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REVIEW ARTICLE

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Systematic review and meta-analysis of the action of gut microbiota and nutrology in celiac disease: state of the art

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Abstract

Introduction: Celiac disease (CD) is one of the most common disorders related to diet, with a global prevalence of about 1%. The aggravations caused by CD promote an imbalance in the gut microbiota (GM). However, it is not yet known specifically how the gut microbiota plays a role in the pathogeny of this disease, and whether microbiota dysbiosis would be the cause or consequence of CD. **Objective:** The present study aimed to correlate the main results of the action of the gut microbiota and functional nutrition for the treatment of celiac disease. **Methods:** This study followed the rules of PRISMA. The research was carried out from June 2021 to 2022 and developed at Scopus, PubMed/Medline, Science Direct, Google Scholar, and Ovid. The quality of the evidence was classified according to the GRADE. The Cochrane instrument was adopted to assess the risk of bias of included studies. For data analysis, Minitab 18® statistical program was used. A common descriptive statistical analysis was performed. The One-Way test (ANOVA) was applied, adopting the α level lower than 0.05 with a statistically significant difference for the 95% CI. **Results:** The present study found thirteen (13) important clinical studies, of which 12 were Randomized Controlled Studies (RCTs) and one (1) Cross-Sectional Observational study of the total of 113 studies evaluated, showing a high quality of scientific evidence in the studies addressed, with a level of scientific evidence AI. Also, the analyzed studies showed high homogeneity in the results (high association=>50%) to studies with larger sample sizes (greater precision), presenting 98.65%. The present study showed that certain diets/probiotics can promote the improvement of GM as well as DC, especially in patients on a gluten-free diet (GFD). Therefore, patients who follow a GFD may be prone to nutritional deficiencies. **Conclusion:** According to the results, although some studies have a small sample size, the main randomized clinical studies showed that the modulation of nutrients/probiotics and the gut microbiota improve the inflammatory process of celiac disease, especially in patients with a gluten-free diet.

Keywords: Celiac Disease. Coeliac Disease. Nutrition. Gut Microbiota. Probiotics.

Introduction

Celiac Disease or Coeliac Disease (CD) is one of the most common disorders related to diet, with a global prevalence of about 1% **[1]**. It is defined as a systemic immune-mediated disease1 triggered by the ingestion of dietary proteins present in wheat, barley, and rye, known as gluten **[2,3]**. Individuals affected by this chronic disease develop a hypersensitivity to the gliadin protein in gluten, which is mediated by T- helper cells and autoantibodies such as anti-tissue transglutaminase, anti-endomysial antibodies and anti-gliadin antibodies. This hypersensitivity appears to be

genetically predisposed, as evident by the predisposition for coeliac disease found in individuals with HLA DQ2 and/or DQ8. The result of this complex immunological reaction is damage to the small intestinal mucosa, which thereby goes on to affect its function of absorption of nutrients **[3]**.

The aggravations caused by CD promote an imbalance in the gut microbiota (GM) **[4]**. To reduce this imbalance, it is believed that the administration of prebiotics and probiotics may be a promising method, which would restore the homeostasis of the gut microbiota **[4]**. Although the pathogeny of CD is not fully determined, studies have found a relationship between the reduced number of beneficial bacteria, such as Bifidobacterium and Lactobacillus, and the presence of this condition **[4]**. There are indications that the changes may impair intestinal homeostasis since it is known that the interactions between microbial flora and the human host play a critical role in maintaining intestinal health. However, it is not yet known specifically how the gut microbiota plays a role in the pathogeny of this disease, and whether microbiota dysbiosis would be the cause or consequence of CD **[4]**.

Due to the alteration of intestinal microbiota, the absorption of both macro and micronutrients is interrupted and this results in several gut- related and unrelated manifestations. The gut-related manifestations are abdominal pain, bloating, vomiting and diarrhea. This results in failure to thrive in children and loss of weight in adults. The gut-unrelated symptoms are anemia, neurological abnormalities such as paraesthesia, dementia, optic atrophy and myopathy and reduced bone density resulting in fractures **[5]**.

Regarding treatment, according to other studies, the most effective way found to stabilize the chronic inflammatory condition of CD was through the administration of prebiotics and probiotics **[6-8]**. This hypothesis stems from the success of this method, which, when applied to patients with inflammatory bowel diseases, restored the balance of the microbiota mainly with the use of prebiotics **[9]**. The therapy consists of an attempt to increase the concentrations of Bifidobacterium and Lactobacillus, microorganisms that make up the normal microbiota responsible for the immunomodulation of inflammatory responses. Therefore, there would be a reduction in inflammatory cytokines, such as TNF-α, IFN-gamma, and IL-2, and an increase in antiinflammatory cytokines, such as IL-10 **[10]**. However, although it is known that prebiotics and probiotics have beneficial effects on the gastrointestinal tract, few studies have investigated this treatment strategy both in patients with inflammatory bowel diseases and in patients with this condition **[11]**.

Also, studies indicate that a gluten-free diet can restore the intestinal composition of bacteria that have suffered a reduction or increase in CD. In addition, patients with CD may continue to manifest gastrointestinal symptoms even under this therapy, as has been observed in children and women **[8]**. In addition, 40-50% of patients still have long-term intestinal inflammation **[9]**.

Therefore, the present study aimed to correlate the main results of the action of the gut microbiota and functional nutrition for the treatment of celiac disease.

Methods

Study Design

This study followed the international model of Systematic Review and Meta-analysis, following the rules of PRISMA (preferred reporting items for systematic reviews and metaanalysis). **Table 1** shows the main variables of the present study that was addressed according to the classification of the acronym PICOS (P = Patients; I = Intervention; C = Control; O = Outcomes; S = Study design).

Table 1. PICOS framework.

POPULATION	Celiac Disease Patients Patients with unregulated gut microbiota
INTERVENTION	Gut Microbiota and Functional Nutrition
CONTROL	Drugs and Gluten Free Diet
OUTCOMES	Improvement of Comorbidities
STUDY DESIGN	Randomized Controlled Trials; Prospective Studies; Retrospective Studies; Case Series

Data sources and research strategy

The search strategies for this systematic review and meta-analysis were based on the descriptors (MeSH Terms) "Celiac Disease; Coeliac Disease; Nutrition; Nutrology; Diet; Gut Microbiota; Probiotics", with publications from 2010 to 2020, to analyze the most recent scientific publications. The research was carried out in June 2021 to 2022 and developed at Scopus, PubMed/Medline, Science Direct, Google Scholar and Ovid, including the clinical trial records. In addition, the combination of the keywords with the Booleans "OR", AND and the operator "NOT" were used to target scientific articles of interest. The title and abstracts were examined under all conditions. The research structure used in the databases is shown in **Table 2**.

Table 2. For an example of the search structure in PubMed, the same search strategy was used in the other databases.

PubMed	Celiac Disease **OR** Coeliac Disease **OR** Nutrition **OR** Nutrology **OR** Diet **OR** Gut Microbiota **OR** Probiotics
	AND
PubMed	Randomized controlled trial **OR** Prospective study **OR** Retrospective study **OR** Observational/Epidemiological studies
	NOT
PubMed	Case reports **OR** Editorials **OR** Letters to the editor **OR** Review study **OR** Meta-analysis

Quality of Studies And Risk of Bias

The quality of the evidence was classified as high, moderate, low, or very low, according to the risk of bias in the body of evidence, openness of comparisons, accuracy, and consistency in the effects of treatment, according to the Grading of Recommendations Assessment, Development, and Evaluation (GRADE). High quality of evidence was attributed to well-designed randomized controlled trials (RCTs) with consistent results. The quality of the evidence was reduced to moderate if 1 of the 4 criteria of quality of the evidence had not been met and lower if 2 or more were not met. Low quality of evidence was attributed to non-randomized studies. The Cochrane instrument was adopted to assess the risk of bias of included studies **[12]**.

Statistical Treatment of Literary Findings

For data analysis, a database was built in a Microsoft Excel spreadsheet that was exported to the Minitab 18® statistical program (version 18, Minitab, LLC, State College, Pennsylvania, USA) (Minitab®) and also to OriginPro® 9 (DPR Group, Inc., Northampton, Massachusetts, USA) (Moberly, Bernards, Waynant, 2018) **[13]**. A common descriptive statistical analysis was performed, obtaining the values of total N, mean, standard deviation, confidence interval (CI), and percentage (frequency) for all predictors. The One-Way test (ANOVA) was applied, adopting the α level lower than 0.05, with a statistically significant difference for the 95% CI. The R-sq (I2) value was analyzed to discover the imprecision or heterogeneity of the analyses, adopting the codes of low association = <25%, medium association 25%<X<50%, and high association = >50%.

Results

After the detailed process of literary search and the use of search filters (PICOS) and MeSH Terms (Tables 1 and 2), the present study found thirteen (13) important clinical studies, of which 12 were Randomized Controlled Studies (RCTs) and one (1) Cross-Sectional Observational study of the total of 113 studies evaluated, showing a high quality of scientific evidence in the studies addressed, with a level of scientific evidence IA, according to GRADE criteria (**Figure 1**). Also, the analyzed studies showed high homogeneity in the results (high association = >50%) to studies with larger sample size (greater precision), presenting 98.65% to the R-sq (I2) value, as shown by the Funnel Plot in Figure 2 through the studies highlighted in red balls.

Figure 1. Study Eligibility (Meta-analysis).

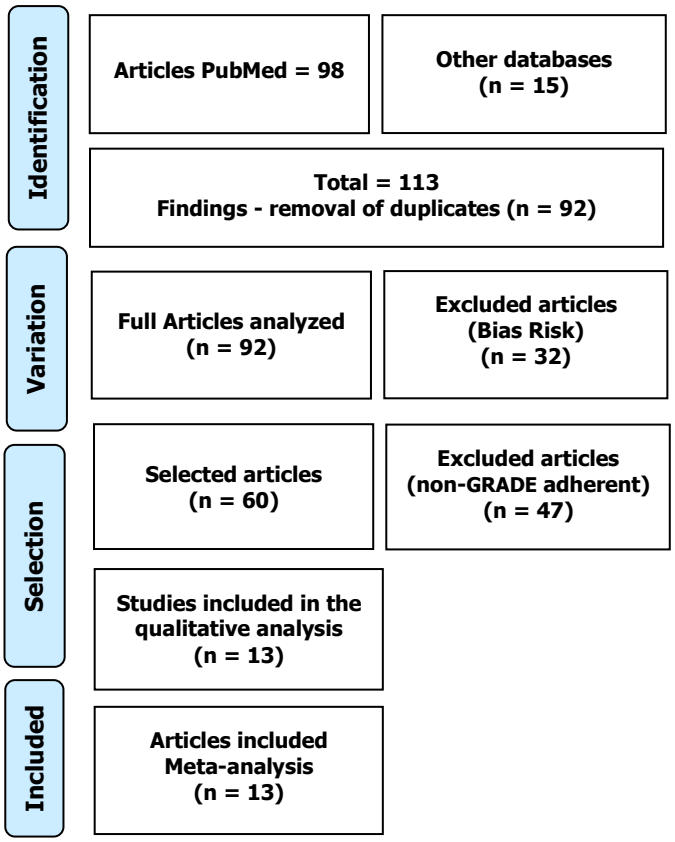


Table 3 shows the results on safety and efficacy of the use of Diets and Gut microbiota presented by the studies of the present work, as well as the p-value of the correlation between the test (diet and probiotics) and control groups in each study listed, Effect Size and Sample Size (1/Standard Error or Precision) values. The results showed that there was a statistical difference between the test and control groups in each study, with

p>0.05 (CI 95%).

Figure 2 presents the results of the risk of bias of the studies using the Funnel Plot. This graph had an asymmetric behavior, suggesting a risk of bias between studies with a small sample size (lower precision) that are shown at the bottom of the graph, with studies with bias (small sample size) being represented by the blue balls.

Table 3. Results on safety and efficacy of the use of Diets and Gut microbiota. The Effect Size (Difference Magnitude) was calculated using the Cohen Test (d). Precision (sample size) was determined indirectly by the inverse of the standard error (1/Standard Error). P-value<0.05 represents no statistically significant difference, at 95% CI.

Authors/Year N = 17	Safety and Efficacy	Test Vs. Control Group (p-value)	Effect Size	1/Standard Error
	Diet and Gut microbiota	Reference:<0.05 (No difference)	Cohen's Test (d)	Precision and Sample Size
Ballestero et al., 2019 [1]	Yes	>0.05	0.013	8.0
Jang et al., 2020 [14]	Yes	>0.05	-0.011	8.6
Sellitto et al., 2012 [15]	Yes	>0.05	0.015	8.2
Krupa-Kozak, Drabińska, Jarocka-Cyrta, 2017 [16]	Yes	>0.05	-0.017	7.8
Primec et al., 2019 [17]	Yes	>0.05	0.021	7.4
Drabińska et al., 2018 [18]	Yes	>0.05	0.016	8.9
Olivares et al., 2014 [19]	Yes	>0.05	0.023	8.3
Klemenak et al., 2015 [20]	Yes	>0.05	-0.100	7.8
Smecuol et al., 2020 [21]	Yes	>0.05	0.100	7.9
Quagliariello et al., 2016 [22]	Yes	>0.05	0.015	6.0
Håkansson et al., 2019 [23]	Yes	>0.05	-0.015	6.2
Roncoroni et al., 2018 [24]	Yes	>0.05	0.120	6.7
Francavilla et al., 2019 [25]	Yes	>0.05	-0.120	7.7

Figure 2. Asymmetrical Funnel Plot, suggesting a risk of bias between studies of small sample sizes that are shown at the base of the graph, with studies with bias represented by the blue balls.

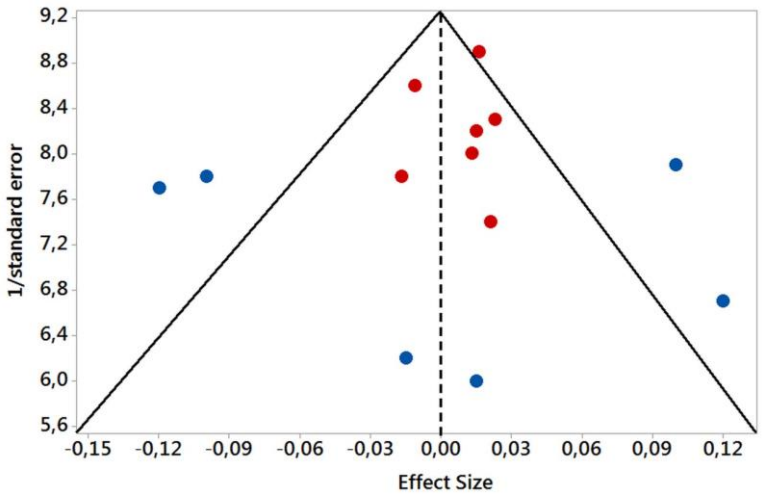


Table 4 presents the general data found in each study that was selected to compose the meta-analysis of the present study, showing the variables Authors, Diet Success, Gut microbiota change, Major Findings, and Follow up.

Table 4. General findings from each RCT study. Code 1 represents "yes", and code 0 denotes "no".

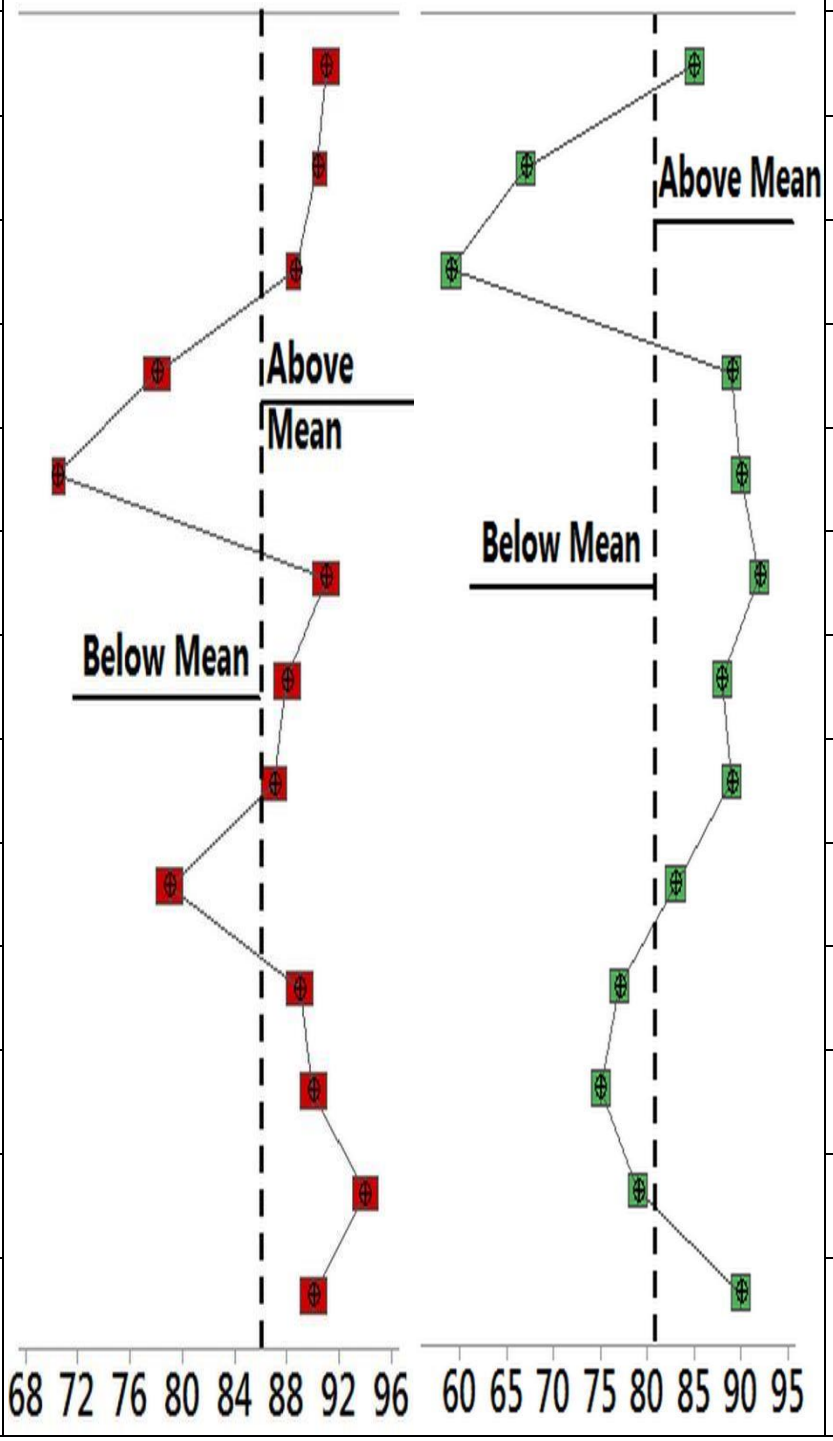
Authors/ Variables	Diet Success	Gut microbiota change	Major Findings	Follow Up (Months)
Ballestero et al., 2019 [1]	1	0	Children and adolescents who follow a gluten-free diet (GFD) seem to follow the same trends as healthy individuals on a normal diet. No effects of dietary restriction or consumption of gluten-free products were observed.	12
Jang et al., 2020 [14]	1	1	Proton pump inhibitors were associated with an increased risk of subsequent celiac disease diagnosis. The analysis did not reveal a significant overall change in the levels of serologic markers of celiac disease for the study cohort in response to PPI treatment. However, one subject developed a marked increase in celiac disease-specific autoantibody response to transglutaminase 2 in conjunction with increased immune reactivity to gluten during the study. The results of this exploratory analysis support further investigation of the molecular mechanisms involved in the contribution of PPIs to the risk of celiac disease through the potential increase in gluten immunopathology and changes in the intestinal microbial population (Order: Actinomycetales).	2
Sellitto et al., 2012 [15]	1	1	Gluten introduction early and late in babies. The data showed that there are differences between the developing microbiota of infants with a genetic predisposition to CD and the microbiota of infants with an unselected genetic background, with a general lack of bacteria of the phylum Bacteriodetes along with a high abundance of Firmicutes and microbiota that do not resembles that of adults even at 2 years of age. Innaddition, metabolomics analysis reveals potentialnbiomarkers for CD prediction.	24
Krupa-Kozak, Drabińska, Jarocka-Cyrta, 2017 [16]	1	1	The identification of the beneficial effects of the Synergy 1 (oligofructose) supplement in children with CD may have important implications for nutritional recommendations for CD patients and for alleviating the harmful effects of celiac disease.	3
Primec et al., 2019 [17]	1	1	Verrucomicrobia, Parcubacteria and some as yet unknown phyla of Bacteria and Archaea may be involved in the disease, indicated by a strong correlation with TNF-α. Likewise, Proteobacteria strongly correlated with the concentration of fecal short-chain fatty acids. The effect of probiotic administration revealed a negative correlation between Verrucomicrobia, some unknown phyla of Bacteria, Synergistetes, Euryarchaeota, and some SCFAs, making them an important target in the microbiome restoration process. Synergistetes and Euryarchaeota may play a role in the anti-inflammatory process in the healthy human gut.	3
Drabińska et al., 2018 [18]	1	1	Synergy 1 applied as a supplement to a gluten-free diet had a moderate effect on the qualitative characteristics of the fecal microbiota, while stimulating the production of bacterial metabolites in children with CD.	3

Olivares et al., 2014 [19]	1	1	The results suggested that Bifidobacterium longum CECT 7347 could help improve the health status of CD patients who tend to have alterations in gut microbiota composition and a biased immune response even on a gluten-free diet.	3
Klemenak et al., 2015 [20]	1	1	Probiotic intervention with the two probiotic strains Bifidobacterium breve BR03 and B. breve B632 showed a positive effect in decreasing the production of the pro-inflammatory cytokine TNF-α in children with CD on a gluten-free diet.	3
Smecuol et al., 2020 [21]	1	1	Use of the Bifidobacterium infant NLS strain as a probiotic. Treatment with B. infant was associated with a decrease in the abundance of Ruminococcus sp. and Bifidobacterium adolescence. The excretion of immunogenic gluten peptides in feces and urine was similar in each treatment period. There were no differences in adverse effects between the two groups. B. Infante NLS-SS improves CD-specific symptoms in a highly symptomatic subset of treated patients. This is associated with a change in the profile of the fecal microbiota.	24
Quagliariello et al., 2016 [22]	1	1	Food supplementation based on two strains of Bifidobacterium breve (B632 and BR03). The comparison between the DC individuals and the Control group revealed a change in the intestinal microbial composition of celiac patients, characterized mainly by the reduction of the Firmicutes/Bacteroidetes ratio of Actinobacteria and Euryarchaeota. Regarding the effects of the probiotic, an increase in Actinobacteria was found, as well as a reestablishment of the physiological relationship Firmicutes/Bacteroidetes. The administration of the B. breve strains helped to restore the healthy percentage of the main microbial components.	3
Håkansson et al., 2019 [23]	1	1	Daily oral administration of L. Plantarum HEAL9 and L. paracasei 8700:2 modulated the peripheral immune response in children with celiac disease autoimmunity.	6
Roncoroni et al., 2018 [24]	1	1	The VAS for abdominal pain was much lower and the visual analog scale (VAS) for fecal consistency increased after treatment in the low GFD FODMAP group (low gluten and with oligosaccharides, disaccharides, monosaccharides, and polyols). Overall well-being increased in both groups, but with a much greater improvement in the low GFD FODMAP. Thus, a short-term FODMAP regimen helped improve psychological health and gastrointestinal symptomatology with greater well-being of CD patients.	1
Francavilla et al., 2019 [25]	1	1	Treatment success was significantly greater in patients receiving probiotics compared with placebo (15.3% vs. 3.8%; $P < 0.04$). Presumed lactic acid bacteria, Staphylococcus and Bifidobacterium, were increased in patients who received probiotic treatment. No adverse events were reported. Thus, probiotic treatment for 6 weeks was shown to be effective in improving the severity of IBS-like symptoms in CD patients on a gluten-free diet, is associated with changes in the intestinal microbiota, characterized by an increase in bifidobacteria.	1.5

By the Forest Plot graph and after Tukey's analysis (ANOVA), it was observed that the mean values in percentage of the safety and efficacy rates (Scale from 0 to 1, 0-100%) of the use of Diets/Probiotics and improvement of the Gut Microbiota were not statistically different among the thirteen studies, with $p=0.158 > 0.05$ (**Table 5**).

Table 5. Forest Plot graph showing the results of Tukey's analysis (ANOVA) the comparison between the average values of Diet Success and Gut Microbiota Change (0 to 1, 0-100% scale), with p>0.05 without a statistical difference (CI 95%), assuming equality of variances.

Authors/ Variables	Diet Success (%) / Gut microbiota change (%)	Test Vs. Control Group (p-value)
Ballestero et al., 2019		>0.05
Jang et al., 2020		>0.05
Sellitto et al., 2012		>0.05
Krupa-Kozak et al., 2017		>0.05
Primec et al., 2019		>0.05
Drabińska et al., 2018		>0.05
Olivares et al., 2014		>0.05
Klemenak et al., 2015		>0.05
Smecuol et al., 2020		>0.05
Quagliariello et al., 2016		>0.05
Håkansson et al., 2019		>0.05
Roncoroni et al., 2018		>0.05
Francavilla et al., 2019		>0.05



Variables	*N Mean (%)*		*StDev*	*95% CI*	*Grouping*	*p-value*
Diet Success Rate (%)	13	86.69	6.82	(81.77; 91.62)	A	0.158
Gut microbiota change (%)	13	81.77	10.08	(76.84; 86.69)	A	

Discussion

In the context of the impact of nutrients and alteration of the intestinal microbiota in celiac disease, the present study highlighted important randomized controlled trials showing that indeed the provision of certain diets can promote the improvement of GM as well as CD, especially in patients with a gluten free-diet (GFD). Therefore, patients who follow a GFD may be prone to nutritional deficiencies.

In this respect, a CD is an immune-mediated enteropathy whose specific trigger is gluten. In this sense, complementary strategies are also being studied, such as GM modulation. Intestinal dysbiosis has been reported in patients with CD, untreated or treated with GFD, compared to healthy subjects. Several studies have identified differential bacterial populations associated with CD patients and healthy individuals. However, it is still unclear whether intestinal dysbiosis is the cause or effect of CD. Furthermore, probiotics have also been considered as a strategy to modulate GM to an anti-inflammatory state **[26]**. Therefore, the present meta-analysis study corroborated the beneficial action of probiotics in GM modulation to attenuate CD.

Still, the present study was necessary, given that studies point to an increase in the prevalence of CD in recent decades. Thus, dietary changes and drug use that may affect GM have been suggested as potential contributors **[14]**.

Studies suggest that aspects of gluten intake may influence the risk of CD occurrence and the timing of its onset, i.e., the quantity and quality of gluten ingested, along with the infant feeding pattern and the age at which gluten is present. introduced into the diet. Combined genomic and metabolomic approaches will be key to deciphering the role of GM in the onset of CD **[15]**.

Besides, despite GFD, several patients with CD have persistent symptoms. Based on this, a systematic review and meta-analysis study evaluated the effectiveness of probiotics in improving gastrointestinal (GI) symptoms and quality of life (QoL) in patients with CD. We found 6 RCTs (n=279 participants). Probiotics were observed to improve gastrointestinal symptoms when assessed by the GI Symptom Rating Scale (mean difference in symptom reduction: -28.7%; 95% confidence interval [CI] -43.96 to -13, 52; p=0.0002). There was no difference in gastrointestinal symptoms after probiotics when different questionnaires were pooled. Bifidobacteria levels increased after probiotics (mean difference: 0.85 log colony forming units (CFU) per gram; 95% CI 0.38-1.32 log CFU per gram; P = 0.0003). No difference in adverse events was observed between probiotics and placebo. Therefore, probiotics may improve gastrointestinal symptoms in CD patients **[27]**.

Conclusion

According to the results, although some studies have a small sample size, the main randomized clinical studies showed that the modulation of nutrients/probiotics and the gut microbiota improve the inflammatory process of celiac disease, especially in patients with a gluten-free diet.

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Data sharing statement

No additional data are available.

Conflict of interest

The authors declare no conflict of interest.

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