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Mucosal Recovery and Mucosal Healing in Biopsy-Defined Adult Celiac Disease

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Abstract Celiac disease (gluten-sensitive enteropathy) is an immune mediated disorder with characteristic histopathological small bowel mucosal changes that respond to a strict gluten-free diet. Recent studies have suggested that complete (rather than partial) mucosal recovery and healing is possible, but in some this may require a more prolonged period than is currently appreciated. In this study, 182 patients (60 males, 122 females) referred for evaluation of symptoms, including diarrhea and weight loss, were selected only if initial biopsies showed characteristic inflammatory changes with severe architectural disturbance. All patients were treated with a strict gluten diet alone and diet compliance regularly monitored. Up to 90% or more of patients showed a complete mucosal response or healing. A time-dependent rate of response was noted with most patients requiring more than 1 year, and even 2 years or more, to respond, however, complete mucosal healing was still possible within 6 months. In this evaluation, females in each of 4 different age ranges had mucosal response and healing rates superior to males, while elderly celiacs had lower rates. Such factors should be considered before labeling a patient with "non-responsive" disease. However, inflammatory changes with persistent architectural disturbance, especially in celiacs with a late diagnosis and resultant late initiation of a gluten-free diet treatment, may be at increased risk for a later small bowel complication, including lymphoma.

Keywords: *adult celiac disease, mucosal healing, villous atrophy, intraepithelial lymphocytosis, gluten-free diet*

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1. Introduction

Celiac disease (gluten-sensitive enteropathy) is an immune-mediated disorder that is accompanied by characteristic inflammatory changes and mucosal architectural alterations in the small intestine [1]. Some changes in untreated disease include elongated crypts with hyperplastic epithelia, reduced height or "flattening" of the villi, increased numbers of immunologically-active cells in the lamina propria, including plasma cells and lymphocytes, as well as increased numbers of intra-epithelial lymphocytes [2]. Expert histopathological classifications have been devised for clinical and investigative purposes, including a means of treatment evaluation [3,4,5,6]. Their precise role continues to be examined and debated, as reflected in the emergence of "new" terms, such as "microscopic enteritis", recorded in a recent consensus meeting [7] along with recent expert commentary [8]. There has also been increased recognition that pathological changes typically seen in untreated celiac disease are not specific, and occur in a variety of other "sprue-like" intestinal disorders [9]. Their recognition continues, even with the modern emergence of drug-induced forms of enteropathy [10], such as olmesartan-induced enteropathy [11] and recently, oxcarbazepine [12]. Most important, only in celiac disease is it recognized that these histopathological changes improve and normalize with a strict gluten-free diet, confirming the gluten-sensitive nature of this disorder and its final biopsy-definition with normalization of the small intestinal mucosa [1,2,3,4].

To some degree, pathological classifications of the severity of architectural change in endoscopic mucosal biopsies have some similarities in all of these different schema with different degrees of villous atrophy, "flattening" or blunting (Marsh 2-3), epithelial lymphocytosis with little or no architectural alteration (Marsh 1) and normal mucosa with intra-epithelial lymphocyte counts defined as less than 25 per 100 enterocytes (Marsh 0). These may be very useful, but a comparative study of different schema has shown that even for expert pathologists, differences in intra-observer error may be significant [6].

In recent years, serologic studies have often been used in follow-up, especially in pediatric populations, in part, to aid in compliance assessment, but even with completely normal levels of different serological markers, persistent inflammatory changes in biopsies may be present [13,14,15,16]. Only a limited number of studies have examined mucosal healing and/or mucosal recovery after over more than 2 years of gluten-free diet treatment. In the present study, long-term evaluation was done using biopsies only with initially severe architectural alterations to estimate rates of mucosal healing and mucosal recovery in celiac disease treated solely with a strict gluten-free diet.

2. Methods

All patients were initially referred from 1982 to 2011 for evaluation of symptoms, including abdominal pain and bloating, diarrhea and/or weight loss. After an overnight fast, most patients were administered intravenous sedative and topical xylocaine spray before the procedure. Some requested that the procedure be done without sedation. Biopsies were routinely obtained from the descending duodenum to confirm visible macroscopic findings, including normal or abnormal appearing mucosa, and exclude any microscopic findings that may account for symptoms. In some patients, additional biopsies were also obtained from the duodenal bulb or more distal duodenum. Endoscopic biopsies were obtained with regular pinch forceps and placed in fixative (eg., Bouin's, formalin) after careful orientation on mesh or filter paper with "the mucosal surface up" in the endoscopy suite. Routine histopathological processing through the biopsy core was performed as previously noted [3,4] and interpreted by experienced endoscopic biopsy pathologists. All biopsies were also independently reviewed at that time by the author investigator as a second trained observer of mucosal biopsy material [2].

Only patients with biopsies showing initially severe architectural changes were included in this evaluation (i.e., crypt hyperplastic villus atrophy, severe "flat" lesion, Marsh 3) with intra-epithelial lymphocytosis, as noted elsewhere [2,3,4,5] and characteristic of untreated celiac disease. Patients with minimal architectural disturbance or epithelial lymphocytosis alone in the initial biopsies were not included because previous North American studies involving both children and adults have suggested that most patients with this limited severity of histopathological change do not have celiac disease [17,18].

All patients were reviewed and monitored by a gastroenterologist and dietitian and treated solely with a strict gluten-free diet. Compliance with the gluten-free diet was defined by ongoing clinical evaluation (along with serological studies after 2000). Subsequent biopsies after gluten-free diet initiation were classified in a similar fashion based on degree of architectural change and epithelial lymphocytosis [2,3,4]. In addition, complete mucosal healing (i.e., normal mucosa, Marsh 0) or mucosal recovery (i.e., significantly improved architecture, but with persistent inflammatory changes or epithelial lymphocytosis alone or normal biopsies (Marsh 0-1), similar to definitions by others [19] were retrospectively recorded. In some, limited, but definite improvement in architecture with persistent inflammatory changes was considered evidence of mucosal responsiveness to a gluten-free diet, but not sufficient to define mucosal recovery or healing. In these patients, re-biopsy was done.

Most had additional biopsies within months up to 1 year from the initial evaluation for histological assessment to confirm improved architecture. In others, biopsies were obtained after 1 year and, in some, up to 20 years or more following their initial biopsies and institution of a gluten-free diet. In some, repeated biopsies showed persistent moderate to severe architectural changes, even after a period of more than 2 years before documenting histopathological improvement. Some patients referred from other gastroenterologists, or developing an unrelated or complicating illness, including collagenous sprue or malignant lymphoma, or receiving corticosteroids or immunosuppressant medications were either not available or prohibited from further biopsy studies.

3. Results

3.1. Study Population

A total of 182 patients (60 males, 122 females) with severe "flat" biopsy lesions (Marsh 3) were included in this long-term biopsy evaluation. Age ranges at the time of the initial biopsy for both males and females were recorded. As shown in Table 1, the percentage of females exceeded the percentage of males in each of the different arbitrary age ranges. Although each of the different age ranges noted were well represented in each group for males and females, over 25% of males and 25% of females evaluated were elderly (i.e., over age 60 years) at the time of the initial biopsy showing characteristic changes of untreated adult celiac disease. Increased initial recognition of adult celiac in the elderly has been examined [20] and reviewed elsewhere [21].

Table 1. Ages of Males and Females at Initial Biopsy*

	15-30 years	31-45 years	46-60 years	61-80+ years
Males	5 (8.3)	15 (25.0)	24 (40.0)	16 (26.7)
Females	23 (18.9)	42 (34.4)	24 (19.7)	33 (27.0)
Total	28 (15.4)	57 (31.3)	48 (26.4)	49 (26.9)

*Total study population (n=182) with severe "flat" biopsy lesion (i.e., crypt hyperplastic villus atrophy, Marsh 3) included 60 males and 122 females. Numbers in brackets, calculated percentages.

Table 2. Overall Mucosal Recovery and Healing Rates*

	15-30 years	31-45 years	45-60 years	61-80+ years
Males	4/5 (80.0)	12/15 (80.0)	21/24 (87.5)	10/16 (62.5)
Females	21/23 (91.3)	39/42 (92.8)	22/24 (91.6)	26/33 (78.8)
Total	25/28 (89.3)	51/57 (89.5)	43/48 (89.6)	36/49 (73.5)

*Mucosal recovery or healing (minimal architectural change, epithelial lymphocytosis or normal; Marsh 1-0). Number in brackets, percentage.

Table 3. Time-Dependence of Mucosal Recovery and Healing

	< 6 months	< 1 year	< 2 years	> 2 years
Males	12/29 (41.4)	24/35 (68.6)	29/38 (76.3)	47/60 (78.3)
Females	22/26 (84.6)	36/43 (83.7)	47/59 (79.7)	108/122 (88.5)
Total	34/55 (61.8)	60/78 (76.9)	76/97 (78.4)	155/182 (85.2)

Number in brackets, percentage.

3.2. Overall Mucosal Recovery and Healing

Table 2 shows rates of recovery and healing in 182 patients. Overall, 155 of 182, or 85.2%, showed minimal changes or completely normal mucosa on a second or subsequent endoscopic duodenal biopsy. For males, the overall rate was 47 of 60, or 78.3%, and females, the overall rate was 108 of 122, or 88.5%. In this evaluation, the absolute rates of mucosal recovery or healing for females exceeded males in each of the 4 arbitrary age ranges.

3.3. Age-related Dependence on Mucosal Recovery or Healing

Table 2 also shows that percentage rates of mucosal recovery or healing were lowest in the elderly compared to patients having an initial biopsy in one of the arbitrarily-defined age ranges. In the elderly, over age 65 years, absolute percentage rates were lowest compared to all other adult age ranges, especially for males.

3.4. Time-Dependence of Mucosal Recovery or Healing

Table 3 shows rates of recovery and healing in 182 patients with biopsies at different times on a gluten-free diet after the initial biopsies. Additional biopsies were done in some patients at times after 1 to 2 years on a gluten-free diet to demonstrate histopathological evidence of mucosal recovery or healing. With increasing time on a gluten-free diet, the overall absolute percentage rates of mucosal recovery and healing increased, especially for males.

3.5. Sex-Dependence of Mucosal Recovery or Healing

Table 2 and Table 3 also show that the rates of mucosal healing and recovery differed in males and females. Overall, the rates were always higher in females compared to males. Interestingly, mucosal recovery and healing could be documented in males and females within 6 months after the initial biopsies, particularly in females. Only after a year or more on a strict gluten-free diet, however, did male rates and female rates approach each other and remain similar.

3.6. Persistence of Inflammatory Changes

Although the majority of patients showed a complete histopathological response to a gluten-free diet, for some this was limited. Despite follow-up biopsies after over more than 2 years, evidence for persistent inflammatory changes and a response that could be defined as mucosal recovery or mucosal healing did not occur. Altogether, a total of 27 of 182 (i.e., 14.8%) had persistent inflammatory changes with architectural change on subsequent biopsies, including 13 males (i.e., 21.7%) and 14 females (i.e., 11.5%) in repeated biopsies. Among males, 1 from the 46 to 60 year age group developed an early stage small bowel adenocarcinoma that was completely resected and 5 in the 61 to 80+ year age group later developed a T-cell lymphoma. Among females, 1 each in the 31 to 45 year and the 61 to 80+ year age group developed collagenous sprue. In addition, 2 females in the 61 to 80+ age group developed a T-cell lymphoma. In other males and females, limited compliance to the gluten-free diet was suspected and 3 females were found to have symptomatic collagenous colitis during treatment with a gluten-free diet. In all of these with persistent architectural change, however, partial improvement compared to the severely abnormal initial biopsies was documented, even in those with the eventual development of a lymphoma.

4. Discussion

This evaluation showed that most patients treated with a strict gluten-free diet responded histopathologically in a subsequent mucosal biopsy with complete mucosal recovery and/or mucosal healing. These findings are consistent with earlier studies [19,22,23], but emphasize that even with severely abnormal initial biopsies, complete mucosal recovery and healing is possible. Although biopsies in celiac disease may show variable or limited degrees of inflammatory change, patients reported in this evaluation were first referred because of symptoms and all selected for this evaluation had initial small intestinal biopsies showing a severe “flat” biopsy lesion, or so-called crypt hyperplastic villus atrophy (i.e., Marsh 3). Patients with histopathologically less severe disease were excluded as were patients lacking gastrointestinal symptoms or referred for biopsy after serological screening. Here, complete mucosal recovery and mucosal healing (defined as normal villus architecture, sometimes with epithelial lymphocytosis, i.e., Marsh 0-1) occurred in most patients, despite an initially severe disturbance of mucosal architecture. This finding contrasts with earlier reports suggesting that initially severe biopsy changes may be predictive of incomplete recovery after a year on a gluten-free diet [24,25]. Here, even within a limited period of 6 months on a strict gluten-free diet, histopathological improvement was entirely possible, including a complete return to normal mucosa. From a practical clinical perspective, however, this time-dependent data also showed that a second biopsy to define mucosal recovery and/or mucosal healing might better be done after at least 1 year following the initial severely abnormal biopsy (not

within months), and best after 2 years on a continuous gluten-free diet.

In the present report, histopathological persistence of duodenal intraepithelial lymphocytosis was also noted in a few patients despite a strict gluten-free diet. This was also emphasized in an earlier report [26], but in that study, oats consumption was implicated. In our patients, concomitant oats consumption was not permitted, and yet, persistent epithelial lymphocytosis was still recorded suggesting that some other, yet-to-be- defined factor (i.e., not oats) is important. Perhaps, other environmental (including dietary) or genetic factors are important. Further studies in this subgroup with persistent intra-epithelial lymphocytosis would be of special interest and are still needed.

In most males and females, up to 90% or more had a complete response to dietary intervention alone. However, both elderly males and females with celiac disease, now recognized more often [20,21], had lower absolute rates of mucosal recovery or mucosal healing compared to younger adults. In about 20% of elderly celiacs (particularly males), mucosal recovery or mucosal healing was more difficult to achieve, even after more than 2 years on a gluten-free diet. This is not an entirely new observation, as others have also noted incomplete histologic recovery even 24 months after initiation of a gluten-free diet and emphasized that mucosal recovery takes time in all age groups [19]. In the elderly, this may be even more important. In part, some factors suggested in the elderly that may be responsible have included more difficult dietary compliance or a mucosa that is simply less responsive to gluten restriction, possibly because of limited capacity for enterocyte adaptation after years and years of chronic gluten ingestion and undetected celiac disease.

Although the patients in this study showed a histopathological response to a gluten-free diet, in some this was limited. Indeed, persistent inflammatory change appeared to be an ongoing risk factor for eventual development of a disease complication, including collagenous sprue or a T-cell lymphoma, especially if the disease was detected late in life. The findings in this patient group also confirm that elderly celiacs with a late initial diagnosis and initiation of a gluten-free diet are at greater risk for a disease complication, including malignancy [27]. It is well appreciated that this risk is linked to persistent inflammatory change and significant architectural disturbance in repeated biopsies despite a gluten-free diet. Ongoing inflammatory disease per se may well be a risk factor for progression to other disease complications, including lymphoma, but in patients here, the celiac mucosa could still initially respond to a gluten-free diet, even if lymphoma was concomitantly present or developed later.

5. Conclusion

In summary, most patients with severely abnormal small intestinal biopsies can respond to a gluten-free diet with complete mucosal recovery and healing, sometimes even within 6 months of initiation of a strict gluten-free diet. This histopathological response, however, appears to be time-dependent, usually requiring more than 1 year and sometimes over 2 years. Not only was this dietary response time-dependent, this evaluation also noted that females with severely abnormal biopsy changes responded earlier after their initial biopsies and had a superior overall response rate compared to males. Such factors should be considered before labeling a patient, even if compliant on a strict gluten-free diet, with so-called “non-responsive” celiac disease. Finally, however, a late diagnosis of adult celiac disease in an elderly patient and a resultant late initiation of a strict gluten-free diet appeared to have lower overall mucosal response and healing rates and, occasionally, development of a small intestinal complication, including lymphoma.

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