

# Is Enzyme Supplementation Effective Strategy to Reduce the Burden of Gluten Free Diet in Celiac Disease?

Aaron Lerner\*

B. Rappaport School of Medicine, Technion-Israel Institute of Technology, Haifa, Israel

\*Corresponding author: [aaronlerner1948@gmail.com](mailto:aaronlerner1948@gmail.com)

**Abstract** Several strategies have been considered for enzymatic detoxification of dietary gluten and to reduce immunogenicity of gliadin peptides. An enzymatic therapy using enterically coated tablets containing caricain (Gluteguard), originated from a papaya, on celiac disease patients challenged with gluten was reported. Glut guard was able to protect these patients from adverse symptoms being induced by gluten challenge. The advantages of the fruit originated preparation are: it does not contain living microbes or bacterial purified or engineered products. It can be considered as a preventive therapy and further step in the future therapeutical strategy race for the celiac affected population benefits.

**Keywords:** celiac disease, enzyme, supplementation, gluten, gluten free diet, microbial transglutaminase, therapy

**Cite This Article:** Aaron Lerner, "Is Enzyme Supplementation Effective Strategy to Reduce the Burden of Gluten Free Diet in Celiac Disease?" *International Journal of Celiac Disease*, vol. 4, no. 2 (2016): 38-39. doi: 10.12691/ijcd-4-2-7.

## 1. Introduction

Certain immunogenic gluten domains are resistant to degradation by mammalian digestive enzymes. Enzymes with the ability to target such domains are potentially of clinical use. In the present issue, Cornell JH and al. [1] have studied the effects of an enzymatic therapy using enterically coated tablets containing caricain, originating from a papaya, on celiac patients challenged with gluten. The oral anti gluten enzyme therapy using Gluteguard was able to protect celiac patients from adverse symptoms being induced by gluten challenge. No exacerbation of the mucosal damage was noticed when gluten and the enzyme supplement were co-ingested. As stressed in the conclusions, preventive enzyme therapy will likely add to the quality of life and well-being of celiacs, especially those who have difficulties in gluten free diet (GFD) adherence.

## 2. Anti-gluten Enzymatic Therapy

Before widening the aspects of enzyme replacement or supplemental therapy in celiac disease (CD), several comments are worthwhile mentioning concerning the study:

(1). One wonder if the inclusion criteria would have been more stringent, the result would have changed or improved. It is possible that by a longer duration of GFD prior the study, a lesser serological activity and a lower intestinal damage, on entry, ingesting the caricain several times a day to imitate gluten consumption along the day and omitting patients with other autoimmune disease, would have improved the outcomes in the treated patients.

(2). There are several possibilities to explain the lack of improvement or deterioration of the intestinal histology in

the treated/control groups, respectively: 1. The intestinal damage on entry, on GFD was quite substantial. 2. The dosage of the caricain was not effective enough. 3. The study duration was too short. 4. It takes longer for GFD to normalize or attenuate the intestinal injury.

(3). No enough information is delivered in the material section concerning Gluteguard. At least, according to the web "the compositions including at least partially purified caricain (or a biologically active fragment, analogue or variant thereof) alone or in combination with other suitable enzymes including bromelain, and/or an intestinal extract" [2].

(4). Since the last author is the founder and chief executive officer of the Gluten Pty Ltd, a disclosure of conflict of interest will be appropriate.

There is no doubt that degrading the gliadin or its toxic/immunogenic peptides is one of the most effective preventing strategies to help the celiac population to cope with GFD [3,4,5]. Serine-containing cytotoxic peptides as found in residues 11-19 of A-gliadin and Tyrosine-containing immunogenic peptides, found in residues 75-86 of A-gliadin are appropriate targets for future therapies. Of particular interest are gluten-degrading enzymes that would be naturally present in the human body, e.g. associated with resident microbial species. Resident and harmless bacteria and/or their derived enzymes could potentially find novel applications in the treatment of CD, in the form of a probiotic agent or as a dietary enzyme supplement. In this regard, several enzymatic preparations might be considered to interrupt the pathogenic cascade induced by gluten [6,7]:

(1). Sourdough bread made from wheat and nontoxic flours and started with selected lactobacilli was tolerated in CD patients [8].

(2). A recombinant protease prolyl endopeptidase derived from the bacterium *Sphingomonas capsulate*.

(3). A recombinant protease cysteine endopeptidase B-isoform 2, derived from barley. Both preparations were combined under the name ALV003.

(4). Germinating enzymes from barley were particularly efficient in the degradation of rye secalin [9].

(5). A prolyl endopeptidases derived from *Aspergillus niger*, called AN-PEP.

(6). Cocktail of enzymes, called STAN1, containing aspergillopepsin from *Aspergillus niger* and dipeptidyl peptidase IV from *Aspergillus oryzae* was also investigated.

(7). Microbial transglutaminase (mTG) was suggested to detoxify gluten by its ability to post translation modify gluten peptide by its deamidating/cross linking capacities [10].

(8). Most recently, four enzyme activity assays, including a gliadin zymogram assay, designed for the selection and discovery of novel gluten-degrading microorganisms from human biological samples were described [11]. Gluten-degrading resident bacteria hold great promise to be developed as probiotics or enzymatic dietary supplements, not only for CD but also for the treatment of non-celiac gluten sensitivity.

In view of the fact that: 1. mTg was most recently suggested as a potential inducer of CD and its gliadin docked complexes were found to be immunogenic in CD [10,12,13,14], 2. all the bacteria residing in the intestinal ecosystem secrete mTg [15], 3. the food processed industries heavily use the enzyme as a protein glue, to improve food qualities [12,13] and 4. Tgase activity is found in the processed food products on the supermarket shelves, one wonders if swallowing whole bacteria for gluten degrading enzyme will introduce additional mTg to the gut lumen. In this respect, it is conceivable that pure enzymes or non-bacteria originated enzymes are more logical to us. The present study uses a fruit originated enzyme, that most probably doesn't contain mTg, but this assumption should be checked since plant mTg is a member of the Tgase family.

### 3. Conclusion

Several strategies have been considered for detoxification of dietary gluten and reduce immunogenicity of gliadin peptides. These approaches are mainly at the preclinical stage with some of them in early and advanced clinical trials. The enzymatic strategy seems logical since it treats the offending gluten before being absorbed and before stimulating the immune system to induce any intestinal

damage. It can be considered as a preventive therapy and not a therapeutically curative one. Time will show which future therapeutical strategy will win the race for the CD population benefits.

### References

- [1] Cornell HJ, Czyzewska A, Macrae FA, Rydzewska G, Nasierowska-Gutmejer A, Bednarczuk A, Stelmasiak T. The Effect of Enzyme Supplementation on Symptoms and Duodenal Histology in Celiac Patients. *International Journal of Celiac Disease* 2016;4(2):40-47.
- [2] [www.patents.justia.com/assignee/glutagen-pty-ltd](http://www.patents.justia.com/assignee/glutagen-pty-ltd).
- [3] Lerner A. New Therapeutic Strategies for Celiac Disease. *Autoimmun Rev* 2010;9:144-147.
- [4] Lerner A. [Potential therapeutic strategies in celiac disease]. *Harefuah* 2012;151:358-361.
- [5] Lerner A. Novel therapeutic strategies for celiac disease. *AgroFood industry hi-tech. European Journal of Nutraceuticals & Functional Foods*. 2013;24:16-20.
- [6] Vanga RR, Kelly CP. Novel therapeutic approaches for celiac disease. *Discov Med*. 2014;17:285-293.
- [7] Rashtak S, Murray JA. Review Article: Celiac Disease, New Approaches to Therapy. *Aliment Pharmacol Ther*. 2012; 35: 768-781.
- [8] Di Cagno R, De Angelis M, Auricchio S, et al. Sourdough bread made from wheat and nontoxic flours and started with selected lactobacilli is tolerated in celiac sprue patients. *Appl Environ Microbiol* 2004;70:1088-1096.
- [9] Stenman SM, Lindfors K, Venäläinen JI, Hautala A, Männistö PT, Garcia-Horsman JA, Kaukovirta-Norja A, Auriola S, Mauriala T, Mäki M, Kaukinen K. Degradation of coeliac disease-inducing rye secalin by germinating cereal enzymes: diminishing toxic effects in intestinal epithelial cells. *Clin Exp Immunol*. 2010;161:242-249.
- [10] Lerner A, Matthias T. Food Industrial Microbial Transglutaminase in Celiac Disease: Treat or Trick. *International Journal of Celiac Disease* 2015;3(1):1-6.
- [11] Helmerhorst EJ, Wei G. Experimental Strategy to Discover Microbes with Gluten-degrading Enzyme Activities. *Proc SPIE Int Soc Opt Eng*. 2014 May 5; 9112.
- [12] Lerner A, Matthias T. Changes in intestinal tight junction permeability associated with industrial food additives explain the rising incidence of autoimmune disease. *Autoimmun Rev* 2015;14:479-89.
- [13] Lerner A, Matthias T. Possible association between celiac disease and bacterial transglutaminase in food processing: a hypothesis. *Nutr Rev* 2015;73:544-552.
- [14] Lerner A, Matthias T. Microbial transglutaminase is a potential environmental inducer of celiac disease. In: *From Autoantibody Research to Standardized Diagnostic Assays in the Management of Human Diseases*. Volume 10th, Eds: K Conrad, Chan EKL, Andrade LEC, Steiner G, Pruijn GJM, Y Shoenfeld. 12th symposium on autoantibodies, 23-26.9.15, Dresden, Germany. Page 227-233, Pabst Science Publishers, Lengerich, Germany, e-pub.
- [15] Lerner A, Aminov R, Matthias T. Dysbiosis may trigger autoimmune diseases via inappropriate posttranslational modification of host proteins. *Front Microbiol*. 2016;7:84.