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Coeliac Disease: Gluten Free Diet and… What Else?

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Abstract

Coeliac Disease (CD) is a permanent gluten intolerance, whose pathogenesis involves multiple factors including genetics and environment. CD has different representations and non-specific symptoms such as diarrhea, bloating, pain, flatulence and constipation may sometimes be misleading. Once diagnosed of CD, patients must adhere to Gluten Free Diet, which consists in the lifelong avoidance of gluten containing foods and of those naturally gluten free but at risk of contamination. This dietary approach is considered the only therapy in order to avoid symptoms exacerbation and to reduce the digestive mucosa inflammation, which has been related to higher risks of lymphoproliferative malignancy and other immunological disorders. However, being on a Gluten Free Diet is not as resolving as it may seem since it has several criticalities. First of all, excluding gluten means limiting food variety so that coeliac patients may have unbalanced intake of several nutrients and develop clinical or subclinical deficiencies. This can be due to scarce attention to qualitative and quantitative composition of diets and poor information about gluten-containing foods, which only patient-tailored dietetic protocol and long-term follow-up can achieve. Secondly, Gluten Free Diet may not result in complete remission of mucosal damage or in resolution of symptoms. Unintentional contamination of gluten or poor adherence to diet are the main culprits of the incomplete mucosal healing but other triggers may be involved. Recent research has focused on the role of FODMAPs in changing gut microbiota and on the improvement of Irritable Bowel Syndrome (IBS) symptoms after their dietary avoidance or reduction. Since CD and IBS may share many clinical presentations, further studies are needed to evaluate if a subgroup of CD patients whose symptoms are not improved by Gluten Free Diet could benefit from a new therapeutic approach consisting in both gluten/wheat and FODMAPs avoidance.

Keywords

Celiac Disease, FODMAPs Diet, Nutritional Deficiencies, Gluten Free Diet

1. Introduction

Coeliac Disease (CD) is a permanent gluten intolerance, related to an abnormal immune response against the two main gluten proteins: glutenin and gliadin. It is a multifactorial condition, since genetics and environmental factors are both involved. Typical symptoms are consequential to intestinal functional impairment and malabsorption: diarrhoea, height and weight growth failure (stunting and wasting), vomiting, unexpected weight loss, dermatitis herpetiformis, asthenia... but others are consequences of abnormal immune activation.

CD has also a different representation, characterized by atypical and non-specific symptoms. For instance, bloating, abdominal pain, flatulence, fatigue, anaemia, infertility or repeated miscarriages are common. More severe conditions are neurological pathologies, altered liver function, mouth ulcers, depression, osteoporosis [1]. According to World Gastroenterology Organisation, CD prevalence in Western countries is around 1%, affecting females and male with a ratio from 1:3 to 1:5 [2], but the heterogeneity of symptoms suggests that many cases are not diagnosed. CD represents a real healthcare challenge; although since progress in technology and in scientific research, the only therapy still known is the Gluten Free Diet, which consists in the complete avoidance of gluten containing foods and of those naturally gluten free but at risk of contamination by the formers. The pathophysiological rationale to Gluten Free Diet is that, since CD is an impaired systemic immune response triggered and maintained by gluten, a complete dietary elimination of this protein leads to resolution or improvement of the chronic inflammation of intestinal mucosae. More recently, the research has focused also on the importance of gut microbiota impairment in CD, for its essential role in the development, modulation and function of the host's defense immunity [3]. As we previously reviewed by analyzing the key role of microbiota in the etiopathogenesis of Inflammatory Bowel Disease (IBD) [4], dysbiosis can be responsible for symptoms of conditions like Crohn Disease and Ulcerative Colitis. Since microbiota composition is regulated by multiple factors such as diet, immune system, genetics, intestinal permeability, it has been hypothesized that gluten could also change gut flora and its interactions with immune systems and environment.

This perspective must be considered when following a Gluten Free Diet, since—as De Palma and colleagues [5] revealed—it remarkably changes gut microbiota composition.

Lifelong adherence to Gluten Free Diet is considered the only therapy in order to avoid symptoms exacerbation and reduce the digestive mucosa insult, which has been related to higher risks of lymphoproliferative malignancy and other immunological disorders [6] [7].

However, according to available literature, being on a Gluten Free Diet is not the magic bullet of CD patients. First of all, excluding gluten means limiting food variety so that coeliac patients may have unbalanced intake of several nutrients and develop clinical or subclinical deficiencies [8]. This is mainly due to the common belief that giving to patients a list of food to avoid is enough in treating CD. On the contrary, attention must be given both to qualitative and quantitative composition of diets and general information about gluten-containing food is just a part of a patient-tailored dietetic protocol and of a long-term follow-up [9] [10]. Another level of criticality of the Gluten Free Diet is the not complete remission of mucosal damage since many authors showed the persistence of a low-grade inflammation [11] and villous atrophy [12] [13]. Unintentional contamination of gluten [14] or poor adherence to diet [15] [16] are the main culprits of the incomplete mucosal healing but other triggers may be involved.

2. Gluten Free Diet and Nutritional Adequacy

Speaking of Gluten Free products, every country has its own laws but generally foods and drinks can be considered Gluten Free if they contain up to 20 ppm gluten (20 mg/kg) [17]. Table 1 lists both foods which naturally does not contain gluten and those representing the Gluten Free "counterparts" of traditional gluten containing products.

One of the eldest data about nutritional adequacy of Gluten Free Diet appeared in 1995, when Kemppainen and colleagues analyzed serum concentrations of haemoglobin, ferritin, iron, vitamin B 12 and erythrocyte folate in coeliac patients, showing that these biochemical parameters were below the reference values despite adherence to diet [18]. More recently, Öhlund *et al.* compared the Nordic Nutrition Recommendations 2004 (NNR-04) and the dietary intake of thirty children and adolescents who entered the Department of Pediatrics, Umeå University Hospital. Analysing their 5-day food records, authors showed that more than a half (13 of 25) children diets did not meet the recommended intakes of energy, dietary fibre, vitamin D, riboflavin, thiamine, magnesium and selenium. On the contrary, Gluten Free Diet of the sample exceeded in su-

Table 1. Gluten containing and gluten free cereals.

GLUTEN-FREE CEREALS	GLUTEN CONTAINING CEREALS
CEREALS AND MINOR CEREALS	Wheat
Corn	Barley
Rice	Rye
Oats*	Kamut
Millet	Triticale
Sorghum	
Teff	***Cereals by-products****
	Bread
PSEUDOCEREALS	Pasta
Amaranth	Snacks
Buckwheat	Biscuits
Quinoa	Malt

*naturally GF but at risk of cross-contamination
**can be suitable for CD patients using GF flours

crose and saturated fats. Also adults seem to be at risk of dietary deficiencies, as Wild *et al.* revealed on Alimentary Pharmacology and Therapeutics [19]. If compared to data of healthy controls from National Diet and Nutrition Survey (NDNS) and the UK Women's Cohort Study (UKWCS), coeliac women consumed significantly ($p < 0.05$) more energy, protein, fat and carbohydrate whilst had significantly ($p < 0.05$) lower intakes of fibre. In relation to male group, Gluten Free Diet supplied significantly ($p < 0.05$) higher energy, fat and carbohydrate than healthy controls, but similar (low) intake of dietary fibre.

Intakes of magnesium, iron, zinc, manganese, selenium and folate in coeliac patients are lower than the comparative population. In men, intakes of magnesium and selenium were below the Recommended Nutrient Intake. Only 32% of under 55 years and 18% of over 55 years of female patients with CD met British Society of Gastroenterology-recommended intakes for calcium. A Polish research enrolled 42 CD women aged 19 - 30 whose 3-day food diary showed that almost one third of the sample did not meet the recommended energy intake [20]. Although intakes of carbohydrate and protein (as % of energy) seemed to be adequate, higher intakes of fat and sucrose and lower intake of fibre were recorded. The intake of thiamine, vitamin C, iron, calcium and potassium were under the recommended amounts, with only 6 women consuming the recommended amount of calcium and 3 subjects consuming the recommended amount of potassium. Latest data in literature give strength to previous results, as we can see from an article by a Slovenian group. The study design was similar to that mentioned above, considering 40 female CD patients and their 3-day food record. When compared to the Slovenian reference values for nutrients intake (D-A-CH) the average energy intake (1630 kcal) was significantly ($p < 0.05$) too low (since recommended daily energy intake was 1800 - 1900 kcal), as well as carbohydrate percentage on total energy (48.2%) and dietary fibre (18.9 g/day). Food diaries also showed a significantly higher proportion of fat (36.4%; $p < 0.05$), lower amounts of calcium (760.7 mg/day; $p < 0.05$) and iodine (96.2 mg/day; $p < 0.05$), whereas the amount of iron (10.2 mg/day; $p < 0.05$) was at the lower limit of the recommended intake. Zinc and potassium were beyond the recommended intake, but this is in line with data from general population in Central Europe [21]. Valente *et al.* focused their attention on B vitamins intake in 20 CD patients and 39 controls, giving attention to the relation between these nutrients and homocysteine metabolism. Results shows that all the CD patients had serum folate levels lower than controls as well as folate dietary intake [22]. Abenavoli *et al.* published a review showing that Gluten Free Diet was linked to an increase in body weight and Fat Mass, a significant increase in triglycerides, total cholesterol and HDL-C serum levels. Moreover, the closer patients adhered to Gluten Free Diet, the higher their risk of overweight or obesity was [23]. Van Hees and colleagues found that Gluten Free Diet leads to a lower dietary intake of vegetable proteins, meaning that serum concentrations of Tryptophan, Tyrosine and Phenilalanine (LNAA) of the CD sample were significantly lower than the control group taken in exam [24]. The mentioned study focused on the

three LNAA intake and their possible influence on depression disease onset but indirectly confirmed the idea that Gluten Free Diet is somehow incomplete, nutritionally speaking.

3. Gluten Free Diet: Between Industrial or Naturally Gluten Free Foods

The already mentioned study by Abenavoli, analysing the effects of Gluten Free Diets on weight and body fat mass, concluded that the higher risk of overweight and obesity in CD population is probably due to the excessive consumption of commercial Gluten Free products, industrially produced with the aim to replace traditional gluten-containing staples (bread, cookies, cakes, snacks and other bakery products…). The majority of gluten-free foods, consumed daily by the CD patients, have a high glycemic load as a consequence of the high content of sugar in glucose syrup, as well as of massive use of rice and potato flours. Since gluten is responsible for most of the characteristics in bakery industry, Gluten Free industry had to draw upon food additives like emulsifiers, lecithin, Gluten Free starches, dairy products, other non-gluten proteins to ensure acceptable results. These additional ingredients change dramatically the nutritional value if compared to traditional gluten containing foods. With reference to Gluten Free food composition, in 2015 Missbach and colleagues published the results of a great data recording on Gluten Free products available on the Austrian market [25]. Comparison with matched gluten-containing foods showed that both prices and nutritional value were different. Although energy content, carbohydrate, fat, saturated fatty acids, fibres and sugar were similar in Gluten Free products and controls, protein content was significantly lower in Gluten Free foods (5.8 ± 3.7 g/100g vs 8.6 ± 2.9 g/100g). Other significant differences are those in potassium content (190 ± 160 mg/100g vs 247.5 ± 130 mg/100g) and zinc content (1.9 ± 0.9 mg/100g vs 4.6 ± 0.4 mg/100g). Similarly, a cross-sectional survey analyzing Australian foodstuffs underlined the poor nutritional profile of Gluten Free products on sale, with high levels of sugars, saturated fats and salt. These data had been recorded even for those categories where Gluten free foods showed similar or better average nutritional value compared with gluten-containing counterparts. Other key aspect is the lower average protein content of gluten free foodstuffs, due to carbohydrate-rich, but protein-poor ingredients such as maize starch, white rice flour, potato starch or tapioca starch [26].

A good compromise—achievable only by educating and giving coeliac patients nutritional tips [27]—is to increase food variety with the naturally Gluten Free, alternative grains, such as quinoa, amaranth, buckwheat, teff, sorghum…

This expedience is already recommended since 2009 when Lee et colleagues [28] compared "traditional" Gluten Free products like rice, potatoes, corn and "alternative" grains (oats, quinoa…) finding out that alternative grains and their by-products provided a higher nutrient profile ($p = 0.002$). More recently, researchers worldwide have confirmed these findings. In 2015 products on European market were analyzed show-

ing a great discrepancy in selenium content between products from popular gluten-free cereals (corn, rice, buckwheat), and those from less popular gluten-free crops (oat, amaranth, teff, and quinoa). The study [29] revealed that relatively new gluten-free flours from oat, quinoa and teff may provide about 2 - 9 times more selenium than traditionally consumed gluten-free flours. Moreover, Journal of Food and Nutrition Research published additional data, which confirm the promising application of quinoa in increasing nutritional quality of GF products. In more detail [30], by mixing quinoa and rice, it is possible to produce breakfast cereals with a protein and fibre profile better than corn by-products, with a lower amount of fatty acids. Another value of quinoa and rice products is the amino acidic profile, which is comparable to the reference protein by FAO/OMS for all essential amino acids.

4. Coeliac Disease: When Gluten Free Diet Is Not Enough

Galli *et al*. in 2014 [31] considered histological findings of 65 CD patients who had been compliant to Gluten Free Diet for a year after diagnosis. Mucosal healing did not occur in the totality of compliant patients, especially in those whose mucosal damage was more severe. So for incomplete resolution of CD symptoms despite adherence to Gluten Free Diet and serum CD-associated antibodies negativity, research focused on other possible triggers of persistent inflammation and symptoms in CD patients. Sanz in 2015 mentioned the possible role of gut microbiota in CD onset and symptoms persistence, suggesting that dysbiosis could be one of the triggers in CD pathogenesis as well as a consequence of it [32]. Moreover, microbiota alterations could be a potential explanation to the persistence of symptoms despite adherence to a long-term Gluten Free Diet, as Wacklin deduced in 2014 [33]. To date, one of the possible triggers of microbiota changes are the so called FODMAPs (Fermentable, Oligosaccharides, Disaccharides, Monosaccharides, and Polyols). FODMAPs are fermentable carbohydrates found in some dairy products (lactose), certain fruits and vegetables, grains (fructans), beans and certain sweeteners such as honey, agave, and sugar alcohols (polyols) and others. The fermentation of these indigestible carbohydrates by intestinal bacteria can cause gastrointestinal symptoms like diarrhea, bloating, pain, flatulence and constipation.

As we already mentioned, these symptoms are common in CD but also in Irritable Bowel Syndrome (IBS), which still remain an uncertain pathological entity. Moreover, some patients with IBS have coeliac disease-like symptoms and conversely CD patients may experience IBS symptoms. Furthermore, about 5% of IBS patients are then diagnosed as affected by CD.

Especially in patients with unresponsive CD, triggers other than gluten, wheat and related proteins are now seen as potential basis of these symptoms: FODMAPs are always more frequently pointed out. Possible mechanisms of FODMAPs related discomfort are still matter of study and have been reviewed by De Giorgio and colleagues [34].

With special regard to IBS, patients who restrict foods with high FODMAPs content significantly improve symptoms, as underlined in the review by Dugum and colleagues [35]. Low FODMAPs diets consist of two phases: the former of complete avoidance of

food high in FODMAPs and the latter of a step-by-step reintroduction of food on the basis of symptoms and individual tolerance. Strict avoidance usually lasts from six to eight weeks, during which a customized and sequential dietary counseling is needed in order to avoid detrimental restrictions which may lead to nutritional deficiencies. The authors agreed upon the resolution of gastrointestinal discomfort (up to 74% in one of the study taken in analysis) after at least 3 weeks of avoidance of FODMAPs. Similar results have been recorded by Maagaard *et al.* [36], Laatikainen [37], Iacovou [38] and Pérez y López [39]. One of the potential mechanism involved in symptoms exacerbation is the change in gut microbiota by diets rich in FODMAPs. Considering that bacteria produce short-chain fatty acids as a result of substrate fermentation, changes in fermentable substrates from diet is likely to cause a change in the bacterial profile [40]. In confirmation of this hypothesis, Staudacher stressed two keypoints in his work: 1) the resolution of symptoms after a four-week low FODMAPs diet and 2) modulation in Bifidobacteria concentration and proportion of gut microbiota [41]. The alteration in gut microbiota by modulating dietary FODMAPs have also been depicted by others studies [42] [43].

Coexistence of CD and FODMAPs intolerance make the Gluten Free Diet ineffective since symptoms does not necessarily disappear with complete avoidance of gluten. Gluten Free products indeed are not always low FODMAPs since they may contain lactose, fructose, polyols and other dietary components ascribable to the FODMAP category. For example, almonds and other nuts, amaranth, flours from legumes, some fruits and vegetables, some sweeteners—despite of being suitable for CD—are listed as high FODMAPs [44].

A Gluten Free Diet undoubtedly reduce FODMAPs load since it is based on rice, corn, potato flours, quinoa etc. which are low in FODMAPs, but it is matter of debate if the improvement of symptoms is due to the avoidance of gluten and wheat or both to the avoidance of fructans and gluten. While gluten content in food is widely known, except a few data and researches, a FODMAP database does not exist yet and packaged food rarely label FODMAPs amount. Monash University is one of the most active group of research on FODMAPs and regularly publishes new updates on FODMAPs in food products. **Tables 2-6** list some of the most common staples of the Gluten Free Diet, differentiating low FODMAPs from products with high FODMAPs content. Limiting Gluten containing products undeniably reduces FODMAPs content in everyday day diet but does not completely eliminate those food components. As tables show, even nuts, pulses, sweeteners and other naturally Gluten Free foods can produce intestinal bloating and discomfort because of FODMAPs. As these fermentable food components are almost ubiquitous, low FODMAPs diets require further precaution and knowledge of food composition.

5. Conclusions

Coeliac Disease is a permanent gluten intolerance, whose manifestation may be extremely variable and whose only therapy is the complete and lifelong avoidance of glu-

Table 2. FODMAPs levels in nuts and seeds (Monash University) [44].

	FODMAP RATING		FODMAP RATING
Cooked chestnuts (84 g)	LOW	**Sunflower seeds (6GR O 1 tsp / <70GR)**	LOW
Peanuts (30GR O 32PZ/ -)	LOW	**Poppy seeds (24GR O 2 tbsp / -)**	LOW
Nuts (30GR O 10PZ / <100GR)	LOW	**Almonds (12GR O 10PZ / <24GR)**	MODERATE
Brazilian Nuts (30GR O 10PZ / <100GR)	LOW	**Hazelnuts (15GR O 10PZ / <30GR)**	MODERATE
Pecan Nuts (30GR O 10PZ / <100GR)	LOW	**Almond flour (24GR / <48GR)**	HIGH
Macadamia Nuts (40GR O 20PZ / -)	LOW	**TAHIN (sesame seed paste) (20GR O 1 tbsp / <40GR)**	HIGH
Pine Nut (14GR O 1 tbsp / <10GR)	LOW	**Cashews**	HIGH
Pumpkin Seeds (23GR O 2 tbsp / <100GR)	LOW	**Pistachios**	HIGH
Sesame Seeds (11GR O 1 tbsp / <66GR)	LOW	**Dates**	HIGH

PZ = pieces.

Table 3. FODMAPs levels in gluten free vegetable beverages (Monash University) [44].

	FODMAP RATING
Soy milk (from beans)	HIGH (galatto-oligosaccarides)
Soy milk from protein flour 250 ml/die	LOW
Almond milk 250 ml/die	LOW
Coconut milk 125 ml/die	LOW
Hemp milk 250 ml/die	LOW
Rice milk 200 ml/die* **	MODERATE (<200 ml/die)
Coconut water (100 ml / <250 ml)	HIGH
Oat beverage	HIGH

ten containing foods. However, being on a Gluten Free Diet is not as simple as it seems as it entails limitation of a wide range of foods, limitations which must be considered for several reasons. Firstly, food choices can be at the basis of nutritional criticalities and disorders, deficiencies and excess of nutrients intake. Secondly but of no less importance, Gluten Free Diet has potentially psychological and social implications since it changes life and habits of patients and their social system. Nutritionally speaking, the more rational management is an in-depth nutritional evaluation and patient's education. Personalization, respect for patients' habits and attention to individual nutritional status is an essential part of an effective management of CD and everyone who has received a coeliac disease diagnosis should receive a personalized dietetic scheme, specifying quality and quantity of food to assume in order to prevent nutritional deficiencies

Table 4. FODMAPs levels in main GF grains (Monash University) [44].

	FODMAP RATING
AMARANTH	LOW
OAT • Oats flakes, instant (pre-cooked) (23gr / <47gr) • Oats flakes, ground (52gr / <105gr) • Oats flakes, whole (105gr / -) • Oat bran (22gr o 2 tbsp / <5 tbsp)	LOW
BUCKWHEAT • Dehulled groats cooked (135gr / -) • Buckwheat flour (100gr / -) • Whole-grain buckwheat flour (100gr)	LOW
MAIZE/CORN • Polenta, cooked (245gr / -) • Corn flour (100gr / -) • Tortillas (57gr / -) • Corn starch (100gr / -) • Corn flakes (gluten free) (50gr / -) • Pop corn (120gr / -)	LOW
MILLET • Dehulled, cooked (184gr / -) • Millet Flour (100gr / -)	LOW
QUINOA • White, black, red, cooked (155gr / -) • Quinoa flour(100gr / -) • Quinoa flakes (50gr / -) • Quinta pasta, cooked (145gr / -)	LOW
RICE • White or brown, cooked (190gr / -) • Rice flour (100gr / -) • Rice cakes (28gr / <56gr) • Rice crackers (34gr / <60gr) • Rice noodles, cooked (220gr / -) • Puffed rice (15gr / <30gr) • Rice flakes (30gr / -)	LOW
SORGHUM • Sorghum flour (100gr / -)	LOW
TAPIOCA • Tapioca (100gr / -)	LOW
TEFF • Teff flour (100gr / -)	LOW
Gluten free pasta (from rice, corn or quinta), cooked (146gr / <219gr)* Gluten free bread (made from allowed ingredients and from sourdough since fructans are pre-digested by natural fermentation)	LOW
Amaranth (puffed) (10gr / <20gr)	MODERATE
Corn cakes (12gr / <24gr)	MODERATE
AMARANTH FLOUR	HIGH
GLUTEN FREE PRODUCT CONTAINING sorbitol (420), mannitol (421), xylitol (967), maltitol (965) and isomalt (953)	HIGH

Table 5. FODMAPs levels in main GF flours (Monash University) [44].

	FODMAP RATING
LENTIL FLOUR	HIGH
LUPIN FLOUR	HIGH
PEA FLOUR	HIGH
SOY FLOUR	HIGH
CAROB FLOUR (6 - 9 g/die)	HIGH

Table 6. FODMAPs levels in some GF sweets and sweeteners (Monash University) [44].

	FODMAP RATING
STRAWBERRY JAM (2 TBSP O 40GR / -) **JAM PREPARED FROM ALLOWED FRUITS AND SWEETENERS**	LOW
DARK CHOCOLATE (30GR / <90GR) **COCOA (2 TSP O 8GR / 5 TSP O 20GR)**	LOW
STEVIA (2GR / -) **SUGAR (1 TBSP)** **CANE SUGAR (1 TBSP/ -)** **MAPLE SYRUP (2 TBSP O 53GR / -)** **RICE SYRUP (1 TBSP O 28GR / -)** **GLUCOSE SYRUP**	LOW
MILK CHOCOLATE/ WHITE CHOCOLATE (15GR / <30GR)	MODERATE
HONEY **AGAVE** **GLUCOSE-FRUCTOSE SYRUP (= HIGH FRUCTOSE CORN SYRUP)** **SWEETENERS LIKE XYLITOL, MANNITOL…**	HIGH

TSP = TEASPOON; TBSP = TABLESPOON.

and to not gain excessive body weight.

A dietitian or nutritionist with experience in CD management should educate patients and pledge for a constant and long-term follow-up to test adherence to gluten free diet, reinforce compliance and clarify doubts and difficulties. An essential part of patients' education is focusing on the right food choices at home and when eating out, making them aware of the better nutritional profile of naturally-gluten free grains and their by-products. As data on food composition underline, gluten free alternatives developed by food industry are not always so healthy so that a good balance among natural products and more processed staples may help to maintain a good nutritional status and avoid an unbalanced diet. Also, Gluten Free Diet may not bring to resolution of symptoms or pledge mucosal healing. These conditions may be due to other factors like an unsolved dysbiosis or food triggers other than gluten. FODMAPs are nowadays matter of several studies, since their dietetic avoidance seems related to an improvement of bloating, abdominal pain, intestinal discomfort. Although Gluten Free Diet reduces lots of FODMAPs containing foods, it does not necessarily reduce the FODMAPs load and this can explain the symptoms persistence in a subgroup of patients. To

a certain extent going gluten free is easier since a low FODMAP diet means watching out for a range of food groups, which is wider than simply avoiding by-products of wheat, rye, barley. Understanding if these food compounds make symptoms worse may pave the way for new therapeutic approaches (*i.e.* gluten/wheat-free **and** low FODMAPs) making dietary intervention of CD more effective.

Future research should address itself on new methods for CD evaluation (and, hopefully, for FODMAPs intolerance) and on its interrelation with other gastrointestinal disease given the shared inflammatory and/or autoimmune pathogenesis. The authors of this review underline the need of further research about microbiota and its modulation induced by diet and dietary limitations. Moreover, constant efforts should be made in order to gain constant information about cross-contamination in food industry and unintentional gluten exposure. Something should also be made in order to find the reasons why Gluten Free diets are not always totally effective on symptoms resolution.

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