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Letter to the Editor

Understanding the role of probiotics in coeliac disease

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We read with great interest the article by Olivares *et al.*[1] entitled 'Double-blind, randomised, placebo-controlled intervention trial to evaluate the effects of *B. longum* CECT 7347 in children with newly diagnosed coeliac disease'. The authors report that administration of *Bifidobacterium longum* CECT 7347 to newly diagnosed coeliac disease (CD) children who were also treated with a gluten-free diet (GFD) produces minimal changes in the gut microbiota and influences the production of some inflammatory markers. However, *B. longum* CECT 7347 does not improve any clinical or symptomatic parameter in addition to that provided by the GFD. Based on these results, it is concluded that the administration of the probiotic could help improve the health status of newly diagnosed CD patients in conjunction with a GFD. We respectfully disagree that the results of this study, although promising, do not yet warrant the recommendation of any probiotic as adjuvant therapy for the GFD in CD.

There is great public interest in the use of probiotics as a safe alternative to the treatment of chronic inflammatory disorders, including CD. However, probiotics are live bacteria and thus clinical recommendation for the treatment of chronic disease should be based on strong clinical evidence. Since the study by Olivares *et al.*[1] does not demonstrate any additional beneficial symptomatic or clinical effect by the addition of *B. longum* CECT 7347 to the GFD, we believe that the claim that this probiotic 'could help improve health of CD patients' is somewhat overstated. Although previous *in vitro* and basic work by the same group suggested potential beneficial effects, the clinical translation of those results, as shown in this study, is not strong. It is also difficult to clearly confer clinical significance and ascribe a beneficial or causative role to the minimal changes observed in the microbiota in this study.In contrast to the lack of symptomatic improvement with *B. longum* CECT 7347, a previous double-blind, randomised, placebo-controlled clinical trial study performed by our group indicated clinical beneficial effects of *B. infantis* natren life start (NLS) super strain on newly diagnosed CD patients[2]. The differences in clinical efficacy between the two studies may relate to differences in study design, probiotic strains and dosing used. One important difference between the two studies is that, unlike the study by Olivares *et al.*[1], *B. infantis* NLS super strain was administered to CD patients on a gluten-containing diet, therefore eliminating the possibility of gluten exclusion as the major reason for improvement. A dietitian expert in CD ensured patients consumed 12 g gluten/d during the study period. The trial performed by Olivares *et al.*[1] was based on the administration of the probiotic in conjunction with a GFD. However, the symptomatic assessment is not clear, and it is difficult to know how many of these subjects were non-responders to the GFD (with or without *B. longum* supplementation), mildly symptomatic despite the GFD or admitted to dietary transgressions during the study. Co-administration of the probiotic with the GFD, as performed in the study of Olivares *et al.*[1], may impair the capacity to detect a symptomatic or biological improvement related to the probiotic.

In conclusion, evidence for the clinical efficacy of probiotics in the treatment of CD patients is in its infancy. Although emerging data are promising, we would like to raise a cautionary note that the evidence is weak and thus solid clinical recommendations are not warranted at this point. Further basic and well-conducted clinical studies that investigate the use of specific probiotics and their mechanisms of action in larger populations are necessary. For instance, patients naive of treatment and/or on a GFD should be well characterised for residual symptoms and potential gluten contamination, as well as other dietary changes associated with the initiation of a GFD that in itself could induce mild changes in the microbiota, innate parameters and symptoms. Moreover, mechanistic evidence linking with clinical efficacy should be sought. In fact, in a follow-up study of the above-mentioned trial[2], we found that administration of *B. infantis* to newly diagnosed coeliac patients consuming gluten decreased mucosal expression of α-defensin-5 compared with placebo and led to similar values as in patients on a GFD[3], suggesting improvement of symptoms, despite gluten exposure, that were correlated with changes in innate immunity.

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