



## Dietary compliance in celiac disease

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### Abstract

Celiac disease is an immune-mediated disorder that causes severe architectural disturbance in the small intestinal mucosa of genetically-predisposed individuals. Impaired absorption of multiple nutrients results and diarrhea and weight loss develop. Evidence has accumulated that a strict gluten-free diet can result in

resolution of diarrhea, weight gain and normalization of nutrient malabsorption. In addition, histopathological changes also normalize, but this histopathological response appears to be time-dependent, sex-dependent and age-dependent. Compliance to a gluten-free diet is difficult and costly resulting in poor compliance and only a limited clinical response. This poses a risk for later long-term complications, including malignancy. A major practical clinical problem is the assessment of compliance to the gluten-free diet. Although symptoms may resolve and serological antibody markers may improve, multiple studies have documented ongoing architectural disturbance and inflammatory change, and with these continued inflammatory changes, a persistent risk for long-term complications. Recent immunological studies have suggested that peptides can be detected in both urine and fecal specimens that may be indicative of limited compliance. At the same time, multiple biopsy studies have demonstrated that complete normalization of the mucosa may occur in some patients within 6 mo of initiation of a gluten-free diet, but more often, up to 2 years or more may be required before repeated biopsies eventually show mucosal recovery and mucosal healing.

**Key words:** Gluten-free diet; Compliance; Dietary recall; Celiac disease; Fecal immunoreactive peptides; Tissue transglutaminase antibodies

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**Core tip:** Celiac disease is an immune-mediated disorder that improves with a strict gluten-free diet. Dietary compliance is essential for symptom resolution and reduction of the risk of long-term complications, including malignancy. Recent evidence suggests that resolution of symptoms and normalization of serological antibody markers on a gluten-free diet occurs, but mucosal inflammatory changes may persist, a critical risk factor for long-term complications. Several recent biopsy studies have documented that the small intestinal mucosa in adult celiac disease may completely

normalize within months, but most require up to 2 years or more to demonstrate mucosal recovery and healing. Histopathological rates of resolution on a gluten-free diet appear to be time-dependent, sex-dependent with higher rates in females, and age-dependent, with lower rates in the very elderly.

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## INTRODUCTION

Celiac disease is an immune-mediated disorder induced by dietary ingestion of gluten-containing foods in genetically-predisposed individuals<sup>[1]</sup>. The disorder causes small intestinal mucosal inflammatory changes and altered architecture, often leading to impaired nutrient absorption, diarrhea and weight loss<sup>[2]</sup>. Several extra-intestinal changes may also occur, or represent the presenting clinical manifestation of underlying occult celiac disease. Treatment currently depends on consumption of a strict gluten-free diet so that mucosal healing can occur and complications minimized. Adherence to a strict gluten-free diet is difficult, costly and compliance difficult to monitor, but a balanced gluten-free diet should be based on a combination of natural gluten-free foods and certified manufactured gluten-free foods. Different factors may influence compliance, particularly age at diagnosis, and reported estimates of lack of compliance are highly variable. Overall, it has been estimated that celiac disease may occur in up to 1% to 3% of serologically-tested or biopsy-screened populations<sup>[3]</sup>.

## DIAGNOSIS OF CELIAC DISEASE

Usually, duodenal mucosal biopsies are obtained during upper endoscopic evaluation from symptomatic patients<sup>[3]</sup>. In some, serological testing has resulted in a high degree of suspicion for possible celiac disease leading to biopsy, while in others, macroscopic changes during endoscopy may be considered abnormal, although not specific, so that microscopic evaluation is done. Biopsies are generally obtained from multiple sites in the proximal duodenum, carefully oriented in the endoscopy suite on filter paper, mesh or another substrate, and submitted in a fixed state to the pathology laboratory. Biopsies are then placed in paraffin, serially sectioned through the biopsy core, placed in a water bath, transferred to glass slides, and finally, stained with routine materials, such as hematoxylin and eosin. Several pitfalls in this process have been previously described<sup>[2,4]</sup> and may lead to over-diagnosis, under-diagnosis or misdiagnosis, including insufficient biopsy sampling related to biopsy

site, number of biopsies, laboratory preparation of biopsy materials and histopathological interpretation. Observer differences in interpretation, particularly if applied to different classification schema, may occur even among expert endoscopic biopsy pathologists<sup>[5]</sup>, despite sampling and preparation of biopsy material at a high level of technical skill in the clinical histopathology laboratory.

## DIFFERENTIAL DIAGNOSIS

During histopathological evaluation, characteristic changes may be noted. In symptomatic patients, severe architectural changes are frequently observed in duodenal mucosa that may suggest the diagnosis of untreated celiac disease. Less significant architectural changes may be detected, often in serologically-positive, but asymptomatic, patients. A specific diagnosis, based on initial biopsy findings alone, however, is not possible, especially with the emergence of additional causes of virtually identical histopathological changes<sup>[6]</sup>. In the past, other diseases, particularly infectious agents, were recognized to cause the same pathological changes, and more recently, medications have become increasingly appreciated<sup>[7,8]</sup>. Because celiac disease has been recognized as a gluten-sensitive enteropathy, a precise diagnosis usually depends on normalization on a strict gluten-free diet. From a clinical perspective, a response to a gluten-free diet in patients with a relatively immediate response to a strict gluten-free diet including resolution of diarrhea, significant weight gain and normalization of blood and serological tests is usually sufficient. Additional biopsy studies specifically to confirm a celiac disease diagnosis may not always be required. In some, biopsies may completely normalize within a period of 6 mo, while others may show persistent structural and inflammatory changes for extended periods. Often, in some, over more than 1 to 2 years on a strict gluten-free diet may be necessary for repeated biopsies to normalize<sup>[9,10]</sup>.

## GLUTEN-FREE DIET TREATMENT

Compliance to a strict gluten-free diet is difficult for the patient, but also difficult for the physician specialist and specialist dietitian to monitor. In general terms, young pre-school children are thought to be the easiest to monitor because meal content and preparation is largely in the control of their parents, however, as children enter puberty and adolescence with increasing autonomy to make dietary choices, this control is gradually lost and monitoring may become exceedingly difficult<sup>[11]</sup>. Interestingly, adult celiacs diagnosed before age 4 years were more compliant compared to those with an initial diagnosis after age 4 years<sup>[12]</sup>. Factors related to the burdens associated with the gluten-free diet in adolescence have been recently examined elsewhere<sup>[13]</sup>. In adults, successful compliance is largely related to the degree

of effort and interest of the patient, education and constant re-education provided by the interested physician and dietitian, and repeated monitoring that ultimately becomes the responsibility of the patient. In addition, referral to a specialist dietitian will aid in ensuring diet is not only gluten-free, but nutritionally adequate (as gluten-free diets may contain added sugars and total fat). As sensitivity to gluten may be highly variable, it would difficult to estimate a "safe gluten threshold" in different individuals with celiac disease. Online forms of intervention may also be useful<sup>[14]</sup>. In some settings, self-help groups may be particularly valuable in providing information not only related to sources of specific gluten-containing foods and the gluten-free diet *per se*, but also the provision of gluten-free recipes and other aids related to the gluten-free diet. In the elderly, compliance sometimes poses added difficulties, especially if the diagnosis is first made during this older age and the prospect of dietary re-training becomes problematic. The gluten-free diet may be difficult to pursue in some countries that have limited access to gluten-free products, or in settings where limited or minimal financial support is available<sup>[15]</sup>, especially from government or other health care providers. Gluten-free diets are generally costly and perceived cost remains a barrier to adherence<sup>[16]</sup>. In some countries, governments may provide a stipend to alleviate costs or, alternatively, consider the costs of a gluten-free diet as an annual tax credit to the well-documented patient with biopsy-defined celiac disease<sup>[17]</sup>. Many restaurants and airlines provide gluten-free food products, if requested, assuming patients and caregivers are aware that these may be available. Likely, public awareness and public pressure on these different commercial venues related to gluten-free products has increased, especially with widening demands related to emergence of other so-called "non-celiac gluten intolerance" disorders. Finally, some have indicated that labeling as "gluten-free" may be problematic, especially for commercial products that may contain small or trace amounts of gluten, and are not strictly gluten-free.

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## CLINICAL ASSESSMENT OF COMPLIANCE

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Measurement of compliance has also emerged as an important issue. Evidence suggests that a lack of compliance results in ongoing or persistent inflammatory change in the small intestine, ultimately resulting in a risk for complications related to untreated or partially treated celiac disease. Severe architectural biopsy changes may also occur in patients with celiac disease even with minimal or no symptoms, indicating that evaluation of symptoms alone is inadequate to assess compliance and not truly predictive of biopsy changes<sup>[18]</sup>. In patients with celiac disease diagnosed and then lost to follow-up or "neglected", both

malignant and non-malignant complications may occur<sup>[19]</sup>. In addition, celiac disease first diagnosed later in life may also be associated with increased celiac disease complications, including lymphoma<sup>[20]</sup>, possibly reflecting a prolonged period of persistent inflammatory change before a precise diagnosis of celiac disease is eventually made and treated.

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## SEROLOGICAL ASSESSMENT OF COMPLIANCE

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Recognizing the futility of symptom resolution to ensure disease remission, compliance has also been routinely monitored with repeated serological evaluation. Initially, this approach was thought to be useful, in part, because an added biopsy to assess healing might not be required. In some patients, particularly pediatric-aged celiacs, this approach appeared to have substantial appeal. Initial studies documented that the levels of some antibodies, particularly IgA-antibodies to tissue transglutaminase, endomysium or de-amidated gluten peptide would fall on a strict gluten-free diet. In most patients, this finding suggested that patient compliance to the gluten-free diet was satisfactory. Unfortunately, in many, even in those with completely normal antibody levels, a second biopsy often showed persistent inflammatory changes suggesting that serological follow-up was an inadequate measure of mucosal healing, even if dietary compliance appeared to be satisfactory<sup>[21-25]</sup>. Additional recent studies have also suggested direct measurement of gluten peptides in fecal material may be done as a marker reflective of dietary adherence<sup>[26]</sup>. In a recent report<sup>[27]</sup>, a high percentage of celiac patients on a gluten-free diet had detectable gluten immunogenic peptides in fecal material suggesting significant limitations in food questionnaires and serological tests for gluten-free diet monitoring in celiac patients. Using this method of fecal gluten detection, about 15% of children less than 3 years of age to almost 40% of teenagers and young adults had values suggesting non-compliance. Interestingly, the same evaluation also found that a higher proportion of male patients were not compliant, possibly owing to milder symptoms in males or greater control sought by females in the same age group<sup>[27]</sup>. In future, the relationship between levels of immunogenic fecal peptides and degree of histopathological changes in the intestinal tract may prove to be clinically useful, but more studies are clearly needed to define sensitivity, specificity, cut-offs and the role of microbiota and other potentially intervening factors that may modify the amount of fecal peptides.

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## BIOPSY EVALUATION

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A variety of studies ranging up to several years have evaluated histopathological changes in celiac disease follow-up biopsies following treatment with a gluten-

free diet<sup>[9,10,28-34]</sup>. In general, complete mucosal healing in adults may sometimes occur within 6 mo, even if severe architectural disturbance is initially present<sup>[10]</sup>, but for most, healing requires a much more extended period on a strict gluten-free diet<sup>[10]</sup>. Indeed, about 80% or more of adult celiac disease patients show mucosal recovery and healing after up to 2 years or more on a gluten-free diet<sup>[9,10,28,31,34]</sup>. Higher percentages of recovery and healing in adult women compared to adult men were also recorded, regardless of the age range evaluated<sup>[10]</sup>. Finally, celiacs initially diagnosed late in life tended to have lower rates of healing<sup>[10]</sup>. Bottom line is that complete mucosal healing occurs, but is time-, sex- and age-dependent.

## CONCLUSION

Adult celiac disease is an immune-mediated disorder that may cause severe architectural disturbance to the small intestinal mucosa associated with an inflammatory response that includes intra-epithelial lymphocytosis. In most, symptoms of diarrhea and weight loss occur, but in others, only limited or minimal intestinal symptoms are present. Diagnosis is achieved with small intestinal mucosal biopsies that demonstrate a characteristic lesion of untreated disease followed by evidence of a response to a gluten-free diet. Serological studies have been useful for screening of populations and case finding. Treatment with a strict gluten-free diet requires patient, physician and dietitian compliance so that symptoms resolve, serological findings normalize and, ultimately, the small intestinal mucosa recovers and healing occurs. Unfortunately, assessing compliance is often challenging since severe biopsy changes may still be present even if symptoms are limited or minimal. Although serological studies with different antibody markers may return to normal, multiple studies have demonstrated that these are poor predictors of histological improvement. In recent years, longer-term studies with re-biopsy have demonstrated that most adults with celiac disease will not only show histopathological improvement with a gluten-free diet, but may, after an extended period of up to 2 years or more, show mucosal recovery and complete healing. The time-dependent nature of this healing process is also influenced by sex with females having higher rates of healing compared to males, and age-dependent with lower rates of healing in very elderly celiac disease patients.

A recent review<sup>[35]</sup> emphasized these important paradigm shifts in management and follow-up of celiac disease, particularly in the now frequently recognized asymptomatic patient. Further research, particularly with emerging measurements (*i.e.*, fecal gluten peptides, serum and urinary metabolomics and specific volatile agents in the urine) should prove useful, not only in clinical diagnosis, but also in dietary compliance and treatment evaluation. Recent published data from North America (including Canada and the United

States) also suggest that northern latitudes may be an added risk factor for clinical expression of celiac disease<sup>[3,36]</sup> and future research may serve to explore these observations.

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