Journal of Cereal Science 95 (2020) 103058

Contents lists available at ScienceDirect

Journal of Cereal Science

journal homepage: http://www.elsevier.com/locate/jcs

Gluten-free diet and gut microbiome

Andrea Polo [a], Kashika Arora [a], Hana Ameur [a], Raffaella Di Cagno [a], Maria De Angelis [b], Marco Gobbetti [a,*]

[a] Faculty of Sciences and Technology, Libera Università di Bolzano, Bolzano, 39100, Italy
[b] Department of Soil, Plant and Food Sciences, University of Bari Aldo Moro, Bari, 70121, Italy

A B S T R A C T

As the only effective therapy against diagnosed celiac disease (CD), the gluten-free diet (GFD) has inevitable repercussion on the gut microbiome composition and functionality. Being the cause or the consequence of the disease, an altered homeostasis of the gut microbiome usually affects CD patients at diagnosis. After describing the main features of this altered physiological condition, this review defines the main nutritional aspects of the GFD and elucidates how this diet regimen does not fully restore the optimal gut microbiome composition and functionality. Unbalanced ratios between beneficial and potentially harmful bacteria are frequently present in fecal materials, biopsy specimens and saliva, used as ecological model systems to observe CD. Metabolome analyses also show how an altered microbiome synthesize different metabolite with respect to healthy conditions. The review concludes illustrating the current supplementations (biotics family), which fortify the GFD with the aim of restoring the homeostasis of the gut microbiome.

1. Introduction

Gluten-related disorders comprise a variety of diseases, being celiac disease (CD), non-celiac gluten sensitivity and gluten allergy the most diffused. CD is an autoimmune pathology, triggered by gluten and affecting the small intestine of genetically susceptible individuals, with broad clinical manifestations derived from multiple contributing factors (Gujral et al., 2012; Singh et al., 2018). The worldwide prevalence of CD based on serological test and biopsy specimens is approximately 1.4 and 0.7%, respectively (Singh et al., 2018). It varies with sex, age and location, increasing to 5.6% in some countries and populations (Gujral et al., 2012).

According to the World Health Organization, a diet is healthy when it contributes to protect against malnutrition in all its forms: under- and over-nutrition (Melini and Melini, 2019). After CD diagnosis in genetically susceptible individuals, a healthy diet has also to protect this part of the worldwide population from malabsorption and recurrent CD symptoms. Indeed, the gluten-free diet (GFD) is the only effective therapy against diagnosed CD. GFD requires the complete exclusion of gluten containing cereals (e.g., wheat, rye, barley, oats, spelt and kamut) and comprises only naturally gluten-free matrices (e.g., legumes, fruits and vegetables, unprocessed meat, fish, eggs and dairy products) and/or substitutes of wheat-based foods manufactured without gluten or having a gluten content lower than 20 ppm, as per the European legislation (EU law 41/2009). Rice, corn, sorghum, buckwheat, quinoa and amaranth, and some minor cereals (fonio, teff and millet) are usually the main ingredients of the gluten-free formulae. The market for gluten-free products increases steadily, and GFD has become more and more popular. While CD patients need to follow a GFD, the vast majority of consumers of gluten-free products buy them for incorrect or misleading purposes: belief of healthier products, weight loss and/or prevention of toxic side-effects of gluten (Reilly, 2016). Internet surveys establish that only ca. 30% of consumers have been diagnosed as CD patients and depend on gluten-free foodstuffs (Dieterich and Zopf, 2019). An example of such misleading purposes is within athletes. A survey on 910 people showed that 41% of Australian athletes have reduced the gluten intake by up to 50–100%, expecting gastrointestinal well-being and ergogenic performance, whose effects have not been scientifically substantiated at all (Lis et al., 2015).

The diet is, at the same time, nourishment for humans and microbes that, very numerous and diverse, populate the human gastrointestinal tract from birth throughout life. The main functions of the gut microbiome are protection against enteropathogens, immune system maturation, modulation of nutrients acquisition and host energy metabolism (Zmora et al., 2019). Maintenance of a beneficial microbiome requires a homeostatic equilibrium within the microbial communities, and between microbes and host. Failure to achieve or maintain this complex homeostasis leads to a dysbiosis framework of gut microbiome, with negative repercussions on health. Dysbiosis events are the cause or the consequence of many intestinal diseases and/or disorders (Reddel et al., 2019). Indeed, intestinal dysbiosis is the hallmark of several immune

* Corresponding author.
E-mail address: Marco.Gobbetti@unibz.it (M. Gobbetti).

https://doi.org/10.1016/j.jcs.2020.103058
Received 14 March 2020; Received in revised form 17 July 2020; Accepted 21 July 2020
Available online 24 July 2020

List of abbreviations

CD	Celiac Disease
GFD	Gluten-Free Diet
AN-PEP	*Aspergillus niger* Prolyl endopeptidase
Asn	Asparagine
CD3	Cluster of Differentiation 3
DGGE	Denaturing Gradient Gel Electrophoresis
FISH	Fluorescent *in situ* Hybridization
HC	Healthy Control
His	Histidine
HLA	Human Leukocyte Antigen
IgA	Immunoglobulin A
IL-10	Interleukin-10
Met	Methionine
OTU	Operational Taxonomic Unit
Pro	Proline
SCFA	Short-chain fatty acids
tCD	Treated celiac diseases
Trp	Tryptophan
VOCs	Volatile Organic Compounds

disorders, including CD, and the role of GFD is controversial (Sanz, 2015).

After describing the state of the gut microbiome at CD diagnosis, this review aims at qualifying the main features of the GFD, focusing on its interference on the gut microbiome composition and functionality of CD patients. Supplementary interventions (biotics family), which may fortify the GFD, are reviewed also.

2. The gut microbiome at CD diagnosis

The definitive observation that 30–40% of the population have the predisposing genotype but the CD prevalence affects only ca. 1% has prompted to search for other factors responsible for the clinical manifestation of the disease (Lammers et al., 2018). Together with other heterogeneous factors, the current evidence supports that dysbiosis (compositional and functional alterations of the gut microbiome) is commonly present in almost all the clinical CD manifestations. To what extent this is the cause or the consequence of the disease, and whether different intestinal diseases (CD, ulcerative colitis, and Crohn's disease) have specific change patterns, have yet to be established (Bascuñán et al., 2019). A presumptive mechanism hypothesizes that microbial dysbiosis (e.g., antibiotic therapy), independent of gluten sensitivity, may activate the innate immune system, resulting in the secretion of pro-inflammatory molecules, epithelial barrier disruption and increased transfer of gluten peptides. This cascade of events ultimately leads to CD development. In agreement with this hypothesis, another epidemiological study sustained that rotaviral infections and other gastrointestinal infections occurring in childhood, before or at the time of diagnosis, might increase the risk of CD development (Pozo-Rubio et al., 2012).

Reviewing literature data on gut microbiome composition and functionality at CD diagnosis suffers of two main limitations. Data accumulated during the last two decades are only slightly comparable because of the analytical technique progresses, from culture-dependent to high throughput sequencing and meta-genome analyses. Besides, some reports compared the status of CD patients during remission to that of healthy people, which, in part, overlaps the interference of the GFD. Table 1 shows the most representative results described during this time. The majority of the observational studies on children and adults at CD diagnosis highlighted alterations of the intestinal microbiome with respect to healthy individuals. The main differences concerned decreases of beneficial species and increases of potential pathogens. Compared to healthy individuals, the presence of *Bifidobacterium* spp. and *Bifidobacterium longum* decreased whereas that of *Bacteroides* spp. increased in fecal materials and duodenal biopsies of CD patients. In addition, the presence of enterobacteria and staphylococci was at the highest levels in CD patients (Collado et al., 2009, 2008). Likewise, other studies (Di Cagno et al., 2009; Sanz et al., 2007) reported how biopsy specimens of CD patients had increased prevalences of *Bacteroides*, *Staphylococcus* and enterobacteria, and concomitant low numbers of *Lactobacillus* and *Bifidobacterium*. The ratio between beneficial *Lactobacillus-Bifidobacterium* to potentially harmful *Bacteroides-Escherichia coli* seemed to be the hallmark of CD. The presence of *Prevotella*, *Clostridium histolyticum* and *Atopobium* also increased in fecal materials of CD patients (Collado et al., 2007). High levels of *Bacteroides* and *Prevotella* together with reduced IgA-coated bacteria in CD patients suggested for a mucosal barrier defect. The consequent speculation was that the mucosal layer of CD patients fails both to stabilize the gut microbiome and to prevent the host from invasion by harmful antigens and pathogens (De Palma et al., 2010). Compared to healthy individuals, dysbiosis of CD patients at diagnosis gave rise to the opportunistic pathogen *Staphylococcus epidermidis* carrying the mecA gene (Sánchez et al., 2012b). The abundance of *Bacteroides fragilis*, coding for metalloproteases, increased in CD patients, presumably playing a pathogenic role. Indeed, *Bacteroides fragilis* strains coding for virulence factors (e.g., metalloproteases) are frequently responsible for opportunistic infections and were demonstrated to aggravate colitis in experimental animal models (Sánchez et al., 2012a). Other duodenal biopsy analysis also demonstrated a higher prevalence of *Bacteroides vulgatus* in children with active CD (Schippa et al., 2010). Healthy infants with at least one first-degree relative with CD and with the predisposing genotype (HLA-DQ2 and HLA-DQ8) harbored higher proportions of Firmicutes (*Clostridium*) and Proteobacteria (*Escherichia/Shigella*), and lower numbers of Actinobacteria, including *Bifidobacterium*. This suggested that HLA genotypes in high-risk patients might select for potentially harmful microbiomes (Olivares et al., 2014b). A comparison between duodenal biopsy specimens of CD and healthy children described a higher incidence of Gram-negative bacteria in the former group (Nistal et al., 2012a; Sánchez et al., 2013). A study on children born during the Swedish CD outbreak (Ou et al., 2009) also speculated about the dominance of rod-shaped bacteria such as *Clostridium* and *Prevotella* as risk factors for CD. Another study (Wacklin et al., 2013) confirmed how Proteobacteria genera (e.g., *Acinetobacter* and *Neisseria*) were associated to gastrointestinal symptoms in CD patients with respect to healthy individuals. Compared to healthy children, duodenal biopsies of CD children at the diagnosis showed higher levels of *Neisseria*, *Streptococcus*, *Serratia* and *Haemophilus* (Cheng et al., 2013; Ou et al., 2009). Unbalanced serum, fecal and urine metabolome also distinguished CD patients at diagnosis (Bertini et al., 2009; Di Cagno et al., 2011, 2009). CD patients showed the lowest levels of serum amino acids, lipids, pyruvate and choline, and the highest levels of glucose and 3-hydroxybutyric acid (Bertini et al., 2009). The modified levels of glucose and ketones suggested alterations of the energy metabolism.

Most of the above results allow the speculation that dysbiosis at least accompanies CD and symptom development, inducing modification of the mucosal barrier that favors a persistent immune activation. Although additional studies are needed to confirm this hypothesis, the main question still concerns whether or not the GFD during remission has the potential to restore the microbiome composition and functionality (see paragraph 4.).

3. The gluten-free diet (GFD)

Today, gluten is the most consumed food protein in Western societies, with an intake of approximately 10–20 g per person per day (Cohen et al., 2019). The exclusion of this protein from the diet almost radically changes the alimentary regimen. Although the GFD is the only convenient therapeutic treatment of CD, literature data show some

Table 1
Representative alterations of the gut microbiome composition of celiac disease patients (CD) at diagnosis in comparison to healthy individuals (HC).

Authors	No. Of subjects	Age interval of CD patients (mean age) (in years)	Methods	Biological sample	Findings
Sanz et al. (2007)	10 CD + 10 HC	1.25–3.75 (2.3)	Culturing + PCR + DGGE	Feces	↑ Diversity of *Lactobacillus* sp. in DGGE profiles; *Lactobacillus curvatus*, *Leuconostoc mesenteroides*, *Leuconostoc carnosum*, *Bifidobacterium infantis*, *B. bifidum* ↓ Diversity of *Bifidobacterium* sp. in DGGE profiles; *Lactobacillus casei* group, *Bifidobacterium longum*, *B. pseudocatenulatum, B. dentium*
Collado et al. (2007)	26 CD + 23 HC	1.0–2.0 (2.19)	Culturing + FISH	Feces	↑ *Bacteroides-Prevotella* group, *Eubacterium rectale-C. coccoides* group, *Clostridium histolyticum*, *Staphylococcus*, *Atopobium*, sulphate-reducing bacteria ↓ *Bifidobacterium* group and Enterobacteriaceae in culture
Collado et al. (2008)	30 CD + 30 HC 25 CD + 8 HC	4.7–5.05 (4.7)	qPCR	Feces Duodenal biopsy	↓ *Bifidobacterium* group ↑ *Bifidobacterium breve* ↓ *Bifidobacterium longum*, *B. catenulatum*
Collado et al. (2009)	30 CD + 30 HC 25 CD + 8 HC	4.7–5.05 (4.7)	qPCR	Feces Duodenal biopsy	↑ *Bacteroides* and *C. leptum* groups, *E. coli, Staphylococcus* group ↓ *Bifidobacterium* group ↑ *Akkermansia muciniphila*, *Bacteroides* and *C. leptum* groups, *E. coli*, *Staphylococcus* group ↓ *C. coccoides* and *Bifidobacterium* group ↓ *Clostridium coccoides* ↓ *C. coccoides* and *Bifidobacterium* group
Di Cagno et al. (2009)	7 CD + 7 HC	6.0–12.0	Culturing + PCR + DGGE + 16S rRNA sequencing	Feces	↑ Bacteroides and *Clostridium* groups ↓ *Lactobacillus* sp., *Bifidobacterium* sp., Enterobacteriaceae
Ou et al. (2009)	33 CD + 18 HC	1.2–16.0 (5.9)	PCR + 16S rRNA gene sequencing	Duodenal biopsy	↑ *Haemophilus* sp.; increase in rod-shaped bacteria ↓ *Neisseria polysaccharea*
Schippa et al. (2010)	10 CD + 10 HC	1.2–16.1 (8.3)	Culturing + PCR + TTGE + 16S rRNA gene sequencing	Duodenal biopsy	↑ *Bacteroides valgatus* and *E. coli* ↓ *Clostridium coccoides*
De Palma et al. (2010)	24 CD + 20 HC	2.1–12 (5.5)	FISH + flow cytometry	Feces	↑ Ratio of Gram-positive to Gram-negative bacteria; *Bacteroides-Prevotella* group ↓ *Bifidobacterium* group, *C. histolyticum*, *C. lituseburense*, *Fecesibacterium prausnitzii* No significant differences in *E. coli*, *Staphylococcus*, *Lactobacillus-Enterococcus* and sulphate-reducing bacteria
Nistal et al. (2012a)	8 CD + 5 HC	1-10 (3.75)	PCR + 16S rRNA gene sequencing	Duodenal biopsy	↑ *Haemophilus*, *Neisseria*, *Acinetobacter*, *Fusobacterium*, *Veillonella* spp. ↓ *Prevotella* and *Streptococcus* spp.
Nistal et al. (2012a)	5 CD + 5 HC	26-38 (31.4)			↑ *Actinomyces*, *Methylobacterium* sp. ↓ *Fusobacterium, Haemophilus, Prevotella, Streptococcus* spp.
Nistal et al. (2012b)	10 CD + 11 HC	13-60 (40.4)	PCR + DGGE	Feces	↑ Diversity of *Lactobacillus* spp. in DGGE profiles; *Bifidobacterium bifidum*, *B. catenulatum* ↓ *Lactobacillus sakei* group
Sánchez et al. (2012a)	20 CD + 20 HC	1.0–8.8 (3.9)	Culturing + PCR + 16S rRNA gene sequencing	Feces	↑ *Bacteroides fragilis, Parabacteroides distasonis* ↓ *Bacteroides ovatus, B. finegoldii*
Sánchez et al. (2012b)	20 CD + 20 HC	5.6	PCR + DNA sequencing	Feces	↑ *Staphylococcus epidermidis*, *S. haemolyticus,* ↓ *S. aureus, Enterococcus* spp.
Sánchez et al. (2013)	32 CD + 8 HC	2-14 (5.1)	Culturing + PCR + 16S rRNA gene sequencing	Duodenal biopsy	↑ Proteobacteria, Actinobacteria, *Klebsiella oxytoca*, *Enterobacteriaceae*, *Staphylococcus epidermidis*, *S. pasteuri* ↓ Firmicutes, *Streptococcus anginosus*, *Streptococcus mutans*, *Actinomyces odontolyticus*
Wacklin et al. (2013)	33 CD + 18 HC	18-67 (39)	PCR + DGGE + 16S rRNA sequencing	Duodenal biopsy	↑ *Acinetobacter, Neisseria* spp. ↓ Bacterial richness and diversity
Cheng et al. (2013)	10 CD + 9 HC	3-14 (9.5)	qRT-PCR		↑ *Prevotella, Haemophilus, Serratia* spp. ↓ *Streptococcus* sp., *P. oralis, R. bromii, P. cinnamivorans, Proteus* and *C. stercorarium* groups
Nistal et al. (2016)	9 CD + 9 HC	not reported	PCR + 16S rRNA gene sequencing	Duodenal biopsy	↑ *Streptococcus* and *Lactobacillus* OTUs ↓ Bacterial richness and diversity
Herrán et al. (2017)	5 CD + 7 HC	25-44 (35)	Culturing + PCR + DGGE + 16S rRNA sequencing	Duodenal biopsy	↑ *Lactobacillus gasseri*, *S. epidermidis*, *S. pasteuri*, *P. aeruginosa*, *S. maltophilia* ↓ *Streptococcus* spp.
Harnett et al. (2017)	45 CD + 27 HC	18-70 (47.3)	PCR	Feces	↑ *Candida* and *Saccharomyces* spp.
Garcia-Mazcorro et al. (2018)	6 CD + 12 HC	25-73 (46.3)	PCR + 16S rRNA gene sequencing	Feces Duodenal biopsy	↑ *Streptococcus* spp. ↓ Bacteriodetes ↑ *Streptococcus* spp. ↓ Bacteriodetes, Fusobacteria, *Pseudomonas, Haemophilus*
Bodkhe et al. (2019)	23 CD + 24 HC	12-43 (15.1)	PCR + 16S rRNA gene sequencing	Feces Duodenal biopsy	↓ *Prevotella*, *Akkermansia, Ruminococcus, Bifidobacterium, Actinomyces* ↑ *Helicobacter* and *Megasphaera, Methanomassiliicoccus* ↓ *Barnesiella*

controversial aspects regarding the nutritional balance. Indeed, the mandatory recourse of using starches, protein substitutes (dairy and egg proteins), fatty acid ingredients, and hydrocolloids and gums into gluten-free formulae imposes nutritional differences with respect to conventional diets containing gluten.

Before describing some of the major nutritional concerns, it is noteworthy to state that divergences among results might be attributed either to differences in dietary habits of healthy individuals used as controls from country to country or to the variability of the gluten-free formulations from brand to brand (Melini and Melini, 2019). In summary, population studies highlighted that the nutritional status of CD patients following a GFD is not always adequate. Regarding the macronutrients intake, several studies agree to define the GFD of children, adolescents and/or adults as rather unbalanced. Generally, GFD supplies a higher intake of sugars and, especially, a lower intake of dietary fibers with respect to gluten containing diets (Thompson et al., 2005). This is mainly due to the overall recipes, but many efforts are currently evident to supplement the GFD with dietary fibers, which compensate the lack of these components from the main ingredients (see paragraph 5.2). Usually, gelatinized starch is higher in formulae using corn and rice starch with respect to conventional wheat and rye flours. Higher is the starch gelatinization and higher is capability of α-amylases to hydrolyze it, which implies a higher glycemic index. Hence, gluten-free products have a high glycemic index (Vici et al., 2016), and their daily intake may increase the risk of developing metabolic syndromes in CD patients. Controversial findings are reported for protein intake. Although one report observed that protein intake in CD patients was high (Mariani et al., 1998), another one (Shepherd and Gibson, 2013) on a female

Table 2
Representative alterations of the gut microbiome composition of celiac disease patients (CD) during remission and gluten-free diet (GFD – treated celiac disease tCD) in comparison to healthy individuals (HC).

Authors	No. Of subjects			Age interval of tCD patients (mean age) (in years)	Methods	Biological sample type	Findings
	CD	tCD	HC				
Nadal et al. (2007)	20	10	8	2.0–7.8 (5.6)	FISH + flow cytometry	Duodenal biopsy	↓ *Atopobium*, *Bifidobacterium*, *Lactobacillus* group, *Eubacterium rectale–Clostridium coccoides* ↓ *Clostridium histolyticum*, *Clostridium lituseburense, Fecesibacterium prausnitzii*, sulphate-reducing bacteria
Collado et al. (2009)	30	18	30	4.8–5.29 (5.4)	qPCR	Feces	↑ *Bacteroides*, *Clostridium leptum* ↓ *Bifidobacterium*
	25	8	8			Duodenal biopsy	↑ *Bacteroides*, *Clostridium leptum*
Di Cagno et al. (2009)	7	7	7	6–12	PCR + DGGE	Feces	↑ *Bacteroides*, Enterobacteria ↓ *Bifidobacterium*, lactic acid bacteria
Schippa et al. (2010)	20	10	10	1.2–16.1 (8.3)	Culturing + PCR + TTGE	Duodenal biopsy	↑ *Bacteroides vulgatus*, *Escherichia coli*
Sánchez et al. (2010)	20	12	8	4.57	PCR- DGGE	Duodenal biopsy	↑ *Bacteroides coprocola, Lactobacillus fermentum*, *Weissella* sp. ↓ *Bacteroides distasonis*, *Bacteroides fragilis/Bacteroides thetaiotaomicron, Bacteroides uniformis*, *Bacteroides vulgatus*
De Palma et al. (2010)	24	18	20	1.0–12.3 (5.5)	FISH + flow cytometry	Feces	↑ *Bacteroides-Prevotella*, Enterobacteriaceae, *Escherichia coli* ↓ The ratio of total Gram-positive to Gram negative bacteria; *Bifidobacterium* sp., *Bifidobacterium longum*, *Clostridium lituseburense*, *Fecesibacterium prausnitzii*
Di Cagno et al. (2011)	–	19	15	6–12 (9.7)	PCR-DGGE	Feces and duodenal biopsy	↑ *Bacteroides*, *Porphyromonas*, *Prevotella*, staphylococci, micrococci, Enterobacteria, *Salmonella, Shigella, Klebsiella* ↓ Lactobacilli, Enterococci, Bifidobacteria
Nistal et al. (2012b)	10	11	11	21–66 (40.4)	DGGE	Feces	↓ *Bifidobacterium* sp., *Lactobacillus sakei*
Sánchez et al. (2012b)	20	20	20	5.6	PCR + DNA sequencing	Feces	↑ *Staphylococcus epidermidis*, *Staphylococcus haemolyticus* ↓ *Staphylococcus warneri, Enterococcus faecium*
Acar et al. (2012)	–	35	35	6–19	Culturing + PCR + 16S rRNA gene sequencing	Saliva	↓ Salivary streptococci and lactobacilli
Sánchez et al. (2013)	32	17	8	3–8 (5.9)	Culturing + PCR + 16S rRNA gene sequencing	Duodenal biopsy	↑ *Streptococcus mitis* group, *Klebsiella oxytoca* ↓ *Streptococcus mutans* group, *Streptococcus anginosus* group
Golfetto et al. (2014)	–	14	42	12-70 (40)	Culturing + microscopy + enzymatic assay	Feces	↓ Bifidobacteria counts
Francavilla et al. (2014)	–	13	13	9.7	Culturing + PCR + 16S rRNA gene sequencing	Saliva	↑ Enterobacteriaceae, Lachnospiraceae, Gemellaceae, *Streptococcus sanguinis*, *Rothia mucilaginosa* ↑ Bacteroidetes (*Porphyromonas* sp., *Porphyromonas endodontalis, Prevotella nanceiensis)* ↓ Total anaerobes; *Streptococcus thermophilus*, Actinobacteria, *Actinomyces, Atopobium*, *Corynebacterium durum*
Wacklin et al. (2014)	18 tCD with symptoms			27–72 (54)	16S rRNA gene sequencing	Duodenal biopsy	In patients with persistent symptoms
	18 tCD asymptomatic			42–75 (63)			↑ Proteobacteria ↓ Microbial richness, *Bacteroides* and Firmicutes
Ercolini et al. (2015)	–	14	–	8.4	Culturing + PCR + 16S rRNA gene sequencing	Saliva	Before starting the Italian-style GFD ↑ Bacteroidetes, Firmicutes (*Clostridium, Eubacterium, Mogibacterium, Catonella, Peptococcus, Filifactor, Peptostreptococcus*) ↑ Actinobacteria (*Actinomyces, Rothia*), Tenericutes (*Bulleidia*) After starting the Italian-style GFD ↑ *Granulicatella*, *Capnocytophaga*, *Porphyromonas*, *Neisseria* ↓ *Prevotella*

population found that the mean intake of protein post-diagnosis was significantly lower with respect to the normal population. It seemed that CD patients on a long-term GFD consume significantly less vegetable protein than healthy controls (Van Hees et al., 2015). Fat intake is commonly higher than that recommended (Öhlund et al., 2010). However, disagreement among studies emerged when the fat intakes of CD subjects adhering to GFD were compared to controls (Zuccotti et al., 2013). Deficiencies in iron, calcium, zinc, vitamin B12, vitamin D and folate are the most common micronutrients inadequacies claimed for newly-diagnosed CD patients (Welstead, 2015). Population studies highlighted that GFD is, in part, ineffective in resolving iron (Thompson et al., 2005), calcium (Penagini et al., 2013), zinc and magnesium (Shepherd and Gibson, 2013), and vitamins B12 and D and folate (Thompson, 2000) deficiencies. Fortification of gluten-free products with food matrices naturally rich in micronutrients (e.g., legumes and pseudo-cereals) is the current trend to fulfill this nutritional gap. Although it is unlike the presence of mycotoxins in most of the processed foods, there is an emerging evidence that people following a GFD, especially without sufficient diversity, may be at higher risk of exposure to certain mycotoxins than those who are under nonrestrictive dietary regime. Indeed, corn, one of the main ingredient of gluten-free products, largely suffers of contamination by mycotoxins (e.g., fumonisins) because of the fungal contamination in the soil and during storage (Wild and Gong, 2009). In some cases, arsenic is frequently present in inorganic form in rice, which is one the most common ingredients for the preparation of gluten-free products (Lai et al., 2015).

Various external factors markedly affect the gut microbiome composition and functionality, and, among them, diet is one of the most important. Despite the beneficial effects on alleviating disease symptoms, it is worthwhile to deepen if GFD has repercussions also on the status of the gut microbiome of CD patients during remission.

4. Gluten-free diet (GFD) and gut microbiome

After CD diagnosis, a number of studies dealt with the effect of GFD to restore the composition and functionality of the gut microbiome (Table 2). Fecal materials and biopsy specimens from CD patients as well as saliva were the main targets, also including metabolome approaches.

4.1. Feces and biopsy specimens

Pioneer studies reported that CD patients after two years of GFD still suffered from an imbalance of the duodenal mucosal microbiome, with a worsening in the reduction of bacterial richness (Collado et al., 2009; Nadal et al., 2007). Although the relative abundances of some potentially pathogenic bacteria such as *Escherichia coli* and *Staphylococcus* decreased, the levels of beneficial *Bifidobacterium* and *Lactobacillus* species remained low. This scenario found further confirmation (Di Cagno et al., 2011) with decreased levels of healthy bacteria, which associated to increases of detrimental species such as *Bacteroides*, *Staphylococcus* spp., *Salmonella*, *Shigella* and *Klebsiella*. Nevertheless, *Bacteroides* is a dominant genus within the human gut microbiome and only some species (e.g., *Bacteroides vulgatus*, *Bacteroides fragilis*) show pro-inflammatory effect, which suggested the need of identifying the species before drawing conclusions. The low abundance of *Bifidobacterium* species seemed to be a distinguishing feature of CD patients also during GFD (Golfetto et al., 2014). Other studies (Bonder et al., 2016; Schippa et al., 2010) supported the conclusion that GFD only partially restores the imbalance at the gut microbiome level. Furthermore, the lower ratio between *Bifidobacterium* and *Bacteroides/Enterobacteria*, which is characteristic of CD patients at diagnosis, persisted during GFD (Di Cagno et al., 2009). Additional support to this information came from a study (De Palma et al., 2009) exploring the effect of GFD on healthy individuals. A decrease of *Bifidobacterium* sp., *B. longum*, *Clostridium lituseburense*, *Lactobacillus* sp. and *Faecalibacterium prausnitzii* was detectable and concomitant with an increase of *Enterobacteriaceae* and *E. coli* strains. GFD seemed to be responsible for a general reduction of the bacterial load at the large intestine lumen, which determined a decreased synthesis of both pro-inflammatory and regulatory cytokines. Compared to gluten-containing diets, GFD contains lower amounts of polysaccharides (e.g., fructans and resistant starch), which exert prebiotic functions (Miranda et al., 2014). These macronutrients reach the distal part of the colon as partially undigested and provide energy to commensal species of the gut microbiome. When the polysaccharide intake is limited, microbial species compete for substrates and opportunistic pathogens may overgrow. In summary, GFD not only influences the microbiome composition but also the immune function. A cohort of CD patients with a persistent symptomatology was compared to a cohort of patients without persistent symptoms, both being under remission for 3 years (Wacklin et al., 2014). The dysbiosis observed in CD patients at diagnosis caused persistent symptoms, even during a strict compliance to GFD. The decrease in gut microbiome diversity, higher levels of Proteobacteria (e.g., *Actinobacter* and *Neisseria*) and lower numbers of Bacteroidetes and Firmicutes, characterized the gut microbiome of CD patients having persistent symptoms.

4.2. Saliva

Saliva, as expression of the oral cavity conditions where digestion processes start, is another microbiome model system suggested to diagnose intestinal diseases, including CD, and the effect of GFD (Zarco et al., 2012). Compared to healthy individuals, the salivary microbiome of CD children under GFD differed (Acar et al., 2012; Ercolini et al., 2015; Francavilla et al., 2014). As estimated by culture-dependent techniques, CD children harbored the lowest prevalence of salivary streptococci and lactobacilli (Acar et al., 2012) and total anaerobes, and increased numbers of *Enterobacteriaceae* (Francavilla et al., 2014). This overview agreed with the lowest values of Shannon diversity and substrate richness, as analyzed through community-level catabolic profiles. Furthermore, 16S rRNA metagenome data showed the lowest richness (Chao1) and diversity (Shannon) indices. The relative abundance of several operational taxonomic units (OTU) differed between salivary samples of CD and healthy children. Within Firmicutes, *Lachnospiraceae*, *Gemellaceae* and *Streptococcus sanguinis* mainly associated with CD children under GFD. CD children also harbored the lowest numbers of *Streptococcus thermophilus*. Other Firmicutes (e.g., *Veillonella parvula*), which usually associated with oral health (Kumar et al., 2005), were at the lowest relative level in the saliva of CD children (Francavilla et al., 2014). Compared to healthy children, CD children under remission showed decreased levels of Bacteroidetes (*Porphyromonas* sp., *Porphyromonas endodontalis*, *Prevotella nanceiensis*), and Actinobacteria, *Actinomyces*, *Atopobium* and *Corynebacterium durum*. *Rothia mucilaginosa*, having the capability to degrade gluten (Fernandez-Feo et al., 2013), was the only Actinobacteria species present at the higher relative level in CD children (Francavilla et al., 2014). The salivary microbiome of fourteen CD Saharawi children underwent investigation passing from an African-to an Italian-style GFD (Ercolini et al., 2015). Compared to Italian-style, African-style GFD was richer in gluten-free cereals, legumes and vegetables, with a lower intake of animal proteins, sugars, starch and fat. Before changing the diet style, Saharawi CD children showed similar alpha-diversity indices but unusual high levels of some Firmicutes (*Clostridium*, *Eubacterium*, *Mogibacterium*, *Catonella*, *Peptococcus*, *Filifactor*, *Peptostreptococcus*), Actinobacteria (*Actinomyces*, *Rothia*) and Tenericutes (*Bulleidia*) with respect to Italian CD children (Ercolini et al., 2015; Francavilla et al., 2014). After starting the Italian-style GFD, the relative abundance of *Granulicatella*, *Capnocytophaga*, *Porphyromonas* and *Neisseria* increased at 30 and, especially, 60 days. These changes somewhat correlated with variations of CD symptoms. Using the relative abundance of core genera and partitioning around medoid clustering, the salivary microbiomes of Italian healthy and CD children, and Saharawi CD children grouped into three salivary types (Fig. 1). OTU co-occurrence/exclusion patterns showed that the

initial equilibrium among microbial species modified according to the diet change, leading to a decrease of the microbial diversity, with a few OTU out-competing the previously established microbiota and becoming dominant. A number of correlations occurred between OTU and dietary components. *Veionella*, *Streptococcus*, *Catonella*, *Mogibacterium*, *Clostridium*, *Peptococcus*, *Gemella* and *Actinobacteria* positively correlated with some dietary components (e.g., fibers) mainly abundant in the African-style GFD. *Bacteroidetes*, *Porphyromonas* and *Capnocytophaga* correlated negatively with carbohydrate and fiber intake, and positively with proteins, iron, calcium, phosphorus, caloric intake and/or lipids. Compared to healthy children, the saliva of CD children under remission showed differences in buffering capacity, IgA levels, minute volume, calcium and Ca/P ratio, and protein composition (Mina et al., 2012, 2008). Such diverse composition of the saliva of CD patients might modify the oral environment and, consequently, the microbiome composition and functionality.

4.3. Metabolome

^{1}H-Nuclear Magnetic Resonance analysis of fecal materials revealed as ethyl-acetate, octyl-acetate, some short-chain fatty acids (SCFA) and free amino acids, including glutamine, acted as presumptive metabolic markers of CD (Di Cagno et al., 2011). This metabolome spectrum found confirmation in another study (Nistal et al., 2012b), which confirmed the incomplete restoration of the gut microbiome after GFD. Compared to CD patients at the diagnosis, the levels of some SCFA were significantly higher in the fecal materials of healthy individuals and CD patients under GFD. Major differences regarded butyric, isovaleric and pentanoic acids. Fecal levels of Trp, Pro, Asn, His, Met, trimethylamine-N-ox and tyramine were higher in CD children under GFD than in healthy children. On the contrary, the fecal levels of total esters were higher in healthy compared to CD children (Di Cagno et al., 2011). Esterification reactions at the colon level might correspond to a microbial strategy to detoxify acids or alcohols (Vitali et al., 2010). The same differences were observable for most of the aldehydes (Di Cagno et al., 2011). According to microbiome composition, the levels of several salivary volatile organic compounds (VOC) differed between CD children under GFD and healthy children (Francavilla et al., 2014). Alcohols and phenols (e.g., 2-ethyl-1-hexanol, 4–1,1,3,3-tetramethylbutyl-phenol, and ethyl alcohol), hydrocarbons (e.g., 1-octadecene), ketones, terpenes, butanoic acid, acetic acid ethyl ester and octanal were the highest in the saliva of healthy children. On the contrary, nonanal, 2-methyloctyl ester, carbon disulfide, halogenated and aromatic hydrocarbons (e.g., 1-chlorodecane and trichloromethane) associated to CD children. Increased levels of 2-propyl-1-pentanol, nonanal, dihydro-4-methyl-2(3H)-furanone and nonanoic acid were present in the breath of healthy children under GFD (Baranska et al., 2013). Increased levels of some alcohols (e.g., 1-octen-3-ol, ethanol and 1-propanol), which were detectable in CD children, might correspond to the synthesis by intestinal bacteria and correlate to non-alcoholic steatohepatitis (Cani et al., 2008), which often associated to occult CD. Salivary microbiome and VOC variously correlated (Francavilla et al., 2014). *Prevotella* sp. positively correlated to levels of nonanal and 1-chlorodecane. *Clostridium durum* positively associated to levels of 1,2,

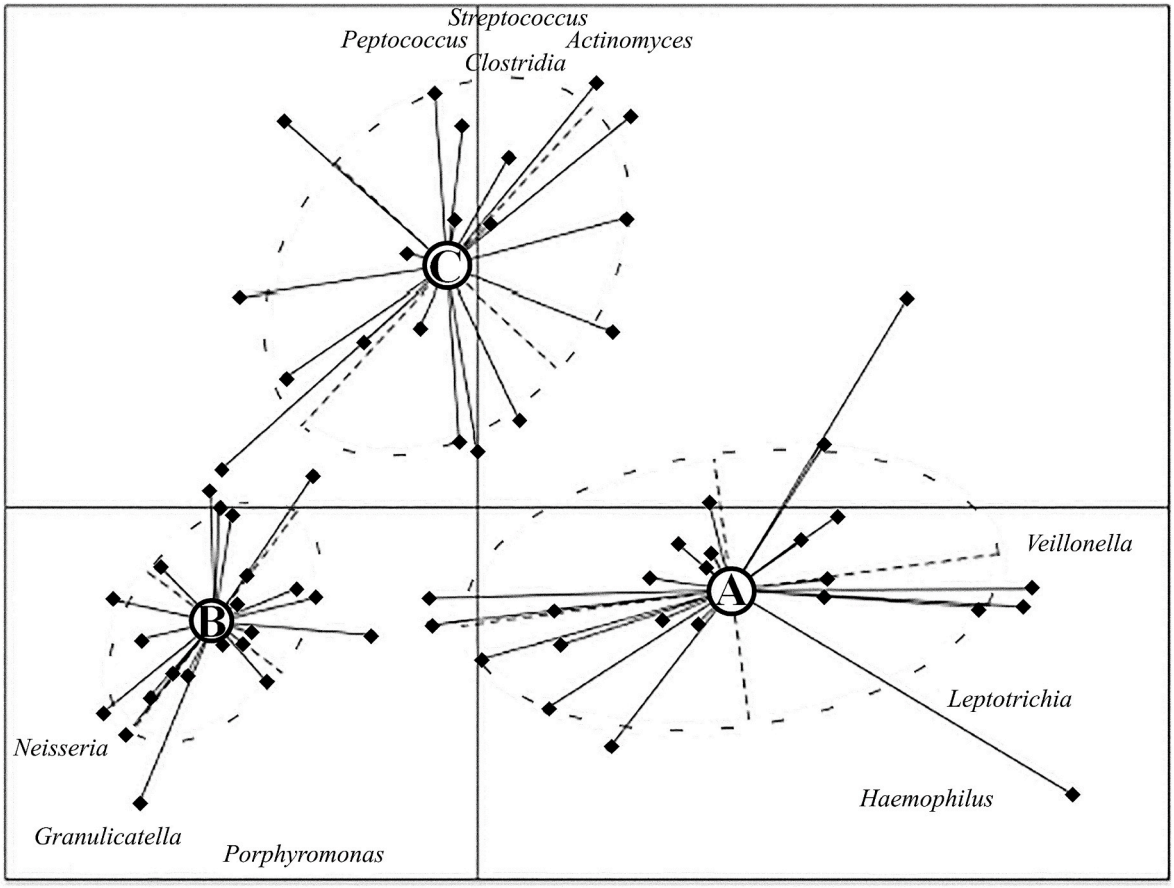

Fig. 1. Medoid cluster analysis of saliva samples from Saharawi CD children depicting the abundance of the core genera into three "salivary types" (A, B and C), as modified from Ercolini et al. (2015). Cluster A shows the abundance of *Haemophilus*, *Veillonella* and *Leptotrichia*, cluster B that of *Porphyromonas*, *Granulicatella* and *Neisseria*, and cluster C that of *Streptococcus*, *Actinomyces*, *Peptococcus* and *Clostridia*. Cluster A includes only saliva samples from Italian healthy and CD children. Saliva samples of Saharawi CD children were grouped into clusters B and C that mainly differed based on dietary habits. Cluster C mainly contained saliva samples of Saharawi CD children under African-style gluten-free diet.

3-trimethylbenzene, 2,6-dimethyl-4-heptanone, 4-methyl-2- hexanone, and 4-methyl-3-penten-2-one. *Granulicatella adiacens*, *Atopobium* sp., and bacilli and *Veillonella parvula*, *Str. thermophilus* and the division SR1 showed correlations with the amounts of 1(3H)-isobenzofuranone (-lactone) and 1-octadecene, and γ-lactone and 1-chlorodecane, respectively. These data supported the hypothesis that GFD affected the microbiome composition and, in turn, the oral metabolome. The salivary metabolome of Saharawi T-CD children markedly differed from Italian healthy and CD children (Ercolini et al., 2015). 1-Propanol, 4-(1, 1,3,3-tetramethylbutyl)-phenol and phenol, heptanal, octanal and nonanal, 2-pentyl furan 1,3-bis 1,1-imethylethyl-benzene; 1-chlorodecane; 1-octadecene, benzene and trichloromethane markedly decreased when Saharawi CD children shifted from the African-style to the Italian-style GFD. At the same time, the levels of other VOC (e.g., acetone, 2-butanone and 3-methylbutanone) increased under Italian-style GFD. Analysis of predicted metagenomes of the salivary microbiome of Saharawi CD children showed a remarkable modification of the metabolic potential of the microbiome following the diet change, with increased amino acid, vitamin and co-factor metabolisms during Italian-style GFD (Ercolini et al., 2015). Indeed, dietary components of GFD affected the salivary metabolome of African CD children. Furans, acetone, ethyl acetate, 2-butanone and 3-methyl-2-butanonewere positively correlated with the intake of proteins. Acetone was also strongly associated to the intake of lipids. Although the limitation of the relatively small number of CD patients analyzed, these data showed that CD patients have a different salivary microbiome and, especially, metabolome compared to healthy individuals and that these metabolome correlated with changes in physical symptoms (De Angelis et al., 2016).

5. The biotics family

Although with some limitations from the studies (e.g., low cohort numbers, heterogeneity of the approaches and techniques) and with the undoubted recent nutritional improvements, the main conclusion from literature concerns that CD patients under GFD are unable to restore the gut microbiome composition and functionality as that of healthy individuals. This almost univocal observation introduced the possibility to supplement the GFD with preparations based on the so-called biotics family. The term biotic derives from the Greek word biōtikós, meaning pertaining to life, and refers to the biological ecosystem made up of living organisms together with their physical environment (Fischbach and Segre, 2016). In particular, the biotics family consists of nutritional strategies, based on probiotics, prebiotics, synbiotics or postbiotics, which may direct the gut microbiome towards a more favorable state for host health.

5.1. Probiotics

Preliminarily, *in vitro* studies showed that specific probiotics were able to prevent the tight junction leakage detectable during the inflammation (Zeng et al., 2008) and to reduce the gliadin-induced increase of the epithelial permeability (Lindfors et al., 2008). Specific *Bifidobacterium* strains carried out regulatory and anti-inflammatory activities by stimulating the IL-10 synthesis in regulatory T cells (Baba et al., 2008). In a similar study (Medina et al., 2008), *Bifidobacterium longum* and *Bifidobacterium bifidum* increased the IL-10 synthesis, and suppressed the production of pro-inflammatory cytokines during *in vitro* treatment of peripheral blood mononuclear cells and co-incubation with fecal materials from CD patients. Other studies with cell cultures and experimental models showed that bifidobacteria decreased the severity of the toxic effects of gluten in CD patients (Laparra and Sanz, 2010). The administration of *Lactobacillus casei* in a mouse model of gliadin-sensitive enteropathy recovered the Gut-Associated Lymphoid Tissue homeostasis and the normal mucosal structure (D'Arienzo et al., 2011). This probiotic induced the recovery of villus blunting, delayed the weight decrease and normalized the levels of Tumor Necrosis Factors.

Other studies explored the *in vivo* effect of the GFD supplemented with probiotic preparations. In a randomized control trial, the intervention with *B. longum* improved the efficacy of the GFD in children with newly diagnosed CD (Olivares et al., 2014a). Under GFD treatment, 33 children randomly received daily capsules containing probiotic or placebo for 3 months. The coupled intervention GFD and probiotic led to the height percentile increase, in terms of growth-related parameters, and to the decrease of peripheral $CD3^+$ T lymphocytes number. *B. longum* caused the decrease of *B. fragilis* and *Enterobacteriaceae*, and the increase of harmless to potentially harmful bacteria ratio. In agreement, the administration of two strains of *Bifidobacterium breve* for 3 months increased the number of Actinobacteria and restored the optimal Firmicutes/Bacteroides ratio, thus re-establishing the gut microbiome homeostasis in CD children under GFD (Quagliariello et al., 2016). In another clinical trial, the administration of the same probiotic preparation (3 months) to 40 CD children under GFD restored the microbiome and incremented the levels of SCFA, mainly acetic acid (Primec et al., 2019). In contrast, the supplementation with the probiotic preparation VSL#3 did not cause any differences in the gut microbiome composition and clinical outcome (Harnett et al., 2016). A complex mixture of 5 strains of lactic acid bacteria and bifidobacteria improved the severity of IBS (Irritable Bowel Symptoms)-type symptoms in 54 randomized CD patients under strict GFD (Francavilla et al., 2019). During probiotic treatment, CD patients mainly evidenced increases of presumptive lactic acid bacteria, *Staphylococcus* sp. and *Bifidobacterium* sp.

Compliance to GFD is heavy and traces of gluten in several processed foods represent a risk for many CD patients (Roma et al., 2010). Therefore, another strategy concerned the use of probiotic and/or enzyme preparation to digest eventual traces of unexpected gluten in foods or an occasional deviance from GFD. The VSL#3 probiotic preparation almost fully hydrolyzed gliadin polypeptides mimicking the sourdough fermentation (De Angelis et al., 2006). Only α2-gliadin fragment 62–75 remained detectable at a very low concentration. Besides, a lesser reorganization of intracellular F-actin with a decreased release of zonulin was evident, which led to a decreased intestinal permeability. Ten probiotic strains, possessing a wide peptidase portfolio, were able to degrade well-known immunogenic epitopes, including gliadin 33-mer peptide, peptide spanning residues 57 to 68 of the α9-gliadin (α9-gliadin peptide 57–68), A-gliadin peptide 62–75 and α-gliadin peptide 62–75. During digestion under simulated gastrointestinal conditions, the probiotic preparation markedly hydrolyzed the wheat bread gluten (ca. 18,000 ppm) to less than 10 ppm after 360 min of treatment. Accordingly, the level of cytokines (interleukin 2 [IL-2], IL-10 and interferon gamma) produced by duodenal biopsy specimens of CD patients who consumed wheat bread digested by probiotics were similar to the baseline value (negative control) (Francavilla et al., 2017). While the level of peptidases in humans is insufficient to fully hydrolyze resistant dietary proteins (Garcia-Horsman et al., 2007), several plant and microbial peptidases have the potential to hydrolyze the peptides responsible for the CD immune response, representing the so-called glutenase oral therapy. ALV003 is an oral protease that combines cysteine- and prolyl-endopeptidases, deriving from barley and *Sphingomonas capsulata*, respectively (M'hir et al., 2012). Randomized, double-blind, placebo controlled phase 2 trials (Lähdeaho et al., 2014) demonstrated that ALV003 attenuated the gluten-induced small intestinal injury in CD patients subjected to GFD, consisting on the daily consumption of up to 2 g gluten that was equivalent to one-half standard slice of bread. Other enzymes capable of degrading gluten were present in other bacterial species (e.g., *Flavobacterium meningosepticum*, *Lactobacillus helveticus*, *Myxococcus xanthus*, *Rothia mucilaginosa*, *Pseudomonas aeruginosa*) or *Aspergillus niger* (Gobbetti et al., 2017). A randomized placebo-controlled trial with AN-PEP, which was administered to CD patients who underwent a gluten challenge (7 g/d), showed no difference between placebo and enzyme therapy in the primary end point of

histologic change by Marsh classification (Tack et al., 2013). A combination of probiotic lactobacilli, AN-PEP and other commercially available food-grade enzymes represented a further and complementary strategy to hydrolyze dietary gluten (Scherf et al., 2018). A solution prepared from wheat, rye or barley, which contained all germinating cereal enzymes, was able to degrade gliadin *in vitro* and hydrolyzed gliadin had a reduced capacity to induce harmful effects on intestinal epithelial cells (Stenman et al., 2010).

Traditionally, food fermentations may take place for a very prolonged time (up to 24 h). This is the case of the sourdough fermentation. Fermentation of wheat flour with sourdough caused a considerable increase of the content of free amino acids compared to non-started flour or the use of other leavening agents (Gobbetti et al., 1994). This observation, together with some empirical information coming from the tradition, has promoted a long-time research (De Angelis et al., 2010; Di Cagno et al., 2010, 2004; 2002; Greco et al., 2011), which aimed at fully degrading gluten during sourdough fermentation. The combination of two commercially food-grade fungal proteases, responsible for primary proteolysis, and ten selected biotypes of sourdough lactic acid bacteria, providing a number of proline-specific peptidases and responsible for secondary proteolysis, caused the complete gluten degradation (to less than 10 ppm) during semi-liquid and long-time sourdough fermentation (Rizzello et al., 2007). *In vitro* and *ex-vivo* assays (Di Cagno et al., 2010; Greco et al., 2011), elucidation of the mechanisms to hydrolyze epitopes (De Angelis et al., 2010) and three clinical challenges (Di Cagno et al., 2010; Greco et al., 2011; Mandile et al., 2017) showed how the baked goods made with hydrolyzed gluten were absolutely safe for CD patients.

5.2. Prebiotics

The use of prebiotics for the overall treatment of intestinal diseases remains insufficiently investigated. As naturally occurring in plant-derived compounds, prebiotics are promising and safe additive to GFD with potentially beneficial repercussions on the gut microbiome of CD patients. Indeed, prebiotics selectively stimulate the growth and activity of potentially health-promoting species at the intestinal level, mainly *Bifidobacterium* and *Lactobacillus*. Increased levels of prebiotic inulin-type fructans in a gluten-free bread formula improved the sensory and nutritional features, enabled the calcium absorption, and potentially modulated the gut microbiome (Capriles and Arêas, 2013). The adherence to a GFD supplemented with oligofructose-enriched inulin delivered health benefits to CD children without any side effects, alleviating intestinal inflammation, restoring and stabilizing gut microbial balance, and reversing nutritional deficiencies through enhanced absorption of vitamins and minerals (Krupa-Kozak et al., 2017). Indirectly, the current trend to integrate gluten-free formulae with naturally gluten-free legumes and/or pseudo-cereals represents an important tool to fortify GFD not only with macro and micronutrients but also with relevant levels of fibers, which exert beneficial prebiotic activities (Gobbetti et al., 2019).

5.3. Postbiotics

As the last born into the family, postbiotics are functional bioactive compounds generated in a matrix during fermentation, which promote health. Postbiotics is the umbrella for all microbial fermentation components, which include metabolites, SCFA, microbial cell fractions, functional proteins, extracellular polysaccharides, cell lysates, teichoic acid, peptidoglycan-derived muropeptides and pili-type structures. Current research data indicate that postbiotics may have direct immunomodulatory and clinically relevant effects, and evidence showed the relief of symptoms in a range of diseases such as infant colic, adult atopic dermatitis and different causes of diarrhea (Wegh et al., 2019). Postbiotics may guarantee some technical advantages (e.g., shelf life) with respect to probiotics and represent a novel approach to fortify the GFD, the exploitation of their potential has to be warranted.

6. Conclusion

Avoiding speculations for those consumers who have not recommendations to adhere, the GFD remains the only effective therapy for CD patients. Efforts for improving the nutritional balance with respect to counterparts containing gluten are concretely increasing. Nevertheless, the only partial ability of the GFD to restore the homeostasis of the gut microbiome seems to be somewhat claimed. Indeed, the dysbiosis accompanying CD (cause or consequence of the disease?) is only slightly conditioned. Multifaceted efforts in fortifying the gluten-free formulae with selected nutrients (e.g., fibers) and in the supplementation of the GFD with additives (e.g., biotic family) are the most promising interventions to drive the gut microbiome composition and functionality. Because of the fundamental importance of the gut microbiome homeostasis, further clinical challenges on CD patients following various gluten-free regimens, especially fortified with probiotics, prebiotics and postbiotics, should be warranted.

Declaration of competing interest

With this statement, the authors of manuscript titled "**Gluten-free diet and gut microbiome**" certify that they have NO affiliations with or involvement in any organization or entity with any financial interest (such as honoraria; educational grants; participation in speakers' bureaus; membership, employment, consultancies, stock ownership, or other equity interest; and expert testimony or patent-licensing arrangements), or non-financial interest (such as personal or professional relationships, affiliations, knowledge or beliefs) in the subject matter or materials discussed in this manuscript.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jcs.2020.103058.

References

Acar, S., Yetkiner, A.A., Ersin, N., Oncag, O., Aydogdu, S., Arikan, C., 2012. Oral findings and salivary parameters in children with celiac disease: a preliminary study. Med. Princ. Pract. 21, 129–133. https://doi.org/10.1159/000331794.

Baba, N., Samson, S., Bourdet-Sicard, R., Rubio, M., Sarfati, M., 2008. Commensal bacteria trigger a full dendritic cell maturation program that promotes the expansion of non-Tr1 suppressor T cells. J. Leukoc. Biol. 84, 468–476. https://doi.org/10.1189/jlb.0108017.

Baranska, A., Tigchelaar, E., Smolinska, A., Dallinga, J.W., Moonen, E.J.C., Dekens, J.A. M., Wijmenga, C., Zhernakova, A., Van Schooten, F.J., 2013. Profile of volatile organic compounds in exhaled breath changes as a result of gluten-free diet. J. Breath Res. 7 https://doi.org/10.1088/1752-7155/7/3/037104.

Bascuñán, K.A., Araya, M., Roncoroni, L., Doneda, L., Elli, L., 2019. Dietary gluten as a conditioning factor of the gut microbiota in celiac disease. Adv. Nutr. 11, 160–174. https://doi.org/10.1093/advances/nmz080.

Bertini, I., Calabró, A., De Carli, V., Luchinat, C., Nepi, S., Porfirio, B., Renzi, D., Saccenti, E., Tenori, L., 2009. The metabonomic signature of celiac disease. J. Proteome Res. 8, 170–177. https://doi.org/10.1021/pr800548z.

Bodkhe, R., Shetty, S.A., Dhotre, D.P., Verma, A.K., Bhatia, K., Mishra, A., Kaur, G., Pande, P., Bangarusamy, D.K., Santosh, B.P., Perumal, R.C., Ahuja, V., Shouche, Y.S., Makharia, G.K., 2019. Comparison of small gut and whole gut microbiota of first-degree relatives with adult celiac disease patients and controls. Front. Microbiol. 10, 137–140. https://doi.org/10.3389/fmicb.2019.00164.

Bonder, M.J., Tigchelaar, E.F., Cai, X., Trynka, G., Cenit, M.C., Hrdlickova, B., Zhong, H., Vatanen, T., Gevers, D., Wijmenga, C., Wang, Y., Zhernakova, A., 2016. The influence of a short-term gluten-free diet on the human gut microbiome. Genome Med. 8, 1–11. https://doi.org/10.1186/s13073-016-0295-y.

Cani, P.D., Bibiloni, R., Knauf, C., Neyrinck, A.M., Delzenne, N.M., 2008. Changes in gut microbiota control metabolic diet–induced obesity and diabetes in mice. Diabetes 57, 1470–1481. https://doi.org/10.2337/db07-1403.Additional.

Capriles, V.D., Arêas, J.A.G., 2013. Effects of prebiotic inulin-type fructans on structure, quality, sensory acceptance and glycemic response of gluten-free breads. Food Funct 4, 104–110. https://doi.org/10.1039/c2fo10283h.

Cheng, J., Kalliomäki, M., Heilig, H.G.H.J., Palva, A., Lähteenoja, H., de Vos, W.M., Salojärvi, J., Satokari, R., 2013. Duodenal microbiota composition and mucosal homeostasis in pediatric celiac disease. BMC Gastroenterol. 13 https://doi.org/10.1186/1471-230X-13-113.

Cohen, I.S., Day, A.S., Shaoul, R., 2019. Gluten in celiac disease more or less? Rambam Maimonides Med. J. 10, 1–6. https://doi.org/10.5041/RMMJ.10360.

Collado, M.C., Calabuig, M., Sanz, Y., 2007. Differences between the fecal microbiota of coeliac infants and healthy controls. Curr. Issues Intest. Microbiol. 8, 9–14.
Collado, M.C., Donat, E., Ribes-Koninckx, C., Calabuig, M., Sanz, Y., 2009. Specific duodenal and faecal bacterial groups associated with paediatric coeliac disease. J. Clin. Pathol. 62, 264–269. https://doi.org/10.1136/jcp.2008.061366.
Collado, M.C., Donat, E., Ribes-Koninckx, C., Calabuig, M., Sanz, Y., 2008. Imbalances in faecal and duodenal Bifidobacterium species composition in active and non-active coeliac disease. BMC Microbiol. 8, 1–9. https://doi.org/10.1186/1471-2180-8-232.
D'Arienzo, R., Stefanile, R., Maurano, F., Mazzarella, G., Ricca, E., Troncone, R., Auricchio, S., Rossi, M., 2011. Immunomodulatory effects of Lactobacillus casei administration in a mouse model of gliadin-sensitive enteropathy. Scand. J. Immunol. 74, 335–341. https://doi.org/10.1111/j.1365-3083.2011.02582.x.
De Angelis, M., Cassone, A., Rizzello, C.G., Gagliardi, F., Minervini, F., Calasso, M., Di Cagno, R., Francavilla, R., Gobbetti, M., 2010. Mechanism of degradation of immunogenic gluten epitopes from triticum turgidum L. var. durum by sourdough lactobacilli and fungal proteases. Appl. Environ. Microbiol. 76, 508–518. https://doi.org/10.1128/AEM.01630-09.
De Angelis, M., Rizzello, C.G., Fasano, A., Clemente, M.G., Simone, C. De, Silano, M., Vincenzi, M. De, Losito, I., Gobbetti, M., 2006. VSL#3 probiotic preparation has the capacity to hydrolyze gliadin polypeptides responsible for Celiac Sprue. Biochim. Biophys. Acta (BBA) - Mol. Basis Dis. 1762, 80–93. https://doi.org/10.1016/j.bbadis.2005.09.008.
De Angelis, M., Vannini, L., Di, R., Cavallo, N., Minervini, F., Francavilla, R., Ercolini, D., Gobbetti, M., 2016. Salivary and fecal microbiota and metabolome of celiac children under gluten-free diet. Int. J. Food Microbiol. 239, 125–132. https://doi.org/10.1016/j.ijfoodmicro.2016.07.025.
De Palma, G., Nadal, I., Collado, M.C., Sanz, Y., 2009. Effects of a gluten-free diet on gut microbiota and immune function in healthy adult human subjects. Br. J. Nutr. 102, 1154–1160. https://doi.org/10.1017/S0007114509371767.
De Palma, G., Nadal, I., Medina, M., Donat, E., Ribes-Koninckx, C., Calabuig, M., Sanz, Y., 2010. Intestinal dysbiosis and reduced immunoglobulin-coated bacteria associated with coeliac disease in children. BMC Microbiol. 10, 1–7. https://doi.org/10.1186/1471-2180-10-63.
Di Cagno, R., Barbato, M., Di Camillo, C., Rizzello, C.G., De Angelis, M., Giuliani, G., De Vincenzi, M., Gobbetti, M., Cucchiara, S., 2010. Gluten-free sourdough wheat baked goods appear safe for young celiac patients: a pilot study. J. Pediatr. Gastroenterol. Nutr. 51, 777–783. https://doi.org/10.1097/MPG.0b013e3181f22ba4.
Di Cagno, R., De Angelis, M., Auricchio, S., Greco, L., Clarke, C., De Vincenzi, M., Giovannini, C., D'Archivio, M., Landolfo, F., Parrilli, G., Minervini, F., Arendt, E., Gobbetti, M., 2004. Sourdough bread made from wheat and non-toxic flours and started with selected lactobacilli is tolerated in Celiac Sprue patients. Appl. Environ. Microbiol. 70, 1088–1096. https://doi.org/10.1128/AEM.70.2.1088-1096.2004.
Di Cagno, R., De Angelis, M., De Pasquale, I., Ndagijimana, M., Vernocchi, P., Ricciuti, P., Gagliardi, F., Laghi, L., Crecchio, C., Guerzoni, M., Gobbetti, M., Francavilla, R., 2011. Duodenal and faecal microbiota of celiac children: molecular, phenotype and metabolome characterization. BMC Microbiol. 11, 1–21. https://doi.org/10.1186/1471-2180-11-219.
Di Cagno, R., De Angelis, M., Lavermicocca, P., De Vincenzi, M., Giovannini, C., Faccia, M., Gobbetti, M., 2002. Proteolysis by sourdough lactic acid bacteria: effects on wheat flour protein fractions and gliadin peptides involved in human cereal intolerance. Appl. Environ. Microbiol. 68, 623–633. https://doi.org/10.1128/AEM.68.2.623-633.2002.
Di Cagno, R., Rizzello, C.G., Gagliardi, F., Ricciuti, P., Ndagijimana, M., Francavilla, R., Guerzoni, M.E., Crecchio, C., Gobbetti, M., De Angelis, M., 2009. Different fecal microbiotas and volatile organic compounds in treated and untreated children with celiac disease. Appl. Environ. Microbiol. 75, 3963–3971. https://doi.org/10.1128/AEM.02793-08.
Dieterich, W., Zopf, Y., 2019. Gluten and FODMAPS — sense of a restriction/when is restriction necessary? Nutrients 11, 1–12. https://doi.org/10.3390/nu11081957.
Ercolini, D., Francavilla, R., Vannini, L., Filippis, F. De, 2015. From an imbalance to a new imbalance : Italian-style gluten-free diet alters the salivary microbiota and metabolome of African celiac children. Sci. Rep. 5, 1–11. https://doi.org/10.1038/srep18571.
Eu law 41, 2009. Commission regulation (EC) No 41/2009. EUR-Lex. Available online. https://eur-lex.europa.eu/legal-content/EN/TXT/?uri=celex:32009R0041.
Fernandez-Feo, M., Wei, G., Blumenkranz, G., Dewhirst, F.E., Schuppan, D., Oppenheim, F.G., Helmerhorst, E.J., 2013. The cultivable human oral gluten-degrading microbiome and its potential implications in coeliac disease and gluten sensitivity. Clin. Microbiol. Infect. 19 https://doi.org/10.1111/1469-0691.12249.
Fischbach, M.A., Segre, J.A., 2016. Signaling in host-associated microbial communities. Cell 164, 1288–1300. https://doi.org/10.1016/j.cell.2016.02.037.
Francavilla, R., De Angelis, M., Rizzello, C.G., Cavallo, N., Dal Bello, F., Gobbetti, M., 2017. Selected probiotic lactobacilli have the capacity to hydrolyze gluten peptides during simulated gastrointestinal digestion. Appl. Environ. Microbiol. 83, 1–12. https://doi.org/10.1128/AEM.00376-17.
Francavilla, R., Ercolini, D., Piccolo, M., Vannini, L., Siragusa, S., De Filippis, F., De Pasquale, I., Di Cagno, R., Di Toma, M., Gozzi, G., Serrazanetti, D.I., De Angelis, M., Gobbetti, M., 2014. Salivary microbiota and metabolome associated with celiac disease. Appl. Environ. Microbiol. 80, 3416–3425. https://doi.org/10.1128/AEM.00362-14.
Francavilla, R., Piccolo, M., Francavilla, A., Polimeno, L., Semeraro, F., Cristofori, F., Castellaneta, S., Barone, M., Indrio, F., 2019. Clinical and microbiological effect of a multispecies probiotic supplementation in celiac patients with persistent IBS-type symptoms: a randomized, double-blind, placebo-controlled, multicenter trial. J. Clin. Gastroenterol. 53, 1–9. https://doi.org/10.1097/MCG.0000000000001023.
Garcia-Horsman, J.A., Venäläinen, J.I., Lohi, O., Auriola, I.S., Korponay-Szabo, I.R., Kaukinen, K., Mäki, M., Männistö, P.T., 2007. Deficient activity of mammalian prolyl oligopeptidase on the immunoactive peptide digestion in coeliac disease. Scand. J. Gastroenterol. 42, 562–571. https://doi.org/10.1080/00365520601019819.
Garcia-Mazcorro, J.F., Rivera-Gutierrez, X., Cobos-Quevedo, O. de J., Grube-Pagola, P., Meixueiro-Daza, A., Hernandez-Flores, K., Cabrera-Jorge, F.J., Vivanco-Cid, H., Dowd, S.E., Remes-Troche, J.M., 2018. First insights into the gut microbiota of Mexican patients with celiac disease and non-celiac gluten sensitivity. Nutrients 10, 1–19. https://doi.org/10.3390/nu10111641.
Gobbetti, M., De Angelis, M., Di Cagno, R., Polo, A., Rizzello, C.G., 2019. The sourdough fermentation is the powerful process to exploit the potential of legumes, pseudo-cereals and milling by-products in baking industry. Crit. Rev. Food Sci. Nutr. 1–16. https://doi.org/10.1080/10408398.2019.1631753.
Gobbetti, M., Pontonio, E., Filannino, P., Giuseppe, C., Angelis, M. De, 2017. How to improve the gluten-free diet : the state of the art from a food science perspective. Food Res. Int. 110, 22–32. https://doi.org/10.1016/j.foodres.2017.04.010.
Gobbetti, M., Simonetti, M.S., Rossi, J., Cossignani, L., Corsetti, A., Damiani, P., 1994. Free D- and L-amino acid evolution during sourdough fermentation and baking. J. Food Sci. 59, 881–884. https://doi.org/10.1111/j.1365-2621.1994.tb08149.x.
Golfetto, L., de Senna, F.D., Hermes, J., Beserra, B.T.S., Franca, F. da S., Martinello, F., 2014. Lower Bifidobacteria counts in adult patients with celiac disease on a gluten-free diet. Arq. Gastroenterol. 51, 139–143. https://doi.org/10.1590/s0004-28032014000200013.
Greco, L., Gobbetti, M., Auricchio, R., Di Mase, R., Landolfo, F., Paparo, F., Di Cagno, R., De Angelis, M., Rizzello, C.G., Cassone, A., Terrone, G., Timpone, L., D'Aniello, M., Maglio, M., Troncone, R., Auricchio, S., 2011. Safety for patients with celiac disease of baked goods made of wheat flour hydrolyzed during food processing. Clin. Gastroenterol. Hepatol. 9, 24–29. https://doi.org/10.1016/j.cgh.2010.09.025.
Gujral, N., Freeman, H.J., Thomson, A.R.B., 2012. Celiac disease: prevalence, diagnosis, pathogenesis and treatment. World J. Gastroenterol. 18 (42), 6036–6059.
Harnett, J., Myers, S.P., Rolfe, M., 2017. Significantly higher faecal counts of the yeasts candida and saccharomyces identified in people with coeliac disease. Gut Pathog. 9, 1–8. https://doi.org/10.1186/s13099-017-0173-1.
Harnett, J., Myers, S.P., Rolfe, M., 2016. Probiotics and the microbiome in celiac disease: a randomised controlled trial. Evidence-based Complement. Alternative Med. 1–16. https://doi.org/10.1155/2016/9048574.
Herrán, A.R., Pérez-Andrés, J., Caminero, A., Nistal, E., Vivas, S., Ruiz de Morales, J.M., Casqueiro, J., 2017. Gluten-degrading bacteria are present in the human small intestine of healthy volunteers and celiac patients. Res. Microbiol. 168, 673–684. https://doi.org/10.1016/j.resmic.2017.04.008.
Krupa-Kozak, U., Drabi, N., Jarocka-cyrta, E., 2017. The effect of oligofructose-enriched inulin supplementation on gut microbiota, nutritional status and gastrointestinal symptoms in paediatric coeliac disease patients on a gluten-free diet : study protocol for a pilot randomized controlled trial. Nutr. J. 16, 1–9. https://doi.org/10.1186/s12937-017-0268-z.
Kumar, P.S., Griffen, A.L., Moeschberger, M.L., Leys, E.J., 2005. Identification of candidate periodontal pathogens and beneficial species by quantitative 16S clonal analysis. J. Clin. Microbiol. 43, 3944–3955. https://doi.org/10.1128/JCM.43.8.3944-3955.2005.
Lähdeaho, M.L., Kaukinen, K., Laurila, K., Vuotikka, P., Koivurova, O.P., Kärjä-Lahdensuu, T., Marcantonio, A., Adelman, D.C., Mäki, M., 2014. Glutenase ALV003 attenuates gluten-induced mucosal injury in patients with celiac disease. Gastroenterology 146. https://doi.org/10.1053/j.gastro.2014.02.031, 1649–16.
Lai, P.Y., Cottingham, K.L., Steinmaus, C., Karagas, M.R., Miller, M.D., 2015. Arsenic and rice: translating research to address health care providers' needs. J. Pediatr. 167, 797–803. https://doi.org/10.1016/j.jpeds.2015.07.003.
Lammers, K.M., Herrera, M.G., Dodero, V.I., 2018. Translational chemistry meets gluten-related disorders. Chemistry 7, 217–232. https://doi.org/10.1002/open.201700197.
Laparra, J.M., 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. https://doi.org/10.1002/jcb.22459.
Lindfors, K., Blomqvist, T., Juuti-Uusitalo, K., Stenman, S., Venäläinen, J., Mäki, M., Kaukinen, K., 2008. Live probiotic Bifidobacterium lactis bacteria inhibit the toxic effects induced by wheat gliadin in epithelial cell culture. Clin. Exp. Immunol. 152, 552–558. https://doi.org/10.1111/j.1365-2249.2008.03635.x.
Lis, D.M., Stellingwerff, T., Shing, C.M., Ahuja, K.D.K., Fell, J.W., 2015. Exploring the popularity, experiences, and beliefs surrounding gluten-free diets in non-celiac athletes. Int. J. Sport Nutr. Exerc. Metabol. 25, 37–45. https://doi.org/10.1123/ijsnem.2013-0247.
M'hir, S., Manel, Z., Chammem, N., Hamdi, M., 2012. Gluten proteolysis as alternative therapy for celiac patients: a mini-review. Afr. J. Biotechnol. 11, 7323–7330. https://doi.org/10.5897/AJB11.726.
Mandile, R., Picascia, S., Parrella, C., Camarca, A., Gobbetti, M., Greco, L., Troncone, R., Gianfrani, C., Auricchio, R., 2017. Lack of immunogenicity of hydrolysed wheat flour in patients with coeliac disease after a short-term oral challenge. Aliment. Pharmacol. Ther. https://doi.org/10.1111/apt.14175.
Mariani, P., Viti, M.G., Montuori, M., La Vecchia, A., Cipolletta, E., Calvani, L., Bonamico, M., 1998. The gluten-free diet: a nutritional risk factor for adolescents with celiac disease? J. Pediatr. Gastroenterol. Nutr. https://doi.org/10.1097/00005176-199811000-00004.
Medina, M., De Palma, G., Ribes-Koninckx, C., Calabuig, M., Sanz, Y., 2008. Bifidobacterium strains suppress in vitro the pro-inflammatory milieu triggered by the large intestinal microbiota of coeliac patients. J. Inflamm. 5 https://doi.org/10.1186/1476-9255-5-19.

Melini, V., Melini, F., 2019. Gluten-free diet: gaps and needs for a healthier diet. Nutrients 11. https://doi.org/10.3390/nu11010170.
Mina, S., Riga, C., Azcurra, A.I., Brunotto, M., 2012. Oral ecosystem alterations in celiac children: a follow-up study. Arch. Oral Biol. 57, 154–160. https://doi.org/10.1016/j.archoralbio.2011.08.017.
Mina, S.S., Azcurra, A.I., Dorronsoro, S., Brunotto, M.N., 2008. Alterations of the oral ecosystem in children with celiac disease. Acta Odontol. Latinoam. 21, 121–126.
Miranda, J., Lasa, A., Bustamante, M.A., Churruca, I., Simon, E., 2014. Nutritional differences between a gluten-free diet and a diet containing equivalent products with gluten. Plant Foods Hum. Nutr. 69, 182–187. https://doi.org/10.1007/s11130-014-0410-4.
Nadal, I., Donant, 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. https://doi.org/10.1099/jmm.0.47410-0.
Nistal, E., Caminero, A., Herrán, A.R., Arias, L., Vivas, S., Ruiz De Morales, J.M., Calleja, S., Sáenz De Miera, L.E., Arroyo, P., Casqueiro, J., 2012a. 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. https://doi.org/10.1002/ibd.21830.
Nistal, E., Caminero, A., Herrán, A.R., Pérez-Andres, J., Vivas, S., Ruiz de Morales, J.M., Sáenz de Miera, L.E., Casqueiro, J., 2016. Study of duodenal bacterial communities by 16S rRNA gene analysis in adults with active celiac disease vs non-celiac disease controls. J. Appl. Microbiol. 120, 1691–1700. https://doi.org/10.1111/jam.13111.
Nistal, E., Caminero, A., Vivas, S., Ruiz De Morales, J.M., Sáenz De Miera, L.E., Rodríguez-Aparicio, L.B., Casqueiro, J., 2012b. Differences in faecal bacteria populations and faecal bacteria metabolism in healthy adults and celiac disease patients. Biochimie 94, 1724–1729. https://doi.org/10.1016/j.biochi.2012.03.025.
Öhlund, K., Olsson, C., Hernell, O., Öhlund, I., 2010. Dietary shortcomings in children on a gluten-free diet. J. Hum. Nutr. Diet. 23, 294–300. https://doi.org/10.1111/j.1365-277X.2010.01060.x.
Olivares, M., Castillejo, G., Varea, V., Sanz, Y., 2014a. 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. https://doi.org/10.1017/S0007114514000609.
Olivares, M., Neef, A., Castillejo, G., De Palma, G., Varea, V., Capilla, A., Palau, F., Nova, E., Marcos, A., Polanco, I., Ribes-Koninckx, C., Ortigosa, L., Izquierdo, L., Sanz, Y., 2014b. The HLA-DQ2 genotype selects for early intestinal microbiota composition in infants at high risk of developing coeliac disease. Gut 64, 406–417. https://doi.org/10.1136/gutjnl-2014-306931.
Ou, G., Hedberg, M., Hörstedt, P., Baranov, V., Forsberg, G., Drobni, M., Sandström, O., Wai, S.N., Johansson, I., Hammarström, M.L., Hernell, O., Hammarström, S., 2009. Proximal small intestinal microbiota and identification of rod-shaped bacteria associated with childhood celiac disease. Am. J. Gastroenterol. 104, 3058–3067. https://doi.org/10.1038/ajg.2009.524.
Penagini, F., Dilillo, D., Meneghin, F., Mameli, C., Fabiano, V., Zuccotti, G.V., 2013. Gluten-free diet in children: an approach to a nutritionally adequate and balanced diet. Nutrients 5, 4553–4565. https://doi.org/10.3390/nu5114553.
Pozo-Rubio, T., Olivares, M., Nova, E., De Palma, G., Mujico, J.R., Ferrer, M.D., Marcos, A., Sanz, Y., 2012. Immune development and intestinal microbiota in celiac disease. Clin. Dev. Immunol. 1–12. https://doi.org/10.1155/2012/654143.
Primec, M., Klemenak, M., Di Gioia, D., Aloisio, I., Bozzi Cionci, N., Quagliariello, A., Gorenjak, M., Mičetić-Turk, D., Langerholc, T., 2019. Clinical intervention using Bifidobacterium strains in celiac disease children reveals novel microbial modulators of TNF-α and short-chain fatty acids. Clin. Nutr. 38, 1373–1381. https://doi.org/10.1016/j.clnu.2018.06.931.
Quagliariello, A., Aloisio, I., Bozzicionci, N., Luiselli, D., D'Auria, G., Martinez-Priego, L., Pérez-Villarroya, D., Langerholc, T., Primec, M., Mičetić-Turk, D., Di Gioia, D., 2016. Effect of Bifidobacterium breve on the intestinal microbiota of coeliac children on a gluten free diet: a pilot study. Nutrients 8, 1–16. https://doi.org/10.3390/nu8100660.
Reddel, S., Putignani, L., Chierico, F. Del, 2019. The impact of low-FODMAPs, gluten-free, and ketogenic diets on gut microbiota modulation in pathological conditions. Nutrients 11, 373. https://doi.org/10.3390/nu11020373.
Reilly, N.R., 2016. The gluten-free diet: recognizing fact, fiction, and fad. J. Pediatr. 175, 206–210. https://doi.org/10.1016/j.jpeds.2016.04.014.
Rizzello, C.G., De Angelis, M., Di Cagno, R., Camarca, A., Silano, M., Losito, I., De Vincenzi, M., De Bari, M.D., Palmisano, F., Maurano, F., Gianfrani, C., Gobbetti, M., 2007. Highly efficient gluten degradation by lactobacilli and fungal proteases during food processing: new perspectives for celiac disease. Appl. Environ. Microbiol. 73, 4499–4507. https://doi.org/10.1128/AEM.00260-07.
Roma, E., Roubani, A., Kolia, E., Panayiotou, J., Zellos, A., Syriopoulou, V.P., 2010. Dietary compliance and life style of children with coeliac disease. J. Hum. Nutr. Diet. 23, 176–182. https://doi.org/10.1111/j.1365-277X.2009.01036.x.
Sánchez, E., Donat, E., Ribes-Koninckx, C., Calabuig, M., Sanz, Y., 2010. Intestinal Bacteroides species associated with coeliac disease. J. Clin. Pathol. 63, 1105–1111. https://doi.org/10.1136/jcp.2010.076950.
Sánchez, E., Donat, E., Ribes-Koninckx, C., Fernández-Murga, M.L., Sanz, Y., 2013. Duodenal-mucosal bacteria associated with celiac disease in children. Appl. Environ. Microbiol. 79, 5472–5479. https://doi.org/10.1128/AEM.00869-13.
Sánchez, E., Laparra, J.M., Sanz, Y., 2012a. Discerning the role of Bacteroides fragilis in celiac disease pathogenesis. Appl. Environ. Microbiol. 78, 6507–6515. https://doi.org/10.1128/AEM.00563-12.
Sánchez, E., Ribes-Koninck, C., Calabuig, M., Sanz, Y., 2012b. Intestinal Staphylococcus spp. and virulent features associated with coeliac disease. J. Clin. Pathol. 65, 830–834. https://doi.org/10.1136/jclinpath-2012-200759.
Sanz, Y., Sánchez, E., Marzotto, M., Calabuig, M., Torriani, S., Dellaglio, F., 2007. Differences in faecal bacterial communities in coeliac and healthy children as detected by PCR and denaturing gradient gel electrophoresis. FEMS Immunol. Med. Microbiol. 51, 562–568. https://doi.org/10.1111/j.1574-695X.2007.00337.x.
Sanz, Y., 2015. Microbiome and gluten. Ann. Nutr. Metab. 67, 28–41. https://doi.org/10.1159/000440991.
Scherf, K.A., Wieser, H., Koehler, P., 2018. Novel approaches for enzymatic gluten degradation to create high-quality gluten-free products. Food Res. Int. 110, 62–67. https://doi.org/10.1016/j.foodres.2016.11.021.
Schippa, S., Iebba, V., Barbato, M., Di Nardo, G., Totino, V., Checchi, M.P., Longhi, C., Maiella, G., Cucchiara, S., Conte, M.P., 2010. A distinctive "microbial signature" in celiac pediatric patients. BMC Microbiol. 10, 1–10. https://doi.org/10.1186/1471-2180-10-175.
Shepherd, S.J., Gibson, P.R., 2013. Nutritional inadequacies of the gluten-free diet in both recently-diagnosed and long-term patients with coeliac disease. J. Hum. Nutr. Diet. 26, 349–358. https://doi.org/10.1111/jhn.12018.
Singh, P., Arora, A., Strand, T.A., Leffler, D.A., Catassi, C., Green, P.H., Kelly, C.P., Ahuja, V., Makharia, G.K., 2018. Global prevalence of celiac disease: systematic review and meta-analysis. Clin. Gastroenterol. Hepatol. 16, 823–836. https://doi.org/10.1016/j.cgh.2017.06.037.
Stenman, S.M., Lindfors, K., Venäläinen, J.I., Hautala, A., Männistö, P.T., Garcia-Horsman, J.A., Kaukovirta-Norja, A., Auriola, S., Mauriala, T., Mäki, M., Kaukinen, K., 2010. Degradation of coeliac disease-inducing rye secalin by germinating cereal enzymes: diminishing toxic effects in intestinal epithelial cells. Clin. Exp. Immunol. 161, 242–249. https://doi.org/10.1111/j.1365-2249.2010.04119.x.
Tack, G.J., van de Water, J.M.W., Bruins, M.J., Kooy-Winkelaar, E.M.C., van Bergen, J., Bonnet, P., Vreugdenhil, A.C.E., Korponay-Szabo, I., Edens, L., von Blomberg, B.M. E., Schreurs, M.W.J., Mulder, C.J., Koning, F., 2013. Consumption of gluten with gluten-degrading enzyme by celiac patients: a pilot-study. World J. Gastroenterol. 19, 5837–5847. https://doi.org/10.3748/wjg.v19.i35.5837.
Thompson, T., 2000. Folate, iron, and dietary fiber contents of the gluten-free diet. J. Am. Diet Assoc. 100, 1389–1396. https://doi.org/10.1016/S0002-8223(00)00386-2.
Thompson, T., Dennis, M., Higgins, L.A., Lee, A.R., Sharrett, M.K., 2005. Gluten-free diet survey: are Americans with coeliac disease consuming recommended amounts of fibre, iron, calcium and grain foods? J. Hum. Nutr. Diet. 18, 163–169. https://doi.org/10.1111/j.1365-277X.2005.00607.x.
Van Hees, N.J.M., Giltay, E.J., Tielemans, S.M.A.J., Geleijnse, J.M., Puvill, T., Janssen, N., Van Der Does, W., 2015. Essential amino acids in the gluten-free diet and serum in relation to depression in patients with celiac disease. PloS One 10. https://doi.org/10.1371/journal.pone.0122619.
Vici, G., Belli, L., Biondi, M., Polzonetti, V., 2016. Gluten free diet and nutrient deficiencies: a review. Clin. Nutr. 1–6 https://doi.org/10.1016/j.clnu.2016.05.002.
Vitali, B., Ndagijimana, M., Cruciani, F., Carnevali, P., Candela, M., Guerzoni, M.E., Brigidi, P., 2010. Impact of a synbiotic food on the gut microbial ecology and metabolic profiles. BMC Microbiol. 10 https://doi.org/10.1186/1471-2180-10-4.
Wacklin, P., Kaukinen, K., Tuovinen, E., Collin, P., Lindfors, K., Partanen, J., Mäki, M., Mättuö, J., 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. https://doi.org/10.1097/MIB.0b013e31828029a9.
Wacklin, P., Laurikka, P., Lindfors, K., Collin, P., Salmi, T., Lähdeaho, M.L., Saavalainen, P., Mäki, M., Mättö, J., Kurppa, K., Kaukinen, K., 2014. Altered duodenal microbiota composition in celiac disease patients suffering from persistent symptoms on a long-term gluten-free diet. Am. J. Gastroenterol. 109, 1933–1941. https://doi.org/10.1038/ajg.2014.355.
Wegh, C.A.M., Geerlings, S.Y., Knol, J., Roeselers, G., Belzer, C., 2019. Postbiotics and their potential applications in early life nutrition and beyond. Int. J. Mol. Sci. 20, 1–23. https://doi.org/10.3390/ijms20194673.
Welstead, L., 2015. The gluten-free diet in the 3rd millennium: rules, risks and opportunities. Diseases 3, 136–149. https://doi.org/10.3390/diseases3030136.
Wild, C.P., Gong, Y.Y., 2009. Mycotoxins and human disease: a largely ignored global health issue. Carcinogenesis 31, 71–82. https://doi.org/10.1093/carcin/bgp264.
Zarco, M.F., Vess, T.J., Ginsburg, G.S., 2012. The oral microbiome in health and disease and the potential impact on personalized dental medicine. Oral Dis. 18, 109–120. https://doi.org/10.1111/j.1601-0825.2011.01851.x.
Zeng, J., Li, Y.Q., Zuo, X.L., Zhen, Y.B., Yang, J., Liu, C.H., 2008. Clinical trial: effect of active lactic acid bacteria on mucosal barrier function in patients with diarrhoea-predominant irritable bowel syndrome. Aliment. Pharmacol. Ther. 28, 994–1002. https://doi.org/10.1111/j.1365-2036.2008.03818.x.
Zmora, N., Suez, J., Elinav, E., 2019. You are what you eat: diet, health and the gut microbiota. Nat. Rev. Gastroenterol. Hepatol. 16, 35–56. https://doi.org/10.1038/s41575-018-0061-2.
Zuccotti, G., Fabiano, V., Dilillo, D., Picca, M., Cravidi, C., Brambilla, P., 2013. Intakes of nutrients in Italian children with celiac disease and the role of commercially available gluten-free products. J. Hum. Nutr. Diet. 26, 436–444. https://doi.org/10.1111/jhn.12026.