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Probiotics for Celiac Disease: A Work in Progress

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Probiotics for Celiac Disease: A Work in Progress

Celiac Disease (CD) or gluten sensitive enteropathy is an autoimmune disorder characterised by variable presentations which respond to exclusion of wheat and other gluten containing products [1]. While exclusion of gluten is the corner stone in the management of this entity, newer therapeutic approaches are now being investigated. These include use of elemental diets, oral prolyl-endopeptidases, IL-15 blockage, transamidation of wheat and use of probiotics [2]. With newer therapeutic approaches it might be possible in future for patients with CD to continue to take gluten while remaining symptom free.

Changes in Gut Microbiota in CD

The microbial composition of the gut of patients with active CD is different from healthy controls. In a report assessing the duodenal microbiota in CD it was noted that the ratio of Lactobacillus–Bifidobacterium to Bacteroides–Escherichia coli was lower in children with active CD vis-à-vis healthy controls [3]. Similar findings in multiple other reports allude to a disordered gut microbiota and dysbiosis in presence of active CD [4,5]. A report suggests that the microbial diversity may be more in untreated CD but this may be related to presence of pathological organisms like Bacteroides and Escherichia coli [6]. The dysbiosis may increase the expression of certain toll like receptors resulting in an increased expression of certain cytokine like IL-10, Interferon-gamma and CXCR6 [7]. In one interesting study on infants who were all vaginally delivered and breastfed, those with presence of HLA-DQ2 genotype (higher risk of CD) had a gut microbiota composition different from low-genetic risk infants. The HLA-DQ2 positive infants had a lower Actinobacteria and higher proportion of Proteobacteria and Firmicutes [8]. This suggests that the gut microbiota may be dependent on HLA association and may be altered in individuals genetically predisposed to CD. However, some studies have not found a difference between the microbiota of those with CD when compared with controls and therefore tend to negate the role of changes in microbiota in causation of celiac disease or its symptoms [9].

Even in patients who are on gluten free diet the microbial composition of the intestinal microbiota may not become similar to non-CD controls. In a report assessing the concentration of fecal Bifidobacterium concentration in CD patients off gluten for two years or more, the fecal concentrations were noted to be lower in CD patients even when they were off gluten [10]. Infact Nistal E et al studied duodenal microbiota using 16S rRNA in children and adults with treated and untreated CD and found that the composition of duodenal microbiota changes with age and that treated adults had reduced bacterial diversity [11]. The predominant phyla is Firmicutes in children and Proteobacteria in adults with CD [12]. There is a recognition of increase in Gram negative organisms in untreated CD while the number of Gram positive microbes decreases. It is however not clear if this is the cause or a consequence of the disease [3]. One report seems to suggest that the microbiotal composition and diversity may influence the clinical manifestations in CD patients [13].

A metabolomic approach to evaluation of changes in microbiota after gluten free diet also suggested similar phenomenon i.e. the restoration of microbiota was not complete and that certain molecules could be used as metabolic signatures of CD [14]. Incidentally the oral microbiota of treated CD patients is also disparate from the microbiota of healthy controls [15]. Therefore the bulk of evidence points to an alteration in the microbiota in patients with CD. It is not clear if this modified microbiota is driven by the disease or drives the symptomatology of the disease.

Probiotic Effects in CD

Probiotic use is common in patients with celiac disease [16]. Probiotics are live microorganisms supplied from outside the human body in dosages which are believed to exert a beneficial effect on health [17]. There is a suggestion that use of gluten-digesting microbes can be helpful in treatment of CD. Gluten is rich in proline residues and resistant to proteolysis in human gut. VSL#3, a probiotic with eight different bacterial strains, has been noted to have gluten degrading properties [18]. The idea was to use this probiotic during food processing to produce tolerable gliadins. It is not clear if in vivo use of this probiotic will also be of any benefit in CD. Use of Sourdough baked products, which utilise long fermentation by natural lactobacilli and fungal proteases, may help in reducing risk of gluten contamination in gluten free products by virtue of their proteolytic action on gluten [19]. Indeed a clinical pilot study in children noted the usage of fermented wheat flour product in known patients with celiac disease did not precipitate clinical, haematological or serological features of CD [20]. Similarly another study in CD patients noted that no changes of CD occurred with use of fully hydrolysed wheat flour products [21].

In a Caco-2 cell model, use of Lactobacillus paracasei (LP) CBA L74 and its supernatant seemed to prevent the entry of gliadin peptides into the cells [22]. In a placebo controlled randomised trial of use of Bifidobacterium longum CECT 7347 with gluten free diet versus gluten free diet alone in children with newly diagnosed CD, the group receiving the probiotic strain was noted to have greater percentile increases in height, and a reduction in TNF-alpha levels and circulating CD3+ lymphocytes [23]. This strain was also found effective in reducing the production of inflammatory cytokines in a rat model of gluten induced enteropathy [24]. The increase in paracellular

permeability which characterises CD may be reversed to some extent by use of probiotics. Coadministration of Lactobacillus rhamnosus GG with gliadin in an in vitro model demonstrated the protective effects of this strain in preventing the gliadin induced barrier dysfunction [25]. In a provocative trial in patients with CD in whom gluten was continued even after diagnosis of CD the patients were randomised to receive either a probiotic Bifidobacterium infantis Natren Life Start (NLS) or placebo. The group of patients receiving probiotic had some improvement in gastrointestinal symptoms but no improvement in intestinal permeability. There was a reduction in serum IgA-tissue-transglutaminase titres in the placebo arm but the clinical implication is not clear [26]. The results indicate that the benefits on intestinal permeability were not realised in vivo or may be strain dependent. Interstingly in vitro reports had indicated some benefit in reduction of gliadin induced increases in intestinal permeability with use of Bifidobacterium [27,28]. Another possible approach could be use of microorganisms with prolyl endopeptidases which may digest gluten and make gluten containing products gluten free for the small bowel [29].

To summarise, use of probiotics in celiac disease remains investigational as of now but may provide a therapeutic approach for management of CD in future, The possible targets of use of probiotics include the opportunity to degrade ingested gluten and maintain barrier function of intestine in wake of exposure to gluten (Table 1).

Pre-ingestion fermentation/degradation of gluten	VSL#3 Prolonged ferementation by lactobacilli and fungal proteases
Gluten digestion after ingestion	Prolyl-endopeptidase containing probiotics
Maintenance of gut barrier	Possible role for Bifidobacterium and Lactobacilli

Table 1: Possible mechanisms of benefit of probiotics in celiac disease

References

1. Kochhar R, Sachdev S, Kochhar R, Aggarwal A, Sharma V, et al. (2012) Prevalence of coeliac disease in healthy blood donors: a study from north India. Dig Liver Dis 44: 530-532.
2. Freeman HJ, Chopra A, Clandinin MT, Thomson AB (2011) Recent advances in celiac disease. World J Gastroenterol 17: 2259-2272.
3. Nadal I, Donat E, Ribes-Koninckx C, Calabuig M, Sanz Y (2007) Imbalance in the composition of the duodenal microbiota of children with coeliac disease. J Med Microbiol 56: 1669-1674.
4. Di Cagno Rizzello R, Gagliardi CG, Ricciuti F, Ndagijimana P, et al. (2009) Different fecal microbiotas and volatile organic compounds in treated and untreated children with celiac disease. Appl Environ Microbiol 75:3963-3971.
5. Sánchez E, Donat E, Ribes-Koninckx C, Fernández-Murga ML, Sanz Y (2013) Duodenal-mucosal bacteria associated with celiac disease in children. Appl Environ Microbiol 79: 5472-5479.
6. Schippa S, Iebba V, Barbato M, Di Nardo G, Totino V, et al. (2010) A distinctive 'microbial signature' in celiac pediatric patients. BMC Microbiol 10: 175.
7. Cheng J, Kalliomäki M, Heilig HG, Palva A, Lähteenoja H, et al. (2013) Duodenal microbiota composition and mucosal homeostasis in pediatric celiac disease. BMC Gastroenterol 13: 113.
8. Olivares M, Neef A, Castillejo G, Palma GD, Varea V, et al. (2014) The HLA-DQ2 genotype selects for early intestinal microbiota composition in infants at high risk of developing coeliac disease. Gut .
9. de Meij TG, Budding AE, Grasman ME, Kneepkens CM, Savelkoul PH, et al. (2013) Composition and diversity of the duodenal mucosa-associated microbiome in children with untreated coeliac disease. Scand J Gastroenterol 48: 530-536.
10. Golfetto L, de Senna FD, Hermes J, Beserra BT, França Fda S, et al. (2014) Lower bifidobacteria counts in adult patients with celiac disease on a gluten-free diet. Arq Gastroenterol 51: 139-143.
11. Nistal E, Caminero A, Herrán AR, Arias L, Vivas S, et al. (2012) Differences of small intestinal bacteria populations in adults and children with/without celiac disease: effect of age, gluten diet, and disease. Inflamm Bowel Dis 18: 649-656.
12. de Sousa Moraes LF, Grzeskowiak LM, de Sales Teixeira TF, Gouveia Peluzio Mdo C (2014) Intestinal microbiota and probiotics in celiac disease. Clin Microbiol Rev 27: 482-489.
13. Wacklin P, Kaukinen K, Tuovinen E, Collin P, Lindfors K, et al. (2013) The duodenal microbiota composition of adult celiac disease patients is associated with the clinical manifestation of the disease. Inflamm Bowel Dis 19:934-941.
14. Di Cagno R, De Angelis M, De Pasquale I, Ndagijimana M, Vernocchi P, et al. (2011) Duodenal and faecal microbiota of celiac children: molecular, phenotype and metabolome characterization. BMC Microbiol 11: 219.
15. Francavilla R, Ercolini D, Piccolo M, Vannini L, Siragusa S, et al. (2014) Salivary microbiota and metabolome associated with celiac disease. Appl Environ Microbiol 80: 3416-3425.
16. Nazareth S, Lebwohl B, Tennyson CA, Simpson S, Greenlee H, et al. (2014) Dietary Supplement Use in Patients With Celiac Disease in the United States. J Clin Gastroenterol .
17. Sharma V, Garg S, Aggarwal S (2013) Probiotics and liver disease. Perm J 17: 62-67.
18. De Angelis M, Rizzello CG, Fasano A, Clemente MG, De Simone C, et al. (2006) VSL#3 probiotic preparation has the capacity to hydrolyze gliadin polypeptides responsible for Celiac Sprue. Biochim Biophys Acta 1762: 80-93.
19. Gobbetti M, Giuseppe Rizzello C, Di Cagno R, De Angelis M (2007) Sourdough lactobacilli and celiac disease. Food Microbiol 24: 187-196.
20. Di Cagno R, Barbato M, Di Camillo C, Rizzello CG, De Angelis M, et al. (2010) Gluten-free sourdough wheat baked goods appear safe for young celiac patients: a pilot study. J Pediatr Gastroenterol Nutr 51: 777-783.
21. Greco L, Gobbetti M, Auricchio R, Di Mase R, Landolfo F, et al. (2011) Safety for patients with celiac disease of baked goods made of wheat flour hydrolyzed during food processing. Clin Gastroenterol Hepatol 9:24-29.
22. Sarno M, Lania G, Cuomo M, Nigro F, Passannanti F, et al. (2014) Lactobacillus paracasei CBA L74 interferes with gliadin peptides entrance in Caco-2 cells. Int J Food Sci Nutr .
23. Olivares M, Castillejo G, Varea V, Sanz Y (2014) Double-blind, randomised, placebo-controlled intervention trial to evaluate the effects of Bifidobacterium longum CECT 7347 in children with newly diagnosed coeliac disease. Br J Nutr 112:30-40.
24. Laparra JM, Olivares M, Gallina O, Sanz Y (2012) Bifidobacterium longum CECT 7347 modulates immune responses in a gliadin-induced enteropathy animal model. PLoS One 7: e30744.
25. Orlando A, Linsalata M, Notarnicola M, Tutino V, Russo F (2014) Lactobacillus GG restoration of the gliadin induced epithelial barrier disruption: the role of cellular polyamines. BMC Microbiol 14: 19.
26. Smecuol E, Hwang HJ, Sugai E, Corso L, Chernavsky AC, et al. (2013) Exploratory, randomized, double-blind, placebo-controlled study on the effects of Bifidobacterium infantis natren life start strain super strain in active celiac disease. J Clin Gastroenterol 47: 139-147.

27. Lindfors K, Blomqvist T, Juuti-Uusitalo K, Stenman S, Venäläinen J, et al. (2008) Live probiotic Bifidobacterium lactis bacteria inhibit the toxic effects induced by wheat gliadin in epithelial cell culture. Clin Exp Immunol 152: 552-558.

28. Laparra JM, Sanz Y (2010) Bifidobacteria inhibit the inflammatory response induced by gliadins in intestinal epithelial cells via modifications of toxic peptide generation during digestion. J Cell Biochem 109: 801-807.

29. Bakshi A, Stephen S, Borum ML, Doman DB (2012) Emerging therapeutic options for celiac disease: potential alternatives to a gluten-free diet. Gastroenterol Hepatol (N Y) 8: 582-588.