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Gluten-Free Diet in Gluten-Related Disorders

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Abstract
A gluten-free diet (GFD) is recommended for all patients with coeliac disease (CD). The spectrum of gluten-related disorders in the early 1980s was simple: CD and dermatitis herpetiformis. In the last few years, wheat allergy, gluten ataxia and noncoeliac gluten sensitivity have become new gluten-related topics. Adherence to GFDs in CD is limited and factors influencing adherence are poorly understood. Noncoeliac gluten sensitivity has stimulated the GFD food industry not only in Australia but all over the world. This article provides an overview of GFD in daily practice.

Introduction

Over the years coeliac disease (CD) has been given various names in the medical literature, including gluten-sensitive enteropathy and coeliac sprue, with the main purpose to differentiate this entity from tropical sprue. A gluten-free diet (GFD) is recommended for all patients with CD. Moreover, the spectrum of gluten-related disorders in the early 1980s was simple: CD and dermatitis herpetiformis (CD of the skin). Things are changing rapidly. Wheat allergy, gluten ataxia and noncoeliac gluten sensitivity (NCGS) are new gluten-related topics, deserving extra comment in this review. The only treatment for CD, dermatitis herpetiformis (DH) and gluten ataxia is lifelong adherence to a GFD. However, adherence is limited and factors influencing adherence are poorly studied and understood (fig. 1).

Coeliac Disease

CD is defined as a tissue-destroying enteropathy of the small bowel with clinical improvement after gluten withdrawal. It only occurs in genetically susceptible individuals. Until the early 1990s, only patients with characteristic symptoms of malabsorption were evaluated for CD. The introduction of CD-related antibodies in the clinical setting lowered the threshold to test for CD. This enabled population-based screening that revealed CD is much more common than previously thought [1].

As opposed to CD patients identified by case-finding, most of the screen-detected patients experience little or no abdominal discomfort or symptoms of malabsorption

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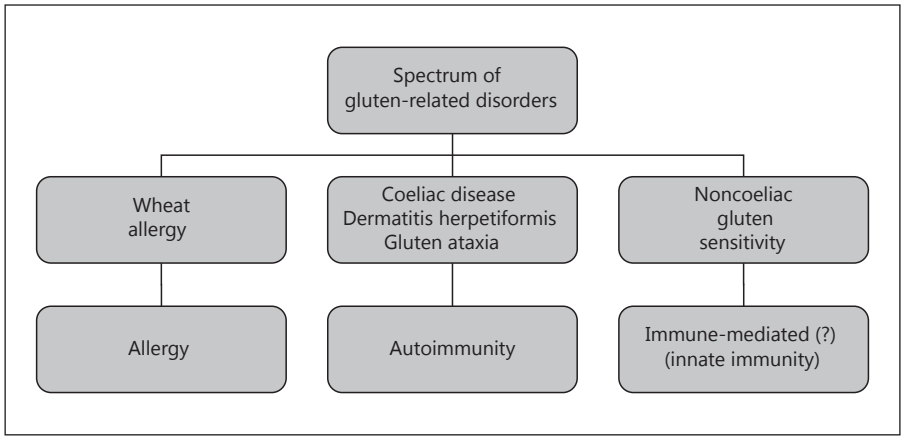

Fig. 1. Spectrum of gluten-related disorders.

[2]. In screen-detected patients, clinical abnormalities such as iron deficiency or osteoporosis can be present and such patients are referred to as atypical CD. The number of patients that actually have been diagnosed is about 20% of the number of CD patients expected based on screenings studies [3].

The realization that many patients were unrecognized and exposed to similar complications as reported in symptomatic CD patients included much discussion as to whether screening in the general population was warranted. Nevertheless, CD screening did not prove cost-effective [4]. The consensus since the early 2000s has been, in addition to case-finding, to screen only high-risk individuals. Screening is recommended for first-degree relatives of CD patients, Down syndrome patients, type I diabetes mellitus, infertility, iron-deficient anaemia, transaminitis, osteoporosis and arthritis [3].

There is a clear benefit of GFD in symptomatic CD patients, which in addition to relief of symptoms is also likely to reduce the risk of complications such as osteoporosis, refractory CD and small intestinal malignancies [5]. However, it is well known that adherence to a GFD is not only an economic burden but also restrictive and can impair quality of life [6]. Therefore, a GFD should be advised to patients when the benefit of such a restrictive therapy has been demonstrated.

Quality of Life of Asymptomatic CD on a GFD

In symptomatic coeliacs, a GFD relieves symptoms, usually within weeks. Adherence to a GFD is accompanied in a lot of countries by sociological and economic, as well as psychological, burdens. Symptomatic coeliacs accept this and appreciate the benefits of a GFD. Asymptomatic coeliacs will not experience direct benefits and therefore consider this as an unnecessary, unwanted and overdone treatment. In line with this, 25% of screen-detected patients regretted being recognized and diagnosed [7].

GFD in Daily Practise

GFD adherence is associated with concern over costs, availability of gluten-free products, concern with gluten exposure and the ability to follow a GFD outside of home. Even the most fanatic patients will have occasional issues with contamination. Some are aware that they are less strict than necessary. Some of our patients believe that they are strictly following the diet, but are making regular errors due to their poor basic education and understanding of the diet.

Evaluation of Dietary Compliance in CD

Decreased compliance over time in asymptomatic adolescents compared with those who presented with typical symptoms of CD has been reported [8]. Interestingly considering the ESPGHAN criteria 2011 is the fact that compliance is higher in children when the diagnosis is confirmed with duodenal biopsy compared to diagnosis by clinical suspicion and no biopsy [9]. Dietary compliance is higher in families in which knowledge about CD is better and in families that belong to a coeliac association. Interestingly, gastroenterologists, dieticians and family physicians provided excellent information to less than 50% of those instructed [10].

Supportive Treatment for Those in Need of a GFD

We have to realize that the adherence to a 'gluten-free' diet is relatively difficult due to:

- Labelling legislation in many countries allows incomplete description of food components.
- Gluten can be found in unexpected sources; for example, as a binder in pharmaceuticals, confectionery, deserts, flavourings and sauces, or as a protein extender in meat products.
- In many cases, especially in developing countries the composition of raw materials is not exactly known even to food manufacturers.
- Current gluten content rules are imprecise: we advise GFDs to be as gluten free as possible in complicated coeliacs like gluten ataxia and refractory celiac disease (table 1) [11].

The strict definition of a GFD remains controversial due to the lack of accurate methods to detect gluten in food. The patients and their relatives should be counselled by a trained dietician [11, 12]. Dietary counselling of patients and the family is the cornerstone of treatment of CD. Major problems are faced by the patients and families on certain issues such as birthday cakes, chocolates, ice creams, biscuits, social functions and travelling. Enjoyable social activities such as birthday parties, sleepovers, summer camp and eating out provide additional challenges to children on a GFD. Airline companies, especially for economy travellers, are not very supportive. Vitamin and mineral deficiencies, including iron, calcium, phosphorus, folate, vitamin B_{12} and fat-soluble vitamins should be looked for especially in the first years of a GFD.

In rapidly developing areas like Eastern Europe, North Africa, Middle East, Iran and India, CD has come to the attention of physicians in the past two decades. The number of patients diagnosed with CD in those countries is still limited. In the past, rice used to be the staple in Southern India, which has a population of 500 million people, but now the people there are now taking wheat ('chapattis') on a daily basis [12]. The market value of gluten-free products and food items has not been properly realized in those countries. The exact number of patients with CD is going to rise and there will be an increased requirement for commercially available food items. Gluten-free is going to become a big business. Legislation for gluten labelling in those countries is insufficient and knowledge of which products are safe is a common problem in daily life.

Table 1. Product groups and products allowed in the 'as gluten-free as possible' diet

Bread	Homemade or baked and wrapped in a 'gluten-free' bakery and made of: gluten-free bread mix with or without wheat starch and a gluten-free logo on the package; gluten-free flour made from (brown) rice, buckwheat, maize, soya with a gluten-free logo on the package or home flour; corn flour, and potato flour Yeast, egg, butter, margarine, oil, sesame seed, linseed, raisins, iodized salt
Sandwich fillings	Cheese Smoked beef, roast beef, liver, salted meat, (raw) ham, bacon, home-made mince Honey, syrup, jam, sugar Egg, herring, shrimps, vegetable salads
Between meals	Milk, buttermilk, yogurt, cottage cheese Tea, coffee with (evaporated) milk, cream or pure whipped cream Homemade biscuits made from the above mentioned flours, homemade meringues or wrapped gluten-free biscuits with the gluten-free logo on the packet Fruit juice, fruit squash and water, mineral water, wine Peanuts or nuts in the shell, dates, gherkins, gluten-free crackers with the gluten-free logo on the packet
Main meal	Broth or soup, homemade from meat, vegetables and pure herbs and spices, or a 100% mixture of these Meat such as steak or a joint, minced fish, game and poultry, each seasoned and prepared oneself Gravy or sauce thickened with corn flour or gluten-free rice flour Fresh or plain frozen vegetables, raw vegetables dressed oneself with oil, vinegar, pepper, salt Potatoes (home-fried), brown rice, pulses, gluten-free pasta with the 'gluten-free' logo on the packet Fruit, compote, homemade custard or whipped puddings thickened with corn flour, gelatin or agar-agar, pure cream (whipped oneself) or sour cream, fruit juice thickened to a sauce with potato flour

In a country like India, it is common practise for families to purchase whole grain and have the flour processed at a small neighbourhood flour mill. It might make sense for underprivileged patients in such villages to use solely home grinding for gluten-free flour.

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Dermatitis Herpetiformis

The role of gluten in CD and DH is clear. The toxic peptide sequences have been defined, the genetic susceptibility loci identified and pathological processes comparatively well known. This chronic skin condition is characterized by an intense burning, itchy and blistering rash. The rash is symmetrically distributed and commonly formed on elbows, knees and the buttocks. Most people with DH will have varying degrees of small intestinal villous atrophy and some even no villous atrophy at all, although signs of enteropathy are present.

Treatment for DH is a GFD for life. In addition, in the majority of patients, dapsone, a drug from the 'sulphone family', may be prescribed to reduce the itching. Response to this medication is dramatic, within 48–72 h.

A strict GFD will result in:

- Improvement of skin lesions, which can take years.
- Reduction in drug dosage for those started on dapsone.
- Flare-ups may require temporary use of dapsone.

Gluten Ataxia

As gluten sensitivity is a systemic illness with diverse manifestations, involvement of the cerebellum is one such extraintestinal manifestation (gluten ataxia). Gluten ataxia is an immune-mediated disease caused by the ingestion of gluten in genetically susceptible individuals [13]. Gluten ataxia is characterized by insidious onset of gait ataxia and with peripheral neuropathy. This diagnosis should be considered in the differential diagnosis of all patients with idiopathic sporadic ataxia. Gastrointestinal symptoms are seldom seen and are not a reliable indicator of the presence or absence of enteropathy. Furthermore, only a small percentage of patients with gluten ataxia show villous atrophy at duodenal biopsy. Antigliadin antibodies are sensitive markers for the diagnosis and on MR imaging up to 60% of patients show cerebellar atrophy. In addition, IgA deposits against TG2 in the small bowel and at extraintestinal sites might be additional markers of the whole spectrum of gluten sensitivity. So far, an early diagnosis and treatment with a GFD can improve ataxia and prevent its progression.

Wheat Intolerance

Wheat allergy is one of the top food allergies in the United States. Wheat allergy is one of the eight most common allergies in the United States. It is estimated that 5% of individuals in westernized nations may have food allergy, although only 0.1% have a documented wheat allergy [14]. Similar to CD, wheat allergy is an immune-mediated reaction to the proteins found in wheat products. In contrast to CD, wheat allergy is an IgE-mediated reaction to the water- and salt-insoluble gliadins, particularly ω–5 gliadin. This gliadin is known as the major allergen of wheat-dependent exercised-induced anaphylaxis ('baker's asthma'). These patients are not allergic towards other prolamin-containing grains, such as rye, barley and oats, from their diet. Therefore, a wheat-free diet is less restrictive in comparison to a strict GFD. In contrast to CD, symptoms of wheat allergy are typical for an IgE-mediated allergy, including itching and swelling in the mouth, nose, eyes and throat; skin rash or swelling; wheezing in the respiratory tract; gastrointestinal symptoms such as cramps, bloating and diarrhoea, and life-threatening anaphylaxis [15]. The gastrointestinal manifestations of wheat allergy and CD can be indistinguishable from each other. Nevertheless, wheat allergy does not cause (permanent) gastrointestinal damage. Wheat allergy usually develops during early infancy or the toddler years and is less common in adolescents and adults. Most children with wheat allergy also have other food allergies. As wheat allergy is a 'classical' IgE-mediated allergy, symptoms can be prevented with strict wheat avoidance and treated with antihistamines and corticosteroids. Affected individuals may need to have epinephrine readily available in case of an anaphylactic reaction, which can be potentially life-threatening.

Gluten Sensitivity

Recent studies suggest the existence of a new condition, NCGS [16]. Many individuals experience better health on a GFD, in absence of typical histological, serological and signs of CD. Furthermore, most of these patients do not carry HLA-DQ2-5 or -8, which is required to develop CD.

An emerging problem in our clinical practice is how to manage patients who experience gluten – or so-called wheat-dependent – symptoms in the absence of the main stigmata of CD.

This syndrome has been described by various names, such as 'gluten sensitivity', 'gluten hypersensitivity' and 'noncoeliac gluten intolerance'. Nowadays, we prefer 'noncoeliac gluten sensitivity'. Leading researchers in CD published the concept of this syndrome 30 years ago in a double-blind crossover trial: 'Gluten-sensitive diarrhea without evidence of celiac disease' [17].

Coeliac centers struggle to define this syndrome. NCGS can be recognized by intestinal symptoms, such as diarrhoea, abdominal discomfort or pain, bloating, and flatulence [16, 18, 19]. Extraintestinal symptoms dominate in our experience: fatigue, headache, lethargy and aphthoid stomal lesions which stabilize, improve and sometimes disappear on a GFD in individuals in whom CD during a proper work-up has been ruled out. NCGS patients tend to come to our outpatient clinic more frequently than CD patients, and our outclinic is reporting more and more severe nonspecific symptoms upon gluten intake by accident than classic CD. Gluten challenge which might be part of the work-up (30 g daily) is generally well tolerated and accepted by coeliacs, but NCGS patients do not accept or tolerate this for longer than a few days.

In general, gastroenterologists regard NCGS as somatization. However, Norwegian researchers recently demonstrated an absence of somatization in NCGS [20]. Personality and quality of life did not differ between NCGS patients and coeliacs. Interestingly, NCGS patients reported more symptoms than CD patients after gluten challenge. Recently, an Australian study provided for the first time high-quality evidence that gluten itself may trigger gut symptoms and fatigue in individuals who do not have CD [19]. So far, the perception has been that gluten intolerance in individuals in Australia without CD was common; the published scientific literature has been negligible. Gluten restriction in the management of NCGS has come and cannot be denied anymore. It is clear that more research in this field is needed in the near future.

Debate about NCGS is everywhere on the Internet. We meet patients advocating a GFD more strict than strict can be (table 1). We recognize well-trained physicians advocating GFDs as an anti-inflammatory diets. In one article found online, 'A musician physician on a mission', advertising for GFD can be found: 'Our digestive tracts had little time to adjust to anything but our inborn hunter-gathered metabolism. Our digestive system can't metabolize gluten etc.' [www.enterolab.com]. In general, there is no scientific support to back them up.

Recently, it was stated by Italian coeliac researchers that 'sense' should prevail over 'sensibility' to prevent a major gluten preoccupation from evolving into the conviction all over the world that gluten is toxic for most of the population [16]. Self-prescription of gluten withdrawal based on Internet information is a growing problem for coeliac outclinics. We cannot correctly diagnose or exclude CD; in NCGS patients they are sure of their intolerance. An individualized approach by gastroenterologists is currently the best approach. We need better criteria for NCGS for our day-to-day clinical practice.

The benefit is clear for the gluten-free products industry; however, coeliacs will also benefit from large NCGS groups on GFD: the economic burden will give rise to new products, product lines, etc. Additionally, competition will most likely have a positive effect on the current high prices for GFD.

Conclusion

Coeliacs and DH patients have had a monopoly on GFDs since the 1950s. The spectrum of gluten-related disorders is dominated in Europe by CD and DH. Since NCGS appeared, especially in Australia and New Zealand, there is gluten-free business everywhere. These disorders have stimulated the food industry. In these countries, gluten-free food is readily available in restaurants. We believe compliance in true coeliacs is an issue and that NCGS patients are true believers for the time they are part of this syndrome and compliance is there.

NCGS may be a new paradigm that is hard for us as coeliac research groups to absorb. Many resist these concepts, finding them unbelievable, unacceptable or both. Rejection is neither rational nor helpful. In Australia, almost 1 million out of 20 million inhabitants are believers in GFDs.

NCGS may be involved in the pathogenesis of a subgroup of irritable bowel syndrome patients, but we lack knowledge which gluten, if any, can contribute to functional bowel disorders [21]. NCGS has yet, by any means, to explain all intolerance to food. It provides a model linking a specific food component with dysfunction.

For coeliacs there is a high priority of highly sensitive noninvasive tests to investigate histologic recovery after GFD to reduce the number of endoscopies and biopsies, but current noninvasive tests are disappointing in this respect [22].

Clinical improvement and seroconversion is no substitute for a biopsy, and histological recovery, especially in adults, is slow and unpredictable [23]. The daily intake of 0.5 mg of gliadin for a 2-year period did not allow mucosal recovery in Catholic women taking communion wafers, who were otherwise improving well on a GFD [24].

Disclosure Statement

The authors declare that no financial or other conflict of interest exists in relation to the content of the article.

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