

Coeliac Disease and Probiotics: Clinicians Need to Provide the Evidence Base for this Unmet Need

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For the last seventy years, a lifelong gluten free diet (GFD) has been the cornerstone of management of coeliac disease (CD) [1]. The principal aim of adherence to the GFD is to reduce small intestinal inflammation, in order to provide symptom relief and promote mucosal healing. This is important, as symptoms associated with CD can negatively impact quality of life [2] and persisting small intestinal inflammation in CD has been associated with an increased risk of hip fractures (158 per 100,000 person-years) [3] and a higher risk of lymphoproliferative malignancy (102 per 100,000 person-years) [4].

While most individuals will display clinical improvement shortly after commencing a GFD, between 7-30% of patients will continue to experience symptoms and/or have persisting intestinal inflammation [5, 6], which is most often due to deliberate or inadvertent ongoing gluten ingestion [7, 8]. Indeed, maintaining complete gluten abstinence is difficult, and adherence may be breached because of the widespread use of gluten as a food additive, high costs of the GFD, palatability and the social restrictions imposed by the GFD [6, 9].

Owing to the difficulties associated with adherence to the GFD, substantial work has focused on developing alternative therapeutic options

in CD [10]. These have included, but are not limited to, gluten degrading enzymes and gluten sequestering polymers, which aim to neutralise, and/or increase the excretion of, immunostimulatory gluten peptides from the gastrointestinal tract [11, 12]; tight junction modulators, which aim to promote intestinal epithelial barrier integrity, in order to reduce the paracellular translocation of gluten peptides towards the immune system that resides within the intestinal tissue [13, 14]; inhibitors of tissue transglutaminase, which impair the enzymatic deamidation of gluten to its more immunostimulatory peptide form [15]; vaccine-based strategies [16] and immunomodulatory agents [17], which seek to promote immunological tolerance towards gluten; and immune cell targeted therapies, which are directed towards dampening critical pro-inflammatory immune responses in CD [10]. However, there is a paucity of high-quality evidence which supports the use of these alternative therapies in CD [10].

The intestinal microbiota is the other major area of interest as a potential therapeutic target in CD. In humans, the length of the intestines is colonised from birth by a microbial community consisting mainly of bacteria, but can also include fungi, viruses and archaea. These commensal microbes within the intestines fulfil important roles in the metabolism of dietary components, and in providing signalling cues that promote the development and maturation of immune cells that reside both within the intestines and at peripheral sites throughout the body [18, 19]. Reciprocally, the intestinal mucosal immune system regulates the colonisation of beneficial commensals within the intestines [20]. Thus, a symbiotic relationship exists between the intestinal mucosal immune system and overlying microbiota, which is now widely regarded as being critical to the maintenance of intestinal (and systemic) health.

An increasing body of evidence suggests that the composition and/or function of the intestinal microbiota is altered in a range of gastrointestinal diseases including irritable bowel syndrome (IBS) [21], colorectal cancer [22], inflammatory bowel disease (IBD) [23] and CD [24, 25], with studies broadly reporting reductions in beneficial bacteria and increases in potentially pathogenic strains. While the precise mechanisms underlying these changes still remain largely unclear, the widely established role that the intestinal microbiota has on maintaining health, and the increasing body of evidence suggesting that it is altered in disease, has generated great interest in whether microbial-based products,

or modulation of the microbiota, might have a beneficial effect on health.

Probiotics are a mixture of live microorganisms that are available over-the-counter, or by prescription, in a variety of forms such as capsules, or food supplements [26]. These products largely comprise 'good' bacteria and claim to promote health benefits towards the host by altering the composition of the resident microbial community and/or regulating downstream signalling pathways that impact the intestinal epithelial barrier and immune system [27, 28]. While guidelines do support their use for certain gastrointestinal diseases such as pouchitis in IBD, IBS, and the prevention of necrotising enterocolitis in pre-term babies and of *Clostridioides difficile* infection [29, 30], the quality of the evidence remains low at present. Despite this, the probiotic industry has grown exponentially over the last decade with estimates that the United States probiotic market will be \$78 billion by 2025 [31]. Previous studies suggest that there is a growing interest not only within the general population, but also in specific patient groups including CD [32].

In this issue of the Journal of Gastrointestinal and Liver Diseases, Joelson et al. [33] extend these findings by evaluating the prevalence and predictors of probiotic use among adults (≥ 18 years old) with self-reported CD. In this interesting paper, the authors analysed data collected from total of 4,909 coeliac patients using a voluntary patient-powered research network questionnaire distributed by the Celiac Disease Foundation (iCureCeliacTM). Information relating to demographic information, symptoms and general health [using the 36-Item Short Form Health Survey (SF-36) and CD quality of life (CD-QOL) scores], adherence to the GFD, and probiotic usage was analysed. Out of 4,909 respondents, 1,160 (23.6%) individuals responded to a question regarding probiotic usage. Of these, 381 (32.8%) respondents reported using probiotics. The authors then compared responses from probiotic users versus non-(probiotic)-users. Interestingly, while mean CD-QOL scores were similar between groups, analysis of SF-36 scores showed that probiotic users reportedly experienced more physical pain (63.7 vs. 69.5, $p=0.006$) and there was a non-significant trend toward reduced physical functioning in probiotic users (84.6 vs. 86.5, $p=0.06$). Furthermore, multivariable logistic regression analysis identified that probiotic users were twice as likely to have been diagnosed with CD over the age of 50 (aOR=2.04, 95%CI: 1.37-3.04), and were almost twice as likely to still be symptomatic despite adherence to a GFD (aOR=1.94, 95%CI: 1.44-2.63).

So, how do these findings inform on the usage of probiotics in adult CD? As the authors point out, the finding that individuals diagnosed with CD over the age of 50 were more likely to use probiotics than those diagnosed at a younger age, could be related to delays in the diagnosis of older individuals, meaning these individuals may have sought alternative therapies such as probiotics for their symptoms [33]. Indeed, previous studies have suggested that the atypical presentations of older individuals, as well as clinician ignorance of undiagnosed CD in older adults, means that a number of older adults may not achieve a correct diagnosis of CD for several years [34, 35]. Alternatively, age differences in health-related

behaviours have been reported, with older individuals more likely to attend health screen checks and seek out information about illness prevention and/or treatments [36]. Therefore, the findings that older individuals with CD were more likely to try probiotics may represent that these are a more health-motivated group of patients.

Perhaps more interesting, was the finding that those who reported persisting symptoms despite adherence to a GFD were more likely to use probiotics. While these data provide no information about the temporal relationship between probiotic usage and self-reported symptoms, it is tempting to speculate that these individuals may have used probiotics as an adjunctive treatment to aide with their persisting symptoms. So, is there any evidence supporting this practice in CD? Mechanistic studies have provided evidence that some probiotic strains may help with the breakdown immunogenic gluten peptides in the gut [37], and in dampening pro-inflammatory responses in murine models of CD [38-41]. However, regarding the latter, the applicability of these findings to human CD is often hampered by limitations of the rodent models themselves [42]. Indeed, clinical studies have demonstrated variable results, with some studies suggests probiotic usage was associated with an improvement in symptoms in coeliac patients [43], while others have not [43]. A recent meta-analysis of seven papers, including 6 randomised controlled trials and 279 participants, found that probiotics improved gastrointestinal symptoms when assessed by the Gastrointestinal Symptoms Rating Scale (mean difference in symptom reduction: -28.7%; 95% CI -43.96 to -13.52; $p=0.0002$) [45]. However, there was no difference in gastrointestinal symptoms after probiotics when different questionnaires were pooled, and the overall certainty of the evidence of the studies in CD ranges from very low to low [45]. Therefore, while data from this and previous studies suggests that probiotics are a common alternative treatment used by patients with CD, it appears that it is unclear whether any health benefits are derived from their use. Importantly, no increase in adverse events have been reported with probiotic use compared with placebo treatments [45]. Therefore, it would seem that the principle of *primum non nocere* is currently not compromised by their continued use presently.

In conclusion, this excellent study by Joelson et al. [33] highlights a major issue in the field of CD – alternative therapies to the GFD are desperately needed. Indeed, 50% of the total cohort of respondents in this study reported a persistence of symptoms despite being on a GFD [33]. The microbiota may have potential as a novel therapeutic target, but there is a scarcity of literature evaluating this field in the context of CD. To this end, high quality mechanistic and clinical studies interrogating the role of the microbiota and microbial products in the pathogenesis and treatment of CD are eagerly awaited.

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