects both clinical care and research endeavours. This problem will need to be addressed, in order to answer important questions including the utility of CD diagnosis in asymptomatic and pauci-symptomatic individuals, and the utility of pharmacologic therapies for CD.

## ACKNOWLEDGEMENTS

*Declaration of personal interests:* Ciaran Kelly has served as a speaker for Salix Pharmaceuticals, ViroPharma Inc, and Robert Michael Communications; a consultant and scientific advisor for Acambis Inc, ActivBiotics Inc, Cambridge Antibody Technology Ltd, Genzyme Inc, LumeRx, Massachusetts Biologics Laboratories, Salix Pharmaceuticals, Trine Pharmaceuticals, IvpCare Inc, MPM Asset Management LLC, Oscient Pharmaceuticals, ViroPharma Inc, Gerson Lehrman Group, Frazier Healthcare Ventures; and providing research support for Acambis, ActivBiotics Inc, Cambridge Antibody Technology Ltd, Massachusetts Biologics Laboratories, and Salix Pharmaceuticals. *Declaration of funding interests:* This study was supported by charitable donations from patients to The Celiac Center at BIDMC, The Celiac Sprue Association, NIH T32 training grant DK07760, and the

Harvard-Thorndike General Clinical Research Center M01 RR01032. Serologic kits were supplied free of charge by INOVA Therapeutics.

## SUPPLEMENTARY MATERIAL

The following supplementary material is available for this article:

Appendix S1. Expert dietitian evaluation of GFD adherence.

This material is available as part of the online article from:

<http://www.blackwell-synergy.com/doi/apt/10.1111/j.1365-2036.2007.03501.x>

(This link will take you to the article abstract).

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## REFERENCES

- West J, Logan RF, Smith CJ, Hubbard RB, Card TR. Malignancy and mortality in people with coeliac disease: population based cohort study. *BMJ* 2004; **329**: 716–9.
- Corrao G, Corazza GR, Bagnardi V, et al. Mortality in patients with coeliac disease and their relatives: a cohort study. *Lancet* 2001; **358**: 356–61.
- Tau C, Mautalen C, De Rosa S, Roca A, Valenzuela X. Bone mineral density in children with celiac disease. Effect of a gluten-free diet. *Eur J Clin Nutr* 2006; **60**: 358–63.
- Dewar DH, Ciclitira PJ. Clinical features and diagnosis of celiac disease. *Gastroenterology* 2005; **4**(Suppl. 1): S19–24.
- Green PH, Fleischauer AT, Bhagat G, Goyal R, Jabri B, Neugut AI. Risk of malignancy in patients with celiac disease. *Am J Med* 2003; **115**: 191–5.
- Zarkadas M, Cranney A, Case S, et al. The impact of a gluten-free diet on adults with coeliac disease: results of a national survey. *J Hum Nutr Diet* 2006; **19**: 41–9.
- Mustalahti K, Lohiniemi S, Collin P, Vuolteenaho N, Laippala P, Maki M. Gluten-free diet and quality of life in patients with screen-detected celiac disease. *Eff Clin Pract* 2002; **5**: 105–13.
- Hogberg L, Grodzinsky E, Stenhammar L. Better dietary compliance in patients with coeliac disease diagnosed in early childhood. *Scand J Gastroenterol* 2003; **38**: 751–4.
- Ciacchi C, Cirillo M, Cavallaro R, Mazzacca G. Long-term follow-up of celiac adults on gluten-free diet: prevalence and correlates of intestinal damage. *Digestion* 2002; **66**: 178–85.
- Abdulkarim AS, Burgart LJ, See J, Murray JA. Etiology of nonresponsive celiac disease: results of a systematic approach. *Am J Gastroenterol* 2002; **97**: 2016–21.
- Leffler DA, Dennis M, Hyett B, Kelly E, Schuppan D, Kelly CP. Etiologies and predictors of diagnosis in nonresponsive celiac disease. *Clin Gastroenterol Hepatol* 2007; **5**: 445–50.
- Vahedi K, Mascart F, Mary JY, et al. Reliability of antitransglutaminase antibodies as predictors of gluten-free diet compliance in adult celiac disease. *Am J Gastroenterol* 2003; **98**: 1079–87.
- Dickey W, Hughes DF, McMillan SA. Disappearance of endomysial antibodies in treated celiac disease does not indicate histological recovery. *Am J Gastroenterol* 2000; **95**: 712–4.
- Sategna-Guidetti C, Grosso S, Bruno M, Grosso SB. Reliability of immunologic markers of celiac sprue in the assessment of mucosal recovery after gluten withdrawal. *J Clin Gastroenterol* 1996; **23**: 101–4.
- Van Meensel B, Hiele M, Hoffman I, et al. Diagnostic accuracy of ten second-generation (human) tissue transglutaminase antibody assays in celiac disease. *Clin Chem* 2004; **50**: 2125–35.
- Sugai E, Vazquez H, Nachman F, et al. Accuracy of testing for antibodies to synthetic gliadin-related peptides in celiac disease. *Clin Gastroenterol Hepatol* 2006; **4**: 1112–7.
- Fera T, Cascio B, Angelini G, Martini S, Guidetti CS. Affective disorders and quality of life in adult coeliac disease patients on a gluten-free diet. *Eur J Gastroenterol Hepatol* 2003; **15**: 1287–92.
- Pietzak MM. Follow-up of patients with celiac disease: achieving compliance with treatment. *Gastroenterology* 2005; **4**(Suppl. 1): S135–41.
- Sorell L, Garrote JA, Galvan JA, Velazco C, Edrosa CR, Arranz E. Celiac disease diagnosis in patients with giardiasis: high value of antitransglutaminase antibodies. *Am J Gastroenterol* 2004; **99**: 1330–2.
- Vecchi M, Folli C, Donato MF, Formenti S, Arosio E, de Franchis R. High rate of positive anti-tissue transglutaminase antibodies in chronic liver disease. Role of liver decompensation and of the antigen source. *Scand J Gastroenterol* 2003; **38**: 50–4.
- Clemente MG, Musu MP, Frau F, Lucia C, De Virgiliis S. Antitissue transglutaminase antibodies outside celiac disease. *J Pediatr Gastroenterol Nutr* 2002; **34**: 31–4.
- Volta U, De Franceschi L, Molinaro N, et al. Frequency and significance of anti-gliadin and anti-endomysial antibodies in autoimmune hepatitis. *Dig Dis Sci* 1998; **43**: 2190–5.
- Lee SK, Lo W, Memeo L, Rotterdam H, Green PH. Duodenal histology in patients with celiac disease after treatment with a gluten-free diet. *Gastrointest Endosc* 2003; **57**: 187–91.