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Aspergillus niger prolyl endopeptidase in celiac disease

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Abstract

We comment here on the article by Stefanolo et al entitled “Effect of Aspergillus niger prolyl endopeptidase in patients with celiac disease on a long-term gluten-free diet”, published in the World Journal of Gastroenterology. Celiac disease is a well-recognized systemic autoimmune disorder. In genetically susceptible people, the most evident damage is located in the small intestine, and is caused and worsened by the ingestion of gluten. For that reason, celiac patients adopt a gluten-free diet (GFD), but it has some limitations, and it does not prevent re-exposure to gluten. Research aims to develop adjuvant therapies, and one of the most studied alternatives is supplementation with Aspergillus niger prolyl endopeptidase (AN-PEP), which is able to degrade gluten in the stomach, reducing its concentration in the small intestine. The study found a high adherence to the GFD, but did not address AN-PEP as a gluten immunogenic peptide reducer, as it was only tested in patients following a GFD and not in gluten-exposing conditions. This study opens up new research perspectives in this area and shows that further study is needed to clarify the points that are still in doubt.

Key Words: Celiac disease; Aspergillus niger prolyl endopeptidase; Gluten immunogenic peptides; Trial; Symptoms; Real-life trial

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Core Tip: Involuntary or voluntary exposure to gluten can lead to severe and persistent symptoms in celiac patients on long-term gluten-free diets. Aspergillus niger prolyl endopeptidase metabolizes gluten before it reaches the small intestine, reducing the celiac disease-specific symptoms. That was demonstrated by the decrease in the concentration of gluten immunogenic peptide.
INTRODUCTION

Celiac disease (CeD) is a systemic autoimmune disorder that occurs in patients with a genetic susceptibility. The introduction of gluten into the diet of one of these individuals results in the activation of specific T-cells that recognize the specific epitopes, characterizing the disease. This response can damage the gastrointestinal tissues and cause the characteristic symptoms. Most of the damage occurs in the small intestine. and it is caused by involuntary or voluntary exposure to gluten. A gluten-free diet (GFD) is recommended in these patients, even if it is a difficult, time-consuming and expensive process, but it represents the only way to avoid the appearance of symptoms. Indeed, after exposure to gluten, these patients can experience enteropathy and persistent symptoms due to intestinal mucosal damage. For this reason, there is a need for novel therapies that can be which can be integrated into a GFD. Mammalian enzymes cannot degrade gluten because of its proline and glutamine-rich sequences. The result is the exposure of the intestinal mucosa is exposed to gluten immunogenic peptides (GIPs), which is necessary in CeD to reactivate gluten T-cells and the disease.

Several probiotics and microbial proteases have been studied for the purpose of degrading more gluten, but the most efficient at this time is Aspergillus niger prolly endopeptidase (AN-PEP).[1-3] Easier optimal conditions with Aspergillus niger prolly endopeptidase efficiently cleaves proteins. AN-PEP is active at a low pH, is resistant to pepsin, and is active in the stomach, reducing the GIP before reaching the small intestine. This oligopeptidase digests gluten into nontoxic fragments, and its use in production of gluten-free food has been proposed recently.[4]. For example, in late 2018, Vega K proposed the GRAS claim for a recombinant strain of Aspergillus niger that has shown a high efficacy for the production of gluten-reduced foods, and currently is also used in beer production (https://www.fda.gov/media/134876/download).

A study by Stefanolo et al[4] examined the effects of AN-PEP in celiac patients following a GFD and the prevention of CeD symptoms during involuntary exposure to gluten. This was an exploratory, placebo-controlled trial. The first phase was a 4-wk run-in period followed by a 4-wk period during which patients were randomized to test (two AN-PEP capsules per meal) and control (placebo) arms. To check the effects of the trial, the authors assayed the stool GIP, CeD-specific serology, and assessed the celiac symptom index (CSI) and quality of life (QoL) using the SF-36 questionnaire. Thirty-seven patients were randomized and 628/640 stool samples were collected. Results show that GIP in 65.6% of total samples (GIP < 0.08 μg/g), was > 0.32 μg/g in 0.5%, which potentially causes mucosal damage, and lower than the run-in period in 44.7%. This was a pilot, double-blind, prospective, randomized, placebo-controlled study. The aim was to explore whether the oral administration of AN-PEP can be used to prevent the effects of exposure to gluten in CeD patients. However the small number of participants (only 37 patients participated in the study) make it inconclusive. The results require confirmation by large cohort studies.

UTILITY OF AN-PEP

Adult patients with CeD on a long-term GFD (more than 2 years) were enrolled between October 2020 and July 2022. The criteria for enrolling patients were: Histological and serological diagnosis of CeD, GFD for more than 2 years, at least one bowel movement per day, ability to provide serum samples, collection of stool samples every Tuesday and Friday, and the ability to answer questionnaires. The exclusion criteria were: Metabolic disorders, refractory CeD, use of drugs that degrade gluten because of its proline and glutamine-rich sequences. The result is the exposure of the intestinal mucosa is exposed to gluten immunogenic peptides (GIPs), which is necessary in CeD to reactivate gluten T-cells and the disease.

Every patient had to collect stool samples every Tuesday and Friday (both in the run-in and the second phase) for subsequent processing with an ELISA kit (IVVLISA GIP-Stool; Biomedical S.L, Sevilla, Spain) to quantify the presence of GIP. A total of 640 stool samples were expected but only 628 arrived and were processed in the laboratory following current protocols.[5-7] The results show that 65.6% of all samples (both run-in and treatment period) had undetectable GIP (< 0.08 μg/g), indicating the effectiveness of GFD, and none of these patients had a GIP > 0.64 μg/g. In the AN-PEP arm, GIP. Decreased in more than 50% of the samples, indicating the effectiveness of AN-PEP. The statistical analysis included comparison of the two arms with the Mann-Whitney or Wilcoxon test (comparison between the beginning and the end of treatment), proportion (χ² test), and comparison of the proportion (McNemar test). The analysis found no statistically significant differences between the results that were compared. However, this study examined only lack of gluten as the experimental condition and did not investigate the condition of exposure to gluten.

Serum samples were assayed for IgA tissue transglutaminase antibodies (tTG IgA ELISA kit, QUANTA LiteTM, h-tTG IgA; Inova Diagnostic Inc., San Diego, CA, United States), and IgA antibodies reacting with deaminated gliadin-derived

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peptides (IgA DGP ELISA kit, QUANTA LiteTM DGP IgA, Inova Diagnostic Inc.). The assay results showed no statistically significant differences between the placebo arm and the AN-PEP arm.

In addition, questionnaires were distributed to the patients before randomization and at the end of the trial. The CSI consisted of 36 items about specific and general symptoms affecting CeD patients, and the SF-36 QoL questionnaire consisted of eight subsections about physical functioning, general health, and mental health. In the CSI, the answer to each question ranges from 1 to 5, where 1 means no symptoms and 5 means symptoms with the highest intensity. A lower score was seen in the AN-PEP arm compared with the placebo, but the difference was not statistically significant. The SF-36 score ranges from 0 to 100, where 0 means poorest health and 100 optimal health status. At the end of the study, the general health score was better in the placebo arm and the vitality and the abdominal pain scores were higher in the AN-PEP arm.

According to current literature, AN-PEP seems to have a positive impact on CeD symptoms because it is able to degrade gluten before it reaches the small intestine, so the mucosa is exposed to a lower gluten load[8,9]. However, the results are not concordant and no consensus exists until now about this issue[10,11].

CONCLUSION

The study did not explore the efficiency of AN-PEP during an exposure to gluten. For this reason, more research is needed to better understand its full potential. In this pilot study, AN-PEP treatment did not significantly decrease the GIP stool concentration. Although this is a pilot study, the results support further investigation of other adjuvant therapies with GFD.

FOOTNOTES

Author contributions: Palmiotrrotta R, Colella M and Cafiero C contributed to this paper; Palmiotrrotta R designed the overall concept and outline of the manuscript; Palmiotrrotta R and Colella M contributed to the discussion and design of the manuscript; Palmiotrrotta R, Colella M and Cafiero C contributed to the writing, editing the manuscript and review of the literature; All authors have read and approved the final manuscript.

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