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Digesting gluten with oral endopeptidases to improve the management of celiac disease

Durham K *et al.* Endopeptidases in celiac disease

Abstract

In our editorial, we want to comment on the article by Stefanolo *et al* titled “Effect of *Aspergillus niger* prolyl endopeptidase in patients with celiac disease on a long-term gluten-free diet”. Celiac disease is an immune-mediated disorder triggered by dietary gluten in genetically predisposed individuals. Although avoiding gluten can permit patients to live symptom-free, ongoing voluntary or involuntary exposure to gluten is common and associated with persistent villous atrophy in small bowel mucosa. As villous atrophy predisposes patients to life threatening complications, such as osteoporotic fractures or malignancies, therapeutic adjuncts to gluten-free diet become important to improve patients’ quality of life and, if these adjuncts can be shown to improve villous atrophy, avoid complications. Oral administration of enzyme preparations, such as endopeptidases that digest gluten and mitigate its antigenicity to trigger inflammation, is one clinical strategy under investigation. The article is about the utility of one endopeptidase isolated from *Aspergillus niger*. We critique findings of this clinical trial and also summarize endopeptidase-based as well as other strategies and how they can complement gluten-free diet in the management of celiac disease.

Key Words: Celiac disease; Gluten-free diet; Endopeptidase; Villous atrophy

Durham K, Ince MN. Digesting gluten with oral endopeptidases to improve the management of celiac disease. *World J Gastroenterol* 2024; In press

Core Tip: Gluten exposure can continue despite a strict gluten-free diet in patients with celiac disease. Adjunct therapeutic interventions such as gluten-digesting endopeptidases can decrease gluten exposure and have potential to improve patients’ quality of life.

INTRODUCTION

Celiac disease is an immune-mediated enteropathy that manifests upon exposure to dietary gluten, which is a common name for dietary proteins- gliadins and glutenins in wheat, hordeins in barley, and secalins in rye^[1]. High proline and glutamine content makes gluten difficult to digest by enzymes of the gastrointestinal tract. If gluten is not digested by intestinal endopeptidases and rather transported into lamina propria, where antigen presenting cells break gluten into smaller peptides, T cell-stimulating antigens are generated as products of gluten metabolism in genetically susceptible individuals that carry human leukocyte antigen (HLA) haplotypes DQ2 and DQ8 (Figure 1). Gluten-derived peptide antigens bound to HLA-DQ2 and DQ8 trigger an inflammatory T cell response and cause celiac disease. Resulting inflammation in the small bowel is characterized by an increase in intraepithelial lymphocytes, crypt cell hyperplasia, and villous blunting, as observed on biopsy^[2].

Celiac disease classically causes symptoms of diarrhea, weight loss, and in children growth failure due to malabsorption, which is also associated frequently with vitamin and mineral deficiencies and extraintestinal manifestations, such as iron deficiency anemia or metabolic bone disease^[3]. Furthermore, celiac disease predisposes individuals to infertility, dermatitis herpetiformis, T cell lymphoma, and small bowel adenocarcinoma^[4,5].

DIFFICULTIES OF AVOIDING GLUTEN

Treatment of celiac disease is in theory simple and involves the avoidance of dietary gluten. Yet practical application of such a measure can be challenging. Requesting strict, lifelong adherence to a gluten-free diet is a provocative directive by healthcare professionals. It has previously been shown that adherence to a gluten-free diet varies between 42%-91% among adults with celiac disease, as such a diet is restrictive, costly, and complicated^[6]. Despite earnest attempts to remove all dietary gluten, patients may unintentionally ingest gluten from food contamination. Recent evidence indicates that patients on a gluten-free diet are often exposed to gluten, which can be due to cross contamination or unintended exposure^[7]. For example rice, which naturally does not

contain gluten, may be contaminated from storage in a silo that had stored wheat or barley in the past. A study from Collin *et al*^[8] in 2004 showed that flour products labeled as “gluten-free” were still found to contain up to 200 ppm gluten. Additionally, improper food handling in restaurants may lead to gluten contamination if utensils are not cleaned or fry oil is not separated^[9]. Such an exposure may interfere with healing of the duodenal villous atrophy and cause persistent symptoms.

Most patients with celiac disease will experience symptom improvement within 4 weeks of following a gluten-free diet. Celiac serologies will notably improve after 6 months, and small bowel histology may take one year to normalize following treatment^[3]. Patients who fail to respond to a gluten-free diet should first be assessed for dietary compliance, and then a diagnostic workup for concurrent disorders be performed, including tests to identify monoclonal lymphocyte proliferation or malignancies. Approximately 10% of non-responders will meet criteria for refractory celiac disease, defined as persistent symptoms and villous atrophy after at least one year on a strict gluten-free diet^[10]. Treatment of refractory celiac disease involves immunosuppression, most commonly steroids, though use of immunomodulators and chemotherapy have also been reported.

ENDOPEPTIDASES AS ADJUNCTS TO GLUTEN-FREE DIET

As evidence suggests that poor response to gluten-free diet or poor dietary compliance predispose to persistent villous atrophy, and as persistent villous atrophy is an independent risk factor for complications including malignancy or mortality^[5], additional strategies besides gluten-free diet are needed for improved management of celiac disease. Novel therapeutic strategies should help to reduce gluten exposure and improve symptoms or decrease the use of immune suppressive medications with severe side effects (*e.g.*, steroids or immune modulators)^[11] in refractory cases. To this end, pharmacologic agents are under development that increase the digestion of gluten within the stomach or proximal small bowel^[12,13]. These include enzymes that digest gluten such as prolyl endopeptidases, cysteine proteases, or subtilisins^[14]. Further

digestion of gluten can mitigate its antigenicity before exposure to small bowel mucosa, and therefore digested gluten would not be expected to trigger an inflammatory response. Another strategic approach is development of medications which reduce gut leakiness, as increase in intestinal permeability has been shown to potentially contribute to symptoms and inflammation in celiac disease^[15].

In this issue of the Journal, Stefanolo *et al*^[16] suggest a novel treatment approach using *Aspergillus niger* prolyl endopeptidase (AN-PEP) to cleave proline-rich areas of gluten. The hypothesis of the authors is based on previous observations that AN-PEP can cleave the gluten, making it less immunogenic to trigger a T cell response and thereby improve inflammation. In this prospective trial, patients completed a 4-week run-in period and then were randomized to receive either AN-PEP capsules with meals or placebo as adjunct therapy to strict gluten-free diet. Treatment groups were blinded and response to therapy was measured by a subjective symptom index and by measuring inflammatory markers. Celiac symptom index (CSI) was used for disease-specific monitoring and quantitation of symptoms. Gluten immunogenic peptide (GIP) concentration in stool was measured as an inflammatory marker, besides measuring the serum concentration of immunoglobulin A (IgA) antibodies against tissue transglutaminase and deamidated gliadin. Although the overall analysis that includes follow-up of 37 patients (treatment group *vs* control group) did not result in striking objective improvement of symptoms or inflammatory markers, there were several findings worth mention.

First, in an attempt to make a causative link between reducing exposure to gluten, decreasing the inflammation, and improving symptoms in a clinical study, the most interesting observation of the study was that five out of six patients in the treatment group with GIP concentration in stool greater than 0.08 mg/g showed more than 50% reduction in GIP concentration, whereas such a reduction was only evident in one out of four patients in the control group. There was also a significant decrease in number of patients with a high CSI score (> 38) following treatment. There appeared to be a trend towards improvement in absolute CSI scores and GIP stool concentrations, albeit it

lacked significance likely due to the small study size and a short follow-up. As any meaningful improvement of serologic markers takes much longer to happen in patients, a prospective study in a larger cohort with longer follow-up would be worthwhile to better characterize the role of AN-PEP endopeptidase in management of celiac disease and its impact on inflammation as well as inflammatory markers. Second, there were no adverse events, suggesting good safety profile of this medication. Third, in this cohort there was remarkable adherence to the treatment with only three of 40 patients (0.75%) failing to take at least 70% of the capsules despite the high pill burden of 6 capsules daily. As adherence is likely to be significantly lower in real world experience with AN-PEP endopeptidase, future research should also take into account *in vivo* stabilization of AN-PEP pharmacokinetically, which can permit once or twice daily dosing and improve compliance.

The patient population of the current study consisted of individuals who reported strictly following a gluten-free diet, and yet they experienced persistent symptoms with average CSI score of 36 at time of randomization. This highlights two things: First, gastrointestinal symptoms can occur due to other reasons in patients with celiac disease and these include irritable bowel syndrome, constipation, lactose or fructose intolerance, or small bowel bacterial overgrowth^[3], which clinicians need to address in patient management. Second, the findings underscore the need for alternative therapeutic interventions besides the gluten-free diet for patients with celiac disease, as dietary changes alone may be insufficient.

AN-PEP was identified as an agent that can digest gluten in the gut before it is taken up by antigen presenting cells in the small intestine to initiate an inflammatory response. Previous clinical studies indicated its safety and effective degradation of gluten in gut lumen^[17,18]. With this current study advancing our knowledge on the potential of AN-PEP to improve symptoms of celiac disease, a search for other enzymes which can degrade gluten and improve symptoms is also under investigation. To this end, it is worth noting that prolyl endopeptidases were isolated from bacterial strains such as *Flavobacterium meningosepticum*, *Sphingomonas capsulata*, and *Myxococcus*

xanthus^[19]. Although these strains are not classically reported among bacterial strains constituting human gut microbiome, oral microbiome has been proposed to include microorganisms that can digest gluten^[20] and fecal microbiota transplantation has been shown to improve symptoms of celiac disease long term in a patient with type II celiac disease resistant to gluten-free diet, who was administered fecal microbiota transplantation to treat *Clostridium difficile* infection^[21]. Whether elements of oral or gut microbiome contains enzymes that can reduce the antigenicity of gluten remains to be established.

CONCLUSION

Patients with celiac disease need long-term follow up to ensure response to gluten-free diet and to monitor for complications. Guidelines from multiple societies agree that follow up should include a dietary interview, anti-tissue transglutaminase titers, and laboratory tests to assess for malabsorption and associated complications^[22]. Positive serology twelve months following initiation of gluten-free diet strongly suggests gluten contamination, and these patients may be ideal candidates for adjunct therapies like gluten-degrading enzymes. Normalization of serology, however, does not necessarily indicate recovery of villous atrophy. Although high titers of IgA antibodies against tissue transglutaminase can successfully predict villous atrophy at diagnosis^[23], symptom control on a gluten-free diet with normalization of anti-tissue transglutaminase titers can fall short in predicting the restoration of villous structure in a significant proportion of patients^[24]. The future development of methods to noninvasively assess for villous atrophy, such as serum and stool markers^[25,26], are pivotal to confirm mucosal healing and demonstrate treatment efficacy. Future research on therapeutic strategies will additionally benefit from the development of animal models that better reflect clinical or pathogenetic features of human celiac disease^[27] and standardized approaches in design and execution of clinical trials^[28].

Taken together, clinical evidence provided by Stefanolo *et al*^[16] in this issue of the Journal attests to a potentially important role of gluten digestion within the intestinal

lumen before transepithelial transport for the treatment of celiac disease. Adherence to gluten-free diet is challenging and even trace amounts of gluten contamination can result in villous atrophy, predisposing patients to an increased risk of complications including malignancies or osteoporotic hip fractures^[4,5,29]. Gluten degrading enzymes may serve as an additional layer of protection against gluten exposure and hold a promising role as an adjunct therapy to a gluten-free diet.

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