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Abstract

A lifelong and strict gluten-free diet (GFD) can fully restore health and improve quality of life in patients with celiac disease and is therefore the basic line of treatment. However, in everyday practice more problems than expected remain: compliance is sometimes difficult to achieve and needs continuous educational and psychosocial support. Persisting symptoms and micronutrient deficiencies, in some cases obesity, are observed. A decreased quality of life has been described particularly in adult women on a GFD. Scientific progress in pathophysiology and also in gluten analysis (R5 ELISA system) has helped to improve evidence-based regulatory solutions for defining and controlling GFD at an international level. Alternative forms of therapy and prevention appear at the horizon today.

Celiac Disease – Hard to Treat and Impossible to Cure?

Celiac disease has rightly been said to be 'tricky to find, hard to treat, impossible to cure' (S. Lohiniemi). However, the situation has greatly improved in recent years due to the progress made both on the scientific and practical levels. New horizons have emerged, starting with celiac-active epitopes in cereal proteins, going beyond the definition of cereals detrimental to celiac patients, and culminating in the evidence-based control of a gluten-free diet (GFD). For practical purposes, and in discussions of celiac disease in the medical literature, 'the term gluten is used to refer to either gluten in wheat or, collectively, to the proteins (e.g. prolamines and glutelins) in just those grains that have been demonstrated to cause harmful health effects in individuals who have coeliac disease' [1]. The diagnosis celiac disease now covers a wide spectrum, which is reflected in therapy [2]. The GFD is, as a rule, indicated in all cases of classic as well as 'silent' celiac disease; however, it is not necessary in latent forms.

At present, the quality and efficacy of the GFD is subject to control both on the food and regulatory level and that of individual patients [2, 3]. The success of the GFD in celiac disease is, however, strongly dependent on compliance, the ascertainment of which is a difficult matter. The beneficial impact of the GFD clearly outweighs the potentially negative effects [4]. A recent report about a celiac cohort in Northern Ireland, which found evidence for a high risk of mortality at the time of diagnosis, has underscored the crucial importance of gluten-free nutrition for all celiac patients on a lifelong basis: the status of

patients 1 year after diagnosis on a GFD showed that malignancy and risk of mortality in this cohort had decreased considerably [5]. The quality of life in celiac patients on a GFD has been an issue raised by different groups over the last few years, and investigations have revealed some unexpected as well as negative effects of the GFD.

From Celiac-Active Epitopes to Unacceptable Grains and vice versa

The subject of nutrition therapy for celiac disease has recently been reviewed in the USA [6–8]. Clinical Guidelines of the North American Society for Pediatric Gastroenterology, Hepatology and Nutrition consider dietary treatment for celiac disease (www.naspghan.org). These comprehensive guidelines stipulate the involvement of a registered dietician trained in working with celiac patients; in addition, the medical monitoring of celiac patients is mandatory. It is essential that the information provided to patients during dietary counseling promotes their motivation and education [8]. Since nutritional deficiencies relating to the inadequate intake of calories/proteins, iron, calcium, magnesium, zinc, vitamin D, vitamin B_{12}, folic acid, niacin, riboflavin and fiber may be present, testing is required and supplementation then needs to be introduced [6]. Obesity among celiac patients on a GFD could pose a practical problem. Cooperation with self-help groups and welfare institutions, such as national and international celiac societies, coupled with lifelong medical follow-up and psychosocial support are important aspects contributing to the success of nutrition therapy in celiac patients. The expense involved in such a therapeutic diet has been estimated to be 115% higher than in a normal control group comprising children and adults, and is a factor that further jeopardizes compliance. However, it was this very factor that led to a successful political campaign for GFD financially subsidized by governmental or health institutions in Finland and Italy.

Gluten is the rubbery wheat storage protein that remains when wheat dough is washed to remove starch. It is unique in terms of its amino acid composition and is high in glutamine and proline. The major protein fractions of gluten are gliadin (alcohol soluble) and glutenin (alcohol insoluble), with soluble gliadin containing monomeric proteins and insoluble glutenin containing aggregated proteins. The protein components and amino acid sequences of gliadin and glutenin are similar and repetitive. Wheat gliadins, rye secalins, barley hordeins and avenin from oats are also known as prolamines, i.e. proteins rich in proline. There is no evidence for a significant relationship between the storage proteins of maize, rice, millet or sorghum and these prolamines. A strong correlation was found between the specific chemical structure of prolamines and the activity of their peptide fragments in celiac disease [3]. Gliadins can be classified into 3 electrophoretical types, namely α, γ and ω. They can also be distinguished according to molecular weight: high, e.g. 67–88 kDa, as in high-molecular-weight glutenin; medium, 34–55 kDa as in ω-gliadin, and low, 28–39 kDa, as in α-gliadin, γ-gliadin or low-molecular-weight glutenin. The typically repetitive sequences found were PQQQF, PQQPFPQQ and QPQ PFPQQTYP (1-letter code for amino acids, P for proline and Q for glutamine). Through the organ culture experiment and also by means of in vivo instillation, specific peptides were shown to induce the celiac-disease-specific small-intestinal enteropathy [3].

Cereal proteins were found to contain several celiac-active 'toxic' epitopes that stimulate intestinal T cells in celiac patients. Differences were evident between individual patients (children as well as adults), and partial overlap was observed between the in vitro intestinal T-cell activity and in vitro/in vivo intestinal epithelial activity of these specific gluten peptides [9–11]. The 33-mer LQLQPFPQPQLPYPQPQLPYPQPQLPYPQP QPF is of particular importance. It is a gliadin

Table 1. Cereals in the GFD

Allowed grains	Forbidden grains
Amaranth	Wheat (all kinds of Triticum)
Buckwheat	Rye
Corn	Triticale
Millet	Barley
Quinoa	Kamut
Rice	(Oats)
Sorghum	
Tef	
Wild rice	

fragment with N-terminal amino acid positions 56–88 and is resistant to proteolytic breakdown. It contains overlapping T-cell epitopes, and its deamidated form is a potent T-cell stimulator which binds strongly to HLA-DQ2 [11]. This 33-mer is an immunodominant epitope. However, the peptide-specific T-cell response in celiac disease is marked by broad diversity. Active peptides have been found in various wheat varieties and also in barley, rye and oats [9, 12]. Celiac-active T-cell epitopes are present in gliadin as well as in glutenin [13]. In a recent clinical challenge study, the celiac activity of high-molecular weight glutenin was observed in 3 adult celiac patients [14].

These findings allow the categorization of grains into permissible and unacceptable (table 1). At present it is anticipated that investigations into T-cell epitopes will help to identify other grains for inclusion into the GFD, e.g. the Ethiopian cereal tef [15].

Oats represent a unique case in celiac disease and are conventionally not included in the GFD. Celiac-active T-cell epitopes are known to be present in avenin from oats [12]. However, clinical data from Scandinavia [16–18] have shown that oats are tolerated by many children and adults with celiac disease. No evidence of harmful effects was found by clinical, laboratory and small-intestinal investigations in 92 Finnish adult patients [16] even after 5 years of follow-up. The same was true for 93 Swedish children who were newly diagnosed as having celiac disease [17] and for 32 Finnish children with established celiac disease [18]. It must be mentioned, however, that several patients dropped out of the first two studies [16, 17]; besides this, long-term follow-up studies are not yet available.

A report on 19 adult celiac patients from Norway, who underwent a challenge with 15 g of oats per day for 12 weeks [19], showed that oats were well tolerated by the majority of patients. However, 1 patient developed subtotal villous atrophy and dramatic dermatitis, and improvement was achieved only by an oats-free diet. Evidence of clinical intolerance to oats [10] was observed in 2 other celiac patients whose intestinal immune response to an oats peptide was similar but not identical to that to wheat peptides.

Cross-contamination, predominantly by barley, is a further, major problem in a GFD which includes oats products. Although immunochemical detection is available (see below) and the technical possibilities for producing oats preparations free of contamination exist, the inclusion of oats in the diet of celiac patients remains controversial and continues to be an unresolved issue. Most national celiac societies, with the exception of Finland, reject oats in the GFD.

Compliance with and Effects of a Gluten-Free Diet

Prerequisites for compliance with a GFD are up-to-date information and proper motivation. Adherence to the diet is best accomplished when the patient understands its role in the alleviation of the symptoms he or she experiences. This was underscored in a study of 22 adolescents who, in comparison to a control group with classic symptoms, showed lower compliance after celiac disease had been detected by screening [20].

Noncompliance ranges from 7 to 55% in celiac patients as a whole and is related to factors such as age, sex, ethnicity, school grade, social class, education, celiac society membership and regular dietetic follow-up [21]. An unbalanced GFD could lead to excessive lipid and protein consumption and, consequently, to obesity [22]. Intensive medical and dietary support is necessary to prevent long-term complications and to achieve satisfactory dietary management [23]. The aim of such a management is not only to ensure compliance, but an adequate nutritional intake as well.

The short-term and long-term responses and alleviation of gastrointestinal symptoms serve as basic diagnostic criteria in celiac disease. However, their occurrence varies individually [24, 25]. The long-term positive effects of the GFD have been proven and even a few years on this diet, during childhood, led to sustained subjective and objective improvements as evidenced by symptom rating, laboratory data and small-intestinal histology [24–26]. Negative side effects, such as psychological burden and stress, induced by a GFD, were found to be more pronounced in women in comparison to men [24]. A broad spectrum of gastrointestinal and psychological symptoms were found in celiac patients on a GFD, and this was associated with a potentially negative impact on the quality of life. Nevertheless, the positive effects of the GFD can clearly be said to outweigh the negative side effects in the treatment of celiac disease.

Short- and long-term observations of celiac patients on a GFD revealed that histological recovery occurs gradually, may take more than 2 years and, in some cases, be incomplete. However, the extent or lack of histological recovery varied considerably in different groups of patients, with low recovery being mainly associated with poor compliance and, additionally, with age over 30 years [27–29]. From the clinical perspective, the treatment of celiac disease by means of a GFD is indicated in all classic cases and also in silent and atypical cases (table 2), but not, however, in latent celiac disease. The situation is further complicated by the fact that a symptomatic and histological response may also be evident in patients with borderline enteropathy (Marsh type 1–2) who do not meet the diagnostic criteria of the European Society for Pediatric Gastroenterology, Hepatology and Nutrition [30].

Table 2. Silent celiac disease – reasons for a GFD

Improvement of intestinal and extraintestinal symptoms
Mucosal recovery (villous architecture, inflammatory infiltration)
Catch-up growth (children and adolescents)
Prevention of
– deficiency symptoms (Fe, Ca, vitamin D, folic acid)
– refractory lesions
– autoimmune diseases
– malignant tumors (small-intestinal lymphoma)

Several other beneficial effects of the GFD have recently been reported, including changes in bone mineral density, improvements in neurological and psychological disorders such as depression, subsiding of severe liver disease, normalization of the serum lipoprotein profile, and the regulation of metabolic parameters in diabetic celiac patients. A detailed discussion of the impact of these changes would go beyond the scope of this chapter. At present, there is no reason to challenge the concept of the GFD as the basic treatment for patients with celiac disease even at a time when alternative therapy forms are being sought or introduced.

Evidence-Based Regulations and Control of Gluten-Free Food

Earlier methods for measuring gluten in food were neither specific nor sufficiently sensitive to detect low gluten levels; besides this, appropriate