Long-term histological follow-up of people with coeliac disease in a UK teaching hospital

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Received 15 January 2010 and in revised form 5 May 2010

Summary

Background: Coeliac disease is a relatively common condition which is usually managed by placing patients on a gluten free diet. Follow up biopsies to confirm histological recovery are controversial with a considerable variation in practice observed.

Aim: To determine the length of time to histopathological recovery in a group of coeliac disease patients and its associations with clinicopathological data.

Design and methods: All patients attending a specialist coeliac disease clinic prior to March 2009 were entered onto a database which recorded various clinicopathological data. The histopathology reports for all duodenal biopsies were reviewed and each biopsy was given a histopathological disease score based on a modified Marsh grade.

Results: Two hundred and eighty-four patients underwent index and at least one subsequent biopsy. Two-hundred and twenty-seven (80%) showed histopathological improvement and 100 (35%) returned to normal (median recovery time 1.9 years, inter-quartile range 1.0–4.8 years). Patients with less severe disease at diagnosis were more likely to show a better response (r=0.281, P<0.0001). Older patients demonstrated a shorter time to histopathological recovery (r=−0.200, P=0.001). Compliance with a gluten free diet was correlated with the best biopsy score (r=−0.134, P=0.040) and degree of histological recovery (r=0.161, P=0.014).

Conclusions: Current guidelines for the timing of repeat biopsy after commencing a gluten free diet are unclear, although 4–6 months has been recommended. This study shows that time to histological recovery is longer than traditionally thought and may need to take into account the patient’s age at diagnosis, the initial disease score and the level of compliance with a gluten free diet.

Introduction

Coeliac disease (CD) is an autoimmune condition principally affecting the small bowel mucosa. Gluten and its effect in patients with CD was first reported by Dicke,1 with subsequent studies revealing other similar toxic storage proteins found in barley and rye. The clinical and histological benefits of a gluten-free diet (GFD) in the management of CD are well recognized,2–5 with Dissanayake et al.,3 showing that the degree of histological recovery is dependent upon how strict the patient adheres to the diet.

CD has been linked to a number of clinical sequelae including gastrointestinal lymphoma,6,7 bone disease,8–12 and rarely, sepsis and pancreatitis,13,14 with some studies suggesting an increase in mortality.15–17 Despite the increased public

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awareness and rapid improvements in diagnostics, CD remains significantly under-diagnosed, with only around 10% of those affected achieving a definitive diagnosis. This highlights the importance of accurate readily available diagnostic tools and reinforces the need for evidence-based post-diagnosis surveillance.

Follow-up post-diagnostic small intestinal biopsies remain controversial, with practice varying between physicians. Current guidelines in the United States and United Kingdom recommend follow-up biopsies 4–6 months after initiating a GFD by which time improvement in small intestinal villous architecture can be expected. Routine practice outside of the guidelines often depends on the degree of mucosal healing and the patients clinical status. In general, if the first follow-up biopsy shows mucosal healing then further biopsies must be justified by the patient’s clinical status, whereas if the first follow-up biopsy shows incomplete mucosal recovery then re-biopsy should be considered. However, follow up data on small intestinal recovery is poor with much of it being derived from children. While small bowel mucosal abnormalities improve on a GFD, such improvement often takes in excess of 12 months. Current guidelines in both countries may therefore result in repeat biopsy well before the small intestinal mucosa has had chance to recover. Such biopsies are not without risk and delaying for a number of months may be more likely to detect a response to a GFD.

This study aimed to examine the length of time to histopathological recovery in a large group of CD patients attending a large UK teaching hospital. Additionally, correlations between histopathological disease score, gender, age and compliance with a GFD were assessed.

Methods

Patients attending a specialist clinic at Leeds Teaching Hospitals Trust, West Yorkshire, UK with a diagnosis of CD were retrospectively entered into an electronic database detailing clinical, pathologic-al and dietary details. The earliest initial biopsy entered on to the database was on 23 July 1971. Patients were entered onto the database under the direction of Prof. Howdle if they had clinical symptoms consistent with CD including weight loss and altered bowel activity, followed by at least one positive biopsy, even if the initial biopsy did not show any definitive morphological features. Concurrent serological data was unfortunately not available to correlate with the histopathological diagnosis; however, many of the more recently added patients will have undergone serological confirmation. All patients on the database with an index small bowel biopsy and at least one follow-up biopsy were identified and the relevant information extracted. No set protocol existed for subsequent biopsies, therefore post-index biopsies were taken at varying time intervals which mirrors routine clinical practice.

All histopathological reporting was performed by specialist gastrointestinal pathologists. The histopathology reports for all duodenal biopsies were collected and each individual biopsy from index to the last one documented was given a histopathological disease score based on a modified Marsh grade (Table 1). For each patient, the index and the follow-up biopsy with the lowest histopathological score (best biopsy) were identified and analyzed in more detail. If the lowest histopathological score was seen more than once, the first occurrence was deemed to be the best biopsy.

The primary outcome measures included time to complete histopathological recovery and time to best biopsy, from the time of the index biopsy. Other data collected included patient demographics, clinico-pathological follow up and the level of compliance with a GFD, which was assessed by self-reporting at varying times during follow up. The recorded compliance closest to the time of the best biopsy was identified and graded as poor compliance, or good compliance (i.e. no significant deliberate reported dietary indiscretions).

The audit was approved by both the audit lead and quality improvement department at the Leeds Teaching Hospitals Trust.

Statistical analyses were performed using the Statistical Package for the Social Sciences (SPSS v15.0, Inc., Chicago, IL). Correlation analyses between gender, age at diagnosis, histopathological disease score and compliance with a GFD were all examined by Spearman’s rank correlation coefficients. Subgroup comparisons of the time to best
biopsy score were assessed using the Mann–Whitney U-test. Time to histopathological recovery according to compliance with a GFD was assessed by the Kaplan–Meier method and differences between the two groups determined using the log rank test. Analyses where the P-value was <0.05 were considered to be statistically significant.

All analyses involving patient age, time to first biopsy and time to best biopsy were carried out on both the raw continuous data and grouped categorical data (e.g. <2, 2–5, >5 years). For such analyses, two sets of correlation coefficients $P$ and $r$ values are presented, the first of which represent analyses carried out on the continuous data and the second on the categorical data.

Results

Study population

On the 1 March 2009, 463 patients were identified on the CD database of which 286 had undergone both an index biopsy and at least one subsequent biopsy. Two patients had missing index histopathological disease scores hence 284 patients were included in the study: 82 males (29%) and 202 females (71%). Demographical and clinico-pathological follow-up data are displayed in Table 2. Fifty-three patients (19%) underwent repeat biopsy within 6 months, 138 (49%) within 1 year, 218 (77%)—within 2 years and 267 (94%) within 5 years. One hundred and forty-eight patients (52%) went on to have a second follow-up biopsy [median number of follow up biopsies = 2, inter-quartile range (IQR) 1–3].

Histopathological score

The number of patients with each histopathological disease score at the time of the initial biopsy and best biopsy is shown in Table 3. The proportion showing histopathological improvement, worsening or no change at the time of best biopsy is shown in Table 4. The 50 patients demonstrating no histopathological change included 12 with normal small bowel mucosal histology at the time of initial biopsy.

Of the 227 patients who showed a degree of histopathological improvement, 100 returned to normal (median complete histopathological recovery time 1.9 years, IQR 1.0–4.8 years, Figure 1). For patients demonstrating a return to histological normalization, a lower disease score at the time of diagnosis (i.e. lesser degree of histological abnormality) appeared to be associated with a more rapid return to normality (Figure 2). Of the 227 patients showing any degree of histopathological recovery, only 17 (7%) had their lowest histopathological disease score 6 months or less from the date of diagnosis, and only six (2.6%) demonstrated complete histological normalization within this 6 month period. Patients with higher stage disease (i.e. more severe) at diagnosis were more likely to have higher stage disease at the time of best biopsy ($r=0.281$, $P<0.0001$). There was no significant relationship between the histopathological disease score at diagnosis and the time to best biopsy ($r=0.042$, $P=0.478$ and $r=0.070$, $P=0.239$). A significant association was seen between the best

Table 2 Patient demographical and clinico-pathological follow up data

<table>
<thead>
<tr>
<th>Variable</th>
<th>Median</th>
<th>IQR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age of patient at diagnosis (years)</td>
<td>44.6</td>
<td>32.3–57.7</td>
</tr>
<tr>
<td>Length of patient follow up (years)</td>
<td>2.9</td>
<td>1.2–7.8</td>
</tr>
<tr>
<td>Number of biopsies taken per patient</td>
<td>3</td>
<td>2–4</td>
</tr>
<tr>
<td>Time from diagnostic biopsy to first follow-up biopsy (years)</td>
<td>1.0</td>
<td>0.6–1.8</td>
</tr>
<tr>
<td>Time from diagnostic biopsy to best follow-up biopsy (years)</td>
<td>1.6</td>
<td>0.9–3.7</td>
</tr>
</tbody>
</table>

Table 3 Number and proportion of patients with each of the histopathological disease scores at the time of the initial biopsy and best biopsy

<table>
<thead>
<tr>
<th>Histopathological disease score</th>
<th>Initial biopsy</th>
<th>Best biopsy</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N</td>
<td>Percentage</td>
</tr>
<tr>
<td>1</td>
<td>12</td>
<td>4.2</td>
</tr>
<tr>
<td>2</td>
<td>15</td>
<td>5.3</td>
</tr>
<tr>
<td>3</td>
<td>59</td>
<td>20.8</td>
</tr>
<tr>
<td>4</td>
<td>94</td>
<td>33.1</td>
</tr>
<tr>
<td>5</td>
<td>104</td>
<td>36.6</td>
</tr>
</tbody>
</table>

Table 4 Number and proportion of patients who showed improvement, worsening or no change in the histopathological disease score at the time of best biopsy

<table>
<thead>
<tr>
<th></th>
<th>N</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Histopathological improvement</td>
<td>227</td>
<td>79.9</td>
</tr>
<tr>
<td>No histopathological change</td>
<td>50</td>
<td>17.6</td>
</tr>
<tr>
<td>Histopathological worsening</td>
<td>7</td>
<td>2.5</td>
</tr>
</tbody>
</table>
biopsy score and the time taken to achieve this with patients with higher initial stage disease taking longer to achieve a better score ($r = -0.156$, $P = 0.008$ and $r = -0.179$, $P = 0.002$).

There was no relationship between age at diagnosis and the initial biopsy score ($r = 0.025$, $P = 0.678$ and $r = 0.029$, $P = 0.628$) or best biopsy score ($r = 0.077$, $P = 0.198$ and $r = 0.087$, $P = 0.142$), or between patient gender and initial biopsy score ($r = -0.013$, $P = 0.826$) or best biopsy score ($r = -0.039$, $P = 0.513$). Patient gender was not related to the time to best biopsy ($r = 0.013$, $P = 0.826$).

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**Figure 1.** Showing the spread of time to histological normalization across the 100 patients who showed complete histological recovery. Time to histological normalization was censored at 5 years. Vertical lines signify the median time and IQR.

**Figure 2.** Showing the speed of histological recovery in the 100 patients demonstrating histological normalization according to the initial histopathological score.
Compliance with GFD

The degree of self-reported compliance was available for 234 (82%) patients. Compliance was reported as being poor in 28 (12%) and good in 206 (88%). There was no correlation between the level of compliance and age at diagnosis ($r = 0.107$, $P = 0.103$ and $r = 0.102$, $P = 0.120$), gender ($r = 0.032$, $P = 0.623$), initial biopsy score ($r = -0.008$, $P = 0.907$) or time to best biopsy ($r = -0.046$, $P = 0.484$ and $r = -0.041$, $P = 0.533$). Using the Kaplan–Meier method, there was a relationship between the proportion of patients demonstrating complete histopathological recovery and compliance with a GFD, although this was not statistically significant (Figure 3).

A positive correlation was seen between the level of compliance and the best biopsy score with good compliers showing lower stage disease at best biopsy ($r = -0.134$, $P = 0.040$). This was confirmed by demonstrating a correlation between the level of compliance and the degree of histological recovery calculated as the initial biopsy score minus the best biopsy score ($r = 0.161$, $P = 0.014$).

Of the patients showing complete histological recovery, seven (9%) reported poor compliance and 75 (91%) reported good compliance. There was no correlation between the level of compliance and time to histopathological normalization in these patients ($r = 0.040$, $P = 0.723$ and $r = 0.017$, $P = 0.882$).

Discussion

CD is a medical condition with important clinical consequences for the patient. While the diagnosis and management are well reported, the optimal follow up schedule including time to repeat biopsy remains uncertain. Current US and UK guidelines are either equivocal or recommend a repeat proximal small bowel biopsy 4–6 months following index biopsy. However, other studies have shown that whilst small bowel histology improves following a GFD, the small bowel does not generally normalize within 12 months, although these studies have tended to be small. Whilst the need for any follow-up biopsy remains controversial amongst physicians, symptom response and serology, are poor predictors of mucosal repair. Histopathological examination allows direct visualization of the degree of mucosal damage, allowing appropriately tailored follow up strategies to be formed using not only gastrointestinal symptoms but also recognizing patients with refractory CD.

Grete et al. reported that recovery of the intestinal mucosa in 22 CD patients continued from 9 to 19 months and was still incomplete after 2–4 years. Wahab et al. found that only 65% of 158 patients reached histological remission (Marsh 0–II) within 2 years. Similarly, Tursi et al. found that 32/42 of newly diagnosed adult CD patients (72%) had normal small bowel histology after 2 years on a GFD. Interestingly they demonstrated incomplete histological and endoscopic recovery in older patients (defined as >30 years), even up to 24 months after starting a GFD, however documentation of dietary compliance was not available. Yachha et al. enrolled 42 children with CD of which 25 underwent repeat biopsies after 1–2 years and 14 had a third biopsy after 3–7 years of a GFD. They found that 94% showed improvement from subtotal to partial villous atrophy after 1–2 years, but none of the patients completely...
normalized after 5 years of a GFD. Contradictory evidence from George et al.\textsuperscript{31} showed that of 84 children undergoing a second biopsy within 1–2 years, 79 (94\%) demonstrated total or near total histological improvement on a GFD.

In a larger group of patients followed up over several years, we have shown that 35\% of CD patients achieved complete histopathological remission (Marsh 0) with a median recovery time of just <2 years. As expected we demonstrated a positive correlation between the level of compliance with a GFD and the degree of histopathological recovery, with good compliers showing a greater degree of recovery. Only 3\% of patients showing some degree of mucosal recovery achieved complete histological normalization within 6 months of diagnosis, the time suggested for repeat biopsy on current guideline schedules. This substantiates the case that early repeat small intestinal biopsies are not beneficial in a patient who is clinically well or improving.

The relationship between patient age at diagnosis and the degree of histological recovery remains unclear in the current literature. Bardella et al.\textsuperscript{26} assessed the histological response to a GFD in 249 patients with clinical remission and found that older age was significantly associated with reduced intestinal normalization. Dissanayake et al.\textsuperscript{3} concluded that the degree of histological recovery was independent of age, although this was based on a small sample of 38 patients. In our study it was actually the younger patients (<45 years) who demonstrated a significantly longer histopathological recovery time when compared to older patients, along with a significantly ($P = 0.035$) longer time to histological normalization. It is possible that older patients demonstrate an increased awareness and/or ability of the need to adhere to a GFD, in order to reduce the clinical sequelae associated with continued gluten consumption, although we recognize that larger studies are required to further clarify this relationship.

A retrospective observational study such as this is not without its limitations. In particular, there was no fixed policy for the timing of follow up biopsies with 23\% of patients not receiving their first follow up biopsy for over 2 years and 6\% for over 5 years. It is therefore not possible to determine whether duodenal mucosal histology had actually improved at an earlier time. To attempt to overcome this problem we chose to analyze categorical grouped data in addition to the raw continuous data, with a significant difference detected on only one occasion. We recognize that some patients may have refused follow up biopsy on account of clinical remission, hence we could potentially be missing out a large group of complete histological responders thus skewing our data. Unfortunately, whilst it is not possible to extract this information from the database, previous studies have shown that persistent villous atrophy is common in those with improved symptoms and who claim to be following a strict GFD.\textsuperscript{32} Another potential bias is that patients who are functionally very sensitive to gluten may suffer recurrent symptoms, be more likely undergo re-biopsy and yet be more likely to stick to a GFD.

Self-reporting of compliance with a GFD is open to erroneous reporting by the patient, however, a 5-day food diary for all patients would be very labor intensive although local unpublished food diary data in a similar cohort of patients suggests that only 3\% of self-reported good compliers are in fact not (D. Wild et al., personal communication). Self-reported measuring of compliance is achievable and therefore used in routine clinical practice far more frequently than objective measures. Despite its obvious problems, we have shown a positive correlation between self-reported dietary compliance and the degree of histological recovery.

In conclusion, this study has shown that repeating the proximal small bowel biopsy 4–6 months after diagnosis and starting a GFD is infrequently achieved, and is unlikely to show complete histological normalization. We believe that optimal follow up should include re-biopsy, the timing of which may be guided by clinical status such as symptom response, hematological, biochemical and serological control along with factors such as patient age at diagnosis, initial histological disease stage and compliance with a GFD. Further prospective studies randomizing patients between early and late re-biopsy are now required in order accurately to establish appropriate strategies for the follow up of CD patients.

Acknowledgements

The authors would like to thank Mr Thomas Fitzgerald from the Leeds Teaching Hospitals Trust for maintaining the database and providing the data for analysis.

Conflict of interest: None declared.

References


Histological follow-up of people with coeliac disease


