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REVIEW

Celiac disease: understanding the gluten-free diet

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Abstract
Purpose The only effective and safe treatment of celiac disease (CD) continues being strict exclusion of gluten for life, the so-called gluten-free diet (GFD). Although this treatment is highly successful, following strict GFD poses difficulties to patients in family, social and working contexts, deteriorating his/her quality of life. We aimed to review main characteristics of GFD with special emphasis on factors that may interfere with adherence to it.
Methods We conducted a search of various databases, such as PubMed, Google Scholar, Embase, and Scielo, with focus on key words such as "gluten-free diet", "celiac disease", "gluten" and "gluten-free diet adherence". Available literature has not reached definitive conclusions on the exact amount of gluten that is harmless to celiac patients, although international agreements establish cutoff points for gluten-free products and advise the use of clinical assessment to tailor the diet according to individual needs. Following GFD must include eliminating gluten as ingredient as well as hidden component and potential cross contamination in foods. There are numerous grains to substitute wheat but composition of most gluten-free products tends to include only a small number of them, especially rice. The diet must be not only free of gluten but also healthy to avoid nutrient, vitamins and minerals deficiencies or excess. Overweight/obesity frequency has increased among celiac patients so weight gain deserves attention during follow up. Nutritional education by a trained nutritionist is of great relevance to achieve long-term satisfactory health status and good compliance.
Conclusions A balanced GFD should be based on a combination of naturally gluten-free foods and certified processed gluten-free products. How to measure and improve adherence to GFD is still controversial and deserves further study.

Keywords Celiac disease · Gluten · Gluten-free diet · Adherence to diet

Introduction

Celiac disease (CD) is a chronic inflammatory bowel condition triggered by consumption of gluten [1, 2]. Its prevalence has been reported to be 1–2 % in North and South America, North Africa, Middle East and India [3, 4] although a higher figure was reported in Saharawi [5]. The only known effective treatment for CD is a strict gluten-free diet (GFD) for life, excluding dietary wheat, rye, barley and hybrids like kamut and triticale. In the majority of patients, strict GFD clearly improves histological lesions, blood biochemistry, clinical manifestations and the risk of CD-related complications [6]. Untreated patients have two to fourfold increased risk of non-Hodgkin's lymphoma, more than 30-fold increased risk of small intestinal adenocarcinoma and 1.4-fold increased risk of death [7]. Although there is no doubt that GFD greatly benefits celiac individuals, adhering to it is difficult because gluten is found hidden in many industrially processed foods; it is also most relevant that strict GFD inevitably restricts patient's social and school/working activities, inducing significant

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effects on patient's quality of life [8]. It has been historically assumed that a strict GFD is nutritionally adequate [9]; however, several studies today indicate that patients on this diet should be monitored for potential nutritional deficiencies [10–12]. Nutritional impact of GFD depends on the length of time that patients remained undiagnosed and the intestinal mucosal injury, which determines the magnitude of nutrients malabsorption [13]. Typically, GFD is based on a combination of foods naturally lacking gluten that are unlikely to be contaminated and special products formulated with gluten-free grains, usually labeled as "gluten-free." Current high consumption of ultra-processed foods and their potential contamination raise concern about the safety of celiac patient's diet [14]. This review critically analyzes dietary and nutritional aspects of GFD, describing relevant aspects of gluten in CD and the GFD, emphasizing peculiarities and consequences of this diet when adhering/not adhering to it.

The gluten-free diet as treatment and as a lifestyle

In recent years, interest on GFD has greatly increased and many people follow it in the absence of CD or other conditions that justify it. Today, three conditions that require treatment with GFD are identified. CD already summarily described is the best known of them. Second, a rather new condition referred to as Non-celiac gluten/wheat sensitivity (NCGS), includes individuals who report symptoms that respond to withdrawal of gluten from the diet in the absence of CD and wheat allergy [15–17]. Recent reports on its prevalence suggest that it may be as high as or even slightly higher than that of CD (0.6–6 %) [18–20]. Of yet unknown pathogenesis, it would be related to partially digested gluten components; the possibility that proteins other than gluten and/or carbohydrate components of the wheat grain might be involved in the development of NCGS has been raised. Yet, available evidence is still insufficient to draw conclusions on its pathogenesis, course or prognosis [21]. Thirdly, wheat allergy is a well recognized but insufficiently understood condition, in which individuals with rapid reactions and high IgE levels are the best described; however, diagnosis may be complicated in cases of delayed reactions that are difficult to associate with the actual intake of wheat [22]. Wheat contains many allergenic proteins, and whether gluten is the only allergen involved is still controversial. Several wheat proteins cross-react with grass pollen allergens and this may cause false-positive results on diagnostic tests [23, 24]. However, recent studies suggest that the main wheat allergens are relatively insoluble gluten proteins (gliadins and glutenins) that do not cross-react with grass pollen allergens [25]. In addition to these three conditions, GFD may be an effective treatment in some inflammatory bowel diseases, with significant reduction in gastrointestinal symptoms, when followed as part of a low-FODMAPs (fermentable oligosaccharides, disaccharides, monosaccharides and polyols) diet [26]. Today, another group is increasing that eliminate gluten consumption; they are individuals that consider GFD a healthier option. For example, nearly 50 % of 910 athletes (including world-class and Olympic medalists) adhere to GFD because they perceive it healthy and providing energy benefits [27]. It is not yet clear whether those consuming gluten-free foods are on strict GFD and the consequence of following or not following it. All in all, this has led to a considerable increase in the gluten-free products market; Markets and Markets research service reports that the global gluten-free product market is projected to reach $6206.2 million, growing at a compounded annual growth rate of 10.2 % by 2018 [28], representing one of the most prosperous markets in the field of food industry.

About gluten

Wheat appeared about 10,000 years ago in the so-called "fertile crescent" in Southeast Asia (current Turkey, Palestine, Lebanon and northern Iraq). Wheat farming dates back to the onset of agriculture, when a variety of wild cereals spontaneously appeared, including wheat and barley [29]. Since then, human beings have consumed increasing amounts of gluten, especially after learning to cook it and later on turning wheat-based doughs into breads [29]. Gluten is the name given to a group of wheat proteins abundantly consumed, 10–20 g per person/day as part of the regular Western diet [2]. Composed by gliadin and glutenins [30], glutenins have not been related to CD while peptides of gliadin are responsible for the typical celiac damages. Gliadin is a 30 kDa alcohol-soluble protein rich in glutamine and proline residues [31]. The polyglutamine sequences are located in the C-terminal domain of gliadin while the glutamine/proline repetitive regions are in a central position in the protein. Four fractions of gliadin have been described: α, β, γ and ω subunits; the α-gliadin subunit has the most intense deleterious effects while β, γ and ω would exert milder toxicity [32–34]. Because wheat is a hexaploid species and some of the genes coding for gluten proteins originate from duplicate loci, one variety of wheat may contain several hundred different gluten proteins. Being a protein of low nutritional value, gluten is massively used by food industries because of its ability to retain air in the protein matrix, facilitating baking and improving several characteristics of ultra-processed products [35]. Among the several attempts that intend to establish new therapeutics for CD, the use of less immunogenic wheat is being currently assessed. There are natural epitope variants that lack immunogenicity due to single or multiple amino acid substitutions; for example, a P to S substitution at the

epitope core position 8 was shown to be sufficient to abolish T cell stimulation [36]. Hexaploid Triticum aestivum is the one most frequently used in food production. It was generated by hybridizing a tetraploid (Triticum turgidum, "pasta wheat") and a diploid (Triticum tauschii) variety. A peptic–tryptic digest of tetraploid wheat gluten demonstrated decreased toxicity in duodenal biopsies of celiac patients when compared with a digest of hexaploid wheat [37]. In the same way, two wheat varieties, one poor in α and β gliadins and the other in α, β, γ and ω gliadins, also demonstrated to be less toxic to duodenal biopsy specimens [32].

Gluten damage in the small intestinal mucosa

Gluten is digested into peptides in the small intestine, but due to characteristics of the human gastric and pancreatic peptidases, relatively large residual proline and glutamine rich peptides remain intact in the intestinal lumen. For about 99 % of individuals, including some of those carrying the CD susceptibility alleles HLA-DQ2 and HLA-DQ8, this is not a problem [38]. However, in celiac patients these partially digested peptides reach the subepithelial region in the small intestinal mucosa. The mechanism through which this occurs is not yet fully understood; it may include paracellular passage through an abnormal or damaged epithelium, trans-epithelial passage, incorporation through dendritic cells or retro IgA transcytosis [2, 39].

Although data on the role of adaptive immunity in the pathogenesis of CD are more abundant, there is also evidence of innate immunity participation. Intraepithelial lymphocytes (IELs) can be activated by luminal cereal proteins, the perforin/granzyme and/or Fas/FasL pathways being essential to the cytotoxicity and apoptosis-inducing activity of IELs on the intestinal celiac epithelium [40–42]. Non-classic class I molecule MICA is expressed on the intestinal epithelium and is a ligand for NKG2D receptor on natural killer T cells, some subsets of CD4 and CD8 T cells [43]. NKG2D can trigger antigen-specific lymphocyte-mediated cytotoxicity and direct cytolytic function in effector CD8 T cells, linking innate and adaptive immunity [44]. The peptide (α-gliadin 31–43) p31–43/49 activates the production of IL-15 and NK receptor-mediated IELs cytotoxicity [44, 45] and also induces apoptosis of enterocytes, upregulates MHC class I molecules, activates MAP kinase pathway and upregulates the expression dendritic cells [46]. Another participant in the pathogenesis of CD is IL-15, of which both intestinal epithelia and dendritic cells/macrophages are major sources in the intestine [41, 47]; its role in the activation of innate and adaptive immunity in CD is currently well confirmed [41, 46, 48]. IL-15 is a potent growth factor for IELs and can counteract the immunosuppressive TGF pathway [48]. Data on IL-21, which are produced by CD4 Th1 T cells, suggest that this would be another driving force of innate immunity, which can act together with IL-15 [49].

Once in the lamina propria, glutamine residues in the gliadin peptide are deamidated to glutamic acid by tissue transglutaminase 2 (tTG2), a phenomenon that results in a complex with high affinity for the DQ2 or DQ8 pockets presents in antigen-presenting cells. The release of pro-inflammatory cytokines such as interferon-γ and others maintain the pro-inflammatory events that result in functional deterioration of the mucosa (including intestinal permeability) [50]; during these processes, activation and release of metalloproteinases are responsible for the typical architectural changes with flattening of villi, increased intraepithelial lymphocytes, hypertrophy of crypts and increased cellularity (mainly lymphocytes and plasmocytes) in the lamina propria [33]. Some α-amylase/trypsin inhibitors (ATIs) from wheat have been shown to be strong activators of innate immune responses in monocytes, macrophages and dendritic cells of celiac and non-celiac individuals, suggesting that cereal ATIs may also contribute to the pathogenesis of CD [51].

The gluten-free diet

It is only after diagnosis is reached by clinical data, serology and small intestinal histology [52, 53] that treatment with GFD should be initiated. Current evidence suggests that patients should be referred to a dietitian with experience on CD, to help the patient design the diet and teach him/her strategies to follow it, making sure that it is not only gluten-free but also nutritionally adequate (see Fig. 1) [54]. There is a rather long list of cereals, grains, seeds, legumes and nuts that may replace gluten (like amaranth, quinoa, millet, sorghum, flax and chickpeas, among others); they all may improve palatability and nutritional quality of GFD, but they are infrequently used, due in part to their higher cost and lesser availability [11]. Instead, gluten-free products commonly contain a short list of ingredients and are not fortified with micronutrients as their wheat-containing counterparts [55]. Among the novel approaches that search improving nutritional qualities of gluten-free products, it is worth mentioning gluten-free breads with quinoa and flaxseed, which have a better balance of polyunsaturated/saturated fatty acid and would supply low levels of trans-fatty acids, with good acceptance [56]. Quinoa and flaxseed are also recommended to improve the amount of ω-3 fatty acids in gluten-free products [57]. Processed foods based on amaranth, quinoa and buckwheat have higher levels of protein, fat, fiber and minerals in comparison with those based on rice and corn, becoming good alternative ingredients for gluten-free products [58].

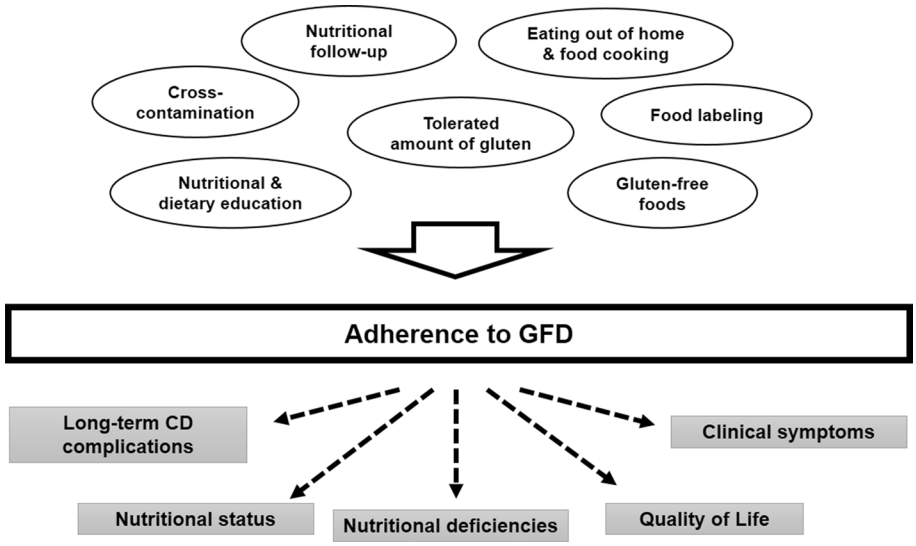

Fig. 1 Gluten-free diet, a milestone in the treatment of celiac disease. Numerous factors influence adherence to gluten-free diet that they must be addressed during treatment and follow-up. In turn, adherence to the diet impacts on the clinical and nutritional course of the disease, its complications and the consequences on the patient's quality of life

Today, novel techniques in food technology are focused on developing intraluminal therapies aiming at reducing gluten immunogenicity or hydrolyzing gluten peptides. So far, efforts to genetically modify grains to diminish the immunogenic components have been unsuccessful. Digestion of dietary gluten has been proposed on the basis of administering oral endopeptidases derived from plants, bacteria or fungi that can hydrolyze gluten peptides along the digestive tract, but the remnant gluten contained in these products and the degree of digestion reached remain uncertain. Another approach under consideration is the pretreatment of sourdough with proteases from lactobacilli added for fermentation, postulating that fermentation will be enough to hydrolyze gluten peptides to non-toxic levels, but again, that the resulting baked products are under the cutoff is to be demonstrated [59, 60].

In general, consumption of oats is safe for celiac patients, but they are usually contaminated with gluten and therefore commonly restrained in GFDs [61]. Lundin et al. [62] described that contamination in commercial oats varied from 1.5 to 400 ppm, in the same package. However, when oats are grown under especial conditions of farming, harvesting and distribution, they can be safely consumed by celiac patients [61]. The controversy remains on wheat starch; in Europe, wheat starch used in gluten-free products is purified to meet Codex Alimentarius requirements, yet, its use is not accepted in the USA [11]. In an open challenge study conducted in Canada, gluten-free products containing wheat starch caused digestive symptoms in celiac patients [63]; in contrast, in a randomized protocol in Finland, patients following GFD with or without wheat starch showed no differences in mucosal recovery, serum antibodies, bone mineral density and nutritional status after 1-year follow-up [64].

How much gluten is tolerated by celiac patients?

Gluten is not totally absent in the so-called "gluten-free products" [65, 66]. The important issue then is to define how much gluten is not harmful for celiac individuals. Numerous studies have investigated the amount of gluten tolerated by patients without suffering small intestinal mucosal alterations and/or without triggering clinical symptoms [67]. Lack of animal models makes difficult to assess this problem and studies available are conducted on series of patients that undergo gluten challenge for rather short periods of time. Therefore, there is no certainty or absolute answers. The variable results obtained in different studies are—at least it part—due to the highly variable gluten sensitivity observed among celiac patients [67]. Ciclitira et al. [68] showed that patients consuming 1.2–2.4 mg gluten/day during 1 week had already detectable histological changes in the small intestinal mucosa; yet, in another study using the same amount of gluten administered during 6 weeks, histological mucosal changes could not be demonstrated [68]. Kaukinen et al. [69] showed that patients that consumed on average 34 mg gluten/day during 8 years did not develop measurable duodenal histological abnormalities, but individuals consuming 34 mg of gluten daily plus 1–2 g of gluten weekly did develop villous atrophy [69]. Catassi et al. [70] administered 100 or 500 mg gluten/day to celiac children during 4 weeks and found that those receiving 100 mg had minimal intestinal mucosal changes while those who received 500 mg had pronounced damage. So far, there is only one prospective, randomized, double-blind, placebo-controlled study [71]; in this study, 39 CD patients were divided into 3 intervention groups receiving 10, 50 mg of gluten or placebo during 3 months. Results showed a significant proportion of patients with persisting morphological alterations in the small intestine

after consuming 50 mg gluten. Authors concluded that prolonged daily intake of 50 mg of gluten produces significant architectural damage of the intestinal mucosa in treated CD patients [71]. More recently in the USA, celiac patients were evaluated for serological and duodenal histological changes after gluten challenge with 3 or 7.5 g gluten for 14 days; authors concluded that consumption of 3 g of gluten during 14 days would be sufficient to induce histological and serological changes [72].

A Health Hazard Assessment for Gluten Exposure conducted by the US FDA in 2011 analyzed the available evidence obtained either by clinical and/or histological indicators [73]. After evaluating all available low dose–response data on the adverse CD-related health effects of gluten, the tolerable daily intake level for gluten in individuals with CD was calculated at 0.4 mg gluten/day for adverse morphological effects and at 0.015 mg gluten/day for adverse clinical effects. Authors stressed that some of the evidence suggested that the tolerable daily intake level for morphological effects, based on a derivation that incorporated a tenfold uncertainty factor for inter-individual differences, may not be enough to protect all celiac individuals [73].

Cutoffs for gluten in foods

In addition to the scientific discussion on the range of gluten consumption that avoids clinical and histological damage, international efforts regulate the amount of gluten that should be present in products described as "gluten-free." Codex Alimentarius represents a consensus of international standards for food safety; it is not enforced by law and up to date following their criteria remains voluntary [74]. In 2008, Codex Alimentarius established that the cutoff for "gluten-free" products was 20 parts per million (ppm or milligrams of gluten per kilogram of product). Many countries have now set local cutoffs, ranging from 20 ppm in Spain, Italy, UK [74], Canada [75] and USA [76], to 10 ppm in Argentina [77] and 3 ppm in Australia, New Zealand [78] and Chile [79].

Estimating the safe threshold of daily gluten consumption should include both the actual content of residual gluten present in the gluten-free products and the total daily consumption of these products [65]. Aiming at assessing the actual maximum daily gluten intake, some European studies have measured gluten ingestion in celiac patients based on the consumption of gluten-free foods. Gibert's evaluation [80] included foods made with gluten-free flour in Italy, Spain, Norway and Germany; they found an average consumption of 233 g per day, which authors considered a low daily gluten intake. A subsequent study [81] by the same authors evaluated the risk of mucosal damage among celiac patients due to potential contamination of gluten-free foodstuffs and found that 94 % of products measured and labeled "gluten-free" contained less than 5 ppm of gluten. These studies have been conducted in Europe and there are no equivalents in other regions. Since consumption and conditions of gluten-free products may greatly differ in different countries, it seems reasonable that these findings should not be automatically inferred to non-European countries.

CD and nutritional status

Due to technological difficulties derived from not using gluten when producing processed products, gluten-free foods often contain more carbohydrates and lipids than their gluten-containing equivalents. This is currently relevant considering that at present obesity is increasing among celiac patients, even at the initial presentation [82]. Celiac patients are at risk of overweight/obesity especially during the first year after initiating GFD; probably influenced by the fact that they can eat without suffering symptoms and feeling ill and that their absorptive capacity improves. If this is combined with consuming high-calorie gluten-free foods, the patient will gain more weight than desired [83]. Mariani et al. [84] reported that fat and protein intake in celiac adolescents was higher than recommended and that commercially available gluten-free biscuits were richer in saturated fat than their gluten-containing equivalents [84]. Wild et al. [85] reported that British female celiac patients consumed more energy from all macronutrients when compared with non-celiac local population, attributing this to higher intake of sweet snacks. In Italy, a multicenter cross-sectional study of 114 children adhering to GFD for at least one year showed that removal of gluten from the diet increased the prevalence of overweight from 8.8 to 11.4 % and obesity from 5.3 to 8 % [86]. Kabbani et al. [87] evaluated the body mass index of 679 celiac patients and reported that at the time of diagnosis patients' body mass index was lower than the general population but after 39.5 months, 20.5 and 11.5 % of patients were overweight and obese, respectively [87].

Today, it is widely accepted that educating celiac patients on what to choose when following GFD is of utmost importance for the long-term outcome. Education must start at diagnosis, with frequent evaluations during the first 6 months of treatment; this not only assesses compliance but also creates the opportunity to explain and teach [61], especially in relation to potential nutritional deficiencies [88] and maintenance of a healthy diet and controlled weight gain [87, 89].

Micronutrients in the GFD

Malabsorption of nutrients is frequently observed among celiac patients presenting with typical and atypical

manifestations [90] and deficiencies of several vitamins and minerals can be expected [91]. Several studies report nutritional deficiencies in both children and adult patients; a Scottish study found vitamin B12 deficiency in 41 % of patients with untreated CD, while 31 % of those B12 deficient were also folate deficient [92]. A Chilean study evaluated micronutrients status in young celiac adults with typical and atypical clinical presentations and found lower levels of hemoglobin, ferritin and copper in both groups of patients as compared to controls, suggesting that patients presenting atypical clinical manifestations should follow the same supplementation regime as those suffering the classical disease [90]. Also in Chile, a recent study revealed that less than 8 % school gluten-free snacks met FAO/WHO recommendations for total calories, total fat, carbohydrates and sodium in the upper, middle and low socioeconomic level, respectively, while none of them were fortified [93]. A Dutch study assessed patients at diagnosis (before starting GFD), measuring their serum levels of folic acid, vitamin A, B6, B12, vitamin D, zinc and iron and found that 87 % of patients had deficient values for at least one serum vitamin or mineral, (especially zinc and iron) [94]. A study of Spanish children collected dietary data before and after one year on GFD and found that patients decreased their consumption of saturated fat, increased monounsaturated fat and increased phosphorus intake; deficient vitamin D intake was detected both before and after the initiation of GFD [95].

Gluten-free diet and the cross-contamination

Cross-contamination refers to the process by which a food is in contact with and incorporates foreign substances potentially harmful to health. Cross-contamination of GFD means that a gluten-free foodstuff acquires gluten; this can occur: a) in the production line, when gluten-free products share the same facilities and/or equipment with gluten-containing products. This type of contamination explains why ingredients declaration in a certain foodstuff is insufficient and actual measurement the gluten content in the final product ready to be consumed is needed; b) at the time of cooking gluten-free foods, at home or when eating out or when consuming ready-to-eat foods; avoiding this requires special care separating gluten-free from gluten-containing kitchen gadgets and utensils, also food ingredients (such as jam, margarine, mayonnaise) and any potential source of gluten present in kitchens [96]. Contamination risk increases when foods are maintained in open containers and sold in bulk, at buffet or salad bars, or at any place where a variety of foods share some space [96].

In the USA, assessment of naturally gluten-free grains, seeds and flours not labeled gluten-free revealed that 7 of 22 samples (32 %) were contaminated with ~20 ppm gluten [12]; authors concluded that these results supported the idea that cross-contamination represents a reasonable and valid concern. A Canadian study assessed to what extent contamination with gluten occurs in naturally gluten-free foods and evaluated 640 samples of flours and starches without gluten, but not labeled as "gluten-free" [97]. Results showed that 9.5 % contained gluten in a range of 5–7995 ppm. Instead, contamination in those flours and starches labeled as "gluten-free" ranged 5–141 ppm [97]. Again, these results justify the need to measure prolamines in the ready-to-eat products.

Non-food gluten sources

The possibility that products other than foods frequently used in daily life may contain gluten at potentially harmful levels represents another concern for several celiac patients. Any product that can be ingested may be a source of gluten, including drugs, dietary supplements, toothpaste, mouth wash, lipstick, postage. Gluten may be present as ingredients, excipients, coatings or capsules, mostly as contaminated starch or dextrin and this may be relevant when the drug or product is chronically consumed. Since gluten is not usually measured in these products, patients should be advised to contact the manufacturer and request information for the specific product they are interested on. On the other hand, topical products such as shampoos, lotions or other toiletries should not be of concern [98].

Follow-up of GFD

Assessing adherence to GFD is one of the most relevant aspects of treatment in CD; unfortunately, it is difficult to measure and until now remains a highly controversial issue. Although routinely used in clinical practice, there is evidence suggesting that serological tests measuring autoimmune antibodies may not be sensitive enough to detect minor yet significant dietary transgressions. In studies of newly diagnosed patients, both tTG and EMA antibodies have been reported to become negative despite persisting histological damage and/or exposure to gluten [99]. Vahedi et al. [100] showed that normalization of EMA is a poor predictor of histological recovery in patients on GFD. Some authors suggest that the use of EMA and clinical signs as markers would be better detecting intestinal damage than to demonstrate healing or the absence of histological damage [6]. Indeed, up to 53 % of patients having either low adherence or fairly good adherence to GFD showed tTG below the cutoff [99]. Ciacci et al. [6] followed a group of patients during two years and concluded that adherence to GFD evaluated by a trained interviewer may be suitable to follow the course of the disease. Other studies also support that the interview by an expert is a good option and it also

offers the opportunity to teach and support GFD, tailoring it to the patient's needs [6, 99, 101].

Several researches are evaluating new approaches to assess adherence to GFD. Some groups developed questionnaires, which are promising when compared with other methods [99, 102]. Peptide α-gliadin 33-mer is resistant to the action of digestive enzymes in the human intestine and has been proposed as marker of gluten ingestion by measuring it in feces [103–105] or in urine [106]. Comino et al. [103] measured the amount of α-gliadin 33-mer in stool by means of monoclonal antibodies (G12) in healthy individuals and celiac patients, showing a positive correlation with the amount of gluten consumed [103]; however, more studies are clearly needed to define sensitivity, specificity, cutoffs and the role of microbiota and other potential intervening factors that may modify the amount of fecal peptides. Measuring the urinary excretion using the same type of monoclonal antibodies represents another noninvasive approach. Gluten immunogenic peptides were detectable in urine from healthy individuals undergoing GFD as early as 4–6 h after a single gluten intake and remained detectable for 1–2 days. About 50 % of celiac patients assessed yielded positive urine assay, revealing transgression of the GFD. Small intestinal biopsies showed that in 89 % of patients with no villous atrophy gluten immunogenic peptides were undetectable in urine, while all patients with measurable urinary peptides showed some degree of intestinal mucosa damage [106].

GFD and quality of life

GFD involves restrictions that may be difficult to accept and follow (Fig. 1). Anxiety, school/working and social situations, persistent clinical manifestations, changes in body composition are all situations associated with long-term GFD [107]. Thus, a major consequence of treatment is deterioration of quality of life [8]. Hallert et al. [108] applied the SF-36 questionnaire to evaluate the perceived health status of Swedish celiac patients who followed GFD for at least 10 years. This questionnaire [109] has 36 items and assessed physical functioning, body pain, general health, vitality, social and emotional functioning, providing a profile of health status and quality of life related to health. Results showed that health status was perceived significantly worse by celiac patients in comparison with non-celiac population [108]. A German study applied (1) a questionnaire of gastrointestinal symptoms, (2) the SF-36 questionnaire and (3) the scale of hospital anxiety and depression, and also found that celiac patients reported lower quality of life related to health [110]. However, depending on the type of questionnaire used other studies report no differences in comparison with general population [111]. In Argentine, Nachman et al. [112] assessed a group of celiac patients at diagnosis and during the first year of treatment, describing that quality of life at diagnosis was better in patients with atypical and silent clinical presentations in comparison with symptomatic celiac individuals; they also found that GFD induced rapid and significant clinical improvement in typical and atypical celiac cases but clinical changes were barely noticed by patients with silent forms of the disease, making more difficult for them to accept long-term dietary restrictions [112]. Based on this evidence, current recommendation is offering tailored made alternatives and strategies to manage GFD. Investing more time and effort during the early stages of diagnosis and initiation of treatment would achieve better long-term management of the condition [111, 113].

Conclusions

So far, it continues to be true that the only effective and safe treatment for CD is strict GFD for life. Even though dietary treatment with GFD is highly successful, following this diet poses difficulties to patients in family, social and school/working situations. Scientific evidence suggests that the least celiac patients eat gluten is better, but available evidence is not enough to draw definitive conclusions on the exact amount of gluten that is safe. International consensus helps in managing the GFD and gluten-free processed products. Following GFD must take into consideration the elimination of gluten as ingredient, as hidden component in processed foods and cross-contamination. GFD must be not only free of gluten, but also healthy, avoiding nutrient, vitamins and minerals deficiencies or excess. Nutritional education by a trained professional is most relevant to achieve a healthy GFD with good compliance. A balanced GFD should be based in a combination of naturally gluten-free foods and certified manufactured gluten-free products.

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