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REVIEW

Review on pediatric coeliac disease from a clinical perspective

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Abstract

Coeliac disease is an immune-mediated condition characterized by chronic inflammation of the small bowel with villous atrophy driven by gluten ingestion in genetically predisposed individuals. It occurs frequently in both children and adults, affecting 1–4% of the population. The disease is associated with both gastrointestinal and extra-intestinal symptoms related to malabsorption and/or immune activation, and autoantibodies to tissue transglutaminase. Removal of gluten from the diet results in resolution of symptoms and enteropathy in the majority of patients. A good diagnostic work-up is important to avoid unnecessary restrictive diets in children. In this review on pediatric coeliac disease, we address epidemiology including predisposing environmental factors and possible preventive strategies, as well as the clinical presentation, diagnosis and follow-up.

What is Known:

•*Primary prevention of coeliac disease is not possible; however, secondary prevention by targeting high-risk groups is recommended.*
•*The diagnosis is safe without duodenal biopsies if specific conditions are met, also in asymptomatic children.*

What is New:

•*HLA-DQ typing is not routinely required for the diagnosis, whereas it can rule out coeliac disease if HLA-DQ2 and HLA-DQ8 are absent.*
•*Follow-up could be improved by a more rational use of (laboratory) tests, increased intention to dietary compliance and quality of life.*

Keywords Coeliac disease · Children and adolescents · Epidemiology · Diagnosis · Follow-up

Abbreviations

AITD	Autoimmune thyroid disease
CD	Coeliac disease
EMA	Endomysial antibodies
ESPGHAN	European Society of Pediatric Gastroenterology, Hepatology and Nutrition
GFD	Gluten-free diet
GIP	Gluten immunogenic peptides
HRQOL	Health-related quality of life
PCD	Potential coeliac disease
T1D	Type 1 diabetes
TGA	Tissue transglutaminase antibodies
ULN	Upper limit of normal

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Introduction

Coeliac disease (CD) is an immune-mediated condition characterized by chronic inflammation of the small bowel with villous atrophy driven by gluten ingestion in genetically predisposed individuals. The disease is associated with both gastrointestinal and extra-intestinal symptoms related to malabsorption and/or immune activation, and autoantibodies to tissue transglutaminase (TGA) [1]. CD is not a classical autoimmune disease, since the trigger, dietary gluten, is of exogenous origin. Removal of gluten from the diet results in resolution of symptoms and enteropathy in the majority of patients.

Gluten is a group of storage proteins found in wheat and similar grains. In CD, deamidated gluten peptides are presented to CD4 + T-cells by HLA-DQ2 and HLA-DQ8-positive antigen-presenting cells. This activation of gluten-reactive T-cells leads to the production of cytokines and antibodies against tissue transglutaminase (TGA) and endomysium (EMA), inducing small-intestinal damage.

The estimated prevalence of CD worldwide is approximately 1% [2], and prevalence ranges from 0.8% in Europe and Oceania to 4.0% in Africa[3]. A considerable increase in the prevalence of CD has been observed worldwide in the past few decades [3–5]. This increase has not only been attributed to increased disease awareness and availability of highly accurate serological screening tests [6–8], but also to a true increase in disease prevalence [2, 3, 5].

However, CD is still a severely underdiagnosed disease [2, 9]. Based on latest scientific insights, this review on childhood CD addresses its epidemiology including predisposing environmental factors and possible preventive strategies, as well as the clinical presentation, diagnosis and follow-up.

Candidate environmental risk factors for celiac disease (CD)

Ample data indicate that, in the genetically susceptible child carrying the HLA-DQ2 and/or HLA-DQ8 genes, environmental factors contribute to CD [4, 5, 10–12]. While the nature and timing of such factors are still poorly defined, a growing body of literature suggests an association with early-life infections and gluten intake with CD development. In 2014, two clinical trials overturned long-standing hypotheses that neither the presence of breastfeeding nor its duration may decrease the risk of CD development [13, 14].

Given that CD typically develops early in life, it has been natural to focus the search for risk factors in infant feeding and other exposures occurring in the first year(s) of life. Early-life infections in general [15] and intestinal viruses in particular [16–18] have prospectively been linked to an increased risk of CD. Experimental evidence also suggests that viral infections may induce a loss of gluten tolerance [19]. Although less clear [20], the role of infections in CD development is supported by reports of a decreased CD risk following rotavirus vaccination [21, 22]. Infections may contribute to CD pathogenesis as they imprint on the developing immune system and induce pro-inflammatory interferons and expression of tissue transglutaminase. Infections can also cause increased gut permeability which might enable epithelial translocation of gluten, a key process early in CD pathogenesis [23–25].

Current data suggest that the gluten quantity ingested in early life, rather than the timing of gluten introduction might affect the risk of CD [13, 14]. Only in the last few years, three prospective studies have concluded that children eating higher quantities of gluten have an increased risk of CD autoimmunity [26–28]. Interestingly, a higher amount of gluten intake may also augment the risk of CD conferred by enteroviruses [18]. Though results have been mixed [14, 29, 30], the effect of gluten-intake levels in early life may be mediated through changes in the child's developing gut microbiome, which perturbations have, albeit inconsistently, been linked to CD [31, 32]. While encouraging, these findings on gluten intake should spur clinical trials before such observations can be translated into dietary recommendations for preventing CD.

Prevention strategies

Prevention is defined as any activity that reduces the burden of mortality or morbidity from disease, taking place at the primary (avoiding disease development), secondary (early detection and treatment) or tertiary level (avoiding complications by improved treatment) [33]. Only a minority of individuals genetically at risk of CD develop the disease. So, environmental and/or lifestyle factors may play a causal role in the development of CD. As described above, some of these factors have been studied, but taken together, primary prevention strategies are not (yet) possible. One could speculate whether changes in microbiome composition through diet or (pro)biotics might influence CD development, but until present, the role of the intestinal microbiota in CD is unclear so more prospective data on this matter are needed [31, 34–38].

Secondary prevention of CD, i.e., an early diagnosis through target serological screening of high-risk groups, such as first-degree relatives of CD patients, patients with Down, Turner or Williams syndrome and patients with other autoimmune diseases or selective IgA deficiency, is already recommended by most international guidelines [1]. Early case finding and mass screening are still controversial because of the ethical implications. Nowadays, regular follow-up to ensure strict adherence to a gluten-free diet (GFD) with nutritional adequacy, to improve quality of life and to prevent disease complications, is the only available, effective tertiary prevention option. Given that the GFD poses a major challenge and requires patient education, continuous motivation and follow-up, many trials are ongoing or underway to explore non-dietary treatment as possible options for tertiary prevention [39–47].

Diagnostic steps

The European Society for Pediatric Gastroenterology, Hepatology and Nutrition (ESPGHAN) working group on CD published in 2012 a ground-breaking set of proposals, leading the way in the pragmatic diagnosis of CD,

enabling a CD diagnosis without duodenal biopsies in case of TGA > 10 × the upper limit of normal (ULN) and positive EMA in a second blood sample [48]. With evolving evidence and time the ESPGHAN group formulated 10 key questions and proposed diagnostic recommendations in 2020 (Fig. 1) [1].

New key 2020 guideline messages were 1. HLA-DQ typing is not now routinely required to make a diagnosis, since CD-specific antibodies only occur in HLA-DQ2 and/or DQ8-positive individuals, 2. Also asymptomatic children can be diagnosed without biopsies, if all criteria are met, and 3. IgG-based tests are not reliable enough to make

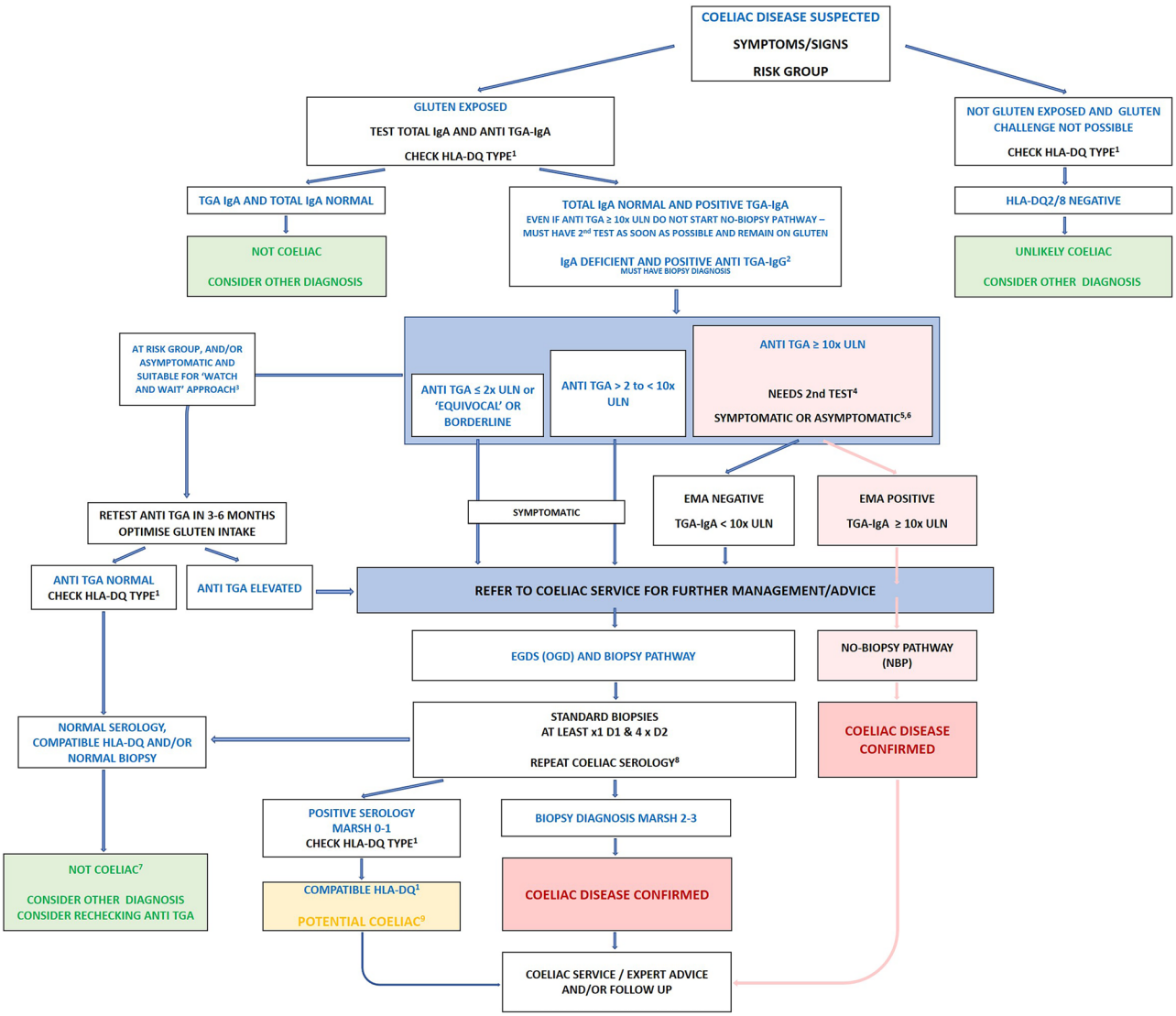

Fig. 1 (1) HLA-DQ typing may be considered at different stages – those who are in at-risk groups as aprimary screening test, in patients who are not gluten exposed and feel they will struggle to do agluten challenge or in those who have normal serology or who have normal biopsies after achallenge. (2) All TGA-IgG positive, selective IgA deficient patients should have endoscopy if CD suspected. (3) For TGA-IgA positive patients, especially in autoimmune at-risk groups (eg T1DM) and those whoare asymptomatic (and especially if TGA-IgA is ≤ 2 X ULN or 'EQUIVOCAL' OR BORDERLINE) consider repeating the TGA-IgA (or TGA-IgG) in 3-6 months whilst the patient remains on normaldiet, as the test may normalise (transient positive antibodies reflecting coeliac autoimmunity). (4) TGA-IgA positive asymptomatic T1DM patients should always have confirmatory biopsies. (5) In centres where EMA-IgA is not available, consider sending the second test to a laboratoryperforming EMA or a second TGA-IgA test may be considered acceptable if a non- biopsy diagnosisis to be considered, rather than proceeding to endoscopy. (6) Discussion regarding endoscopy or a non-biopsy option is essential when a patient isasymptomatic in order to ensure that the family fully understand the implications of the results andto ensure committed long-term adherence to gluten free diet. (7) Other causes of symptoms need to be carefully considered if, after full investigation there is noevidence of CD. (8) TGA-IgA (or TGA-IgG) should be repeated before, or at endoscopy if the procedure is 1 month ormore after the initial test. (9) Potential coeliac disease patients need to be discussed with the coeliac service/ coeliac expert toensure a definitive plan is in place

a diagnosis in low IgA for age or selective IgA-deficient patients and all in this group should be biopsied. Importantly, no significant co-diagnoses will be missed by the non-biopsy approach. Other significant issues included recommendations for duodenal biopsy requirements, key histological criteria were detailed, and importantly the diagnosis and management of "potential" CD, meaning positive CD-specific serology with normal duodenal histology, was discussed; these issues will be addressed in subsequent sections of the review.

Some future directions in CD diagnosis

With the continued evidence for accurate non-biopsy in children, the last year has seen an acceptance of ESPGHAN guidance for symptomatic adults [49]. Beyond ESPGHAN 2020, there are a number of different serology strategies in use including (due to unavailability of EMA-IgA in many centers) a second TGA-IgA test instead of EMA-IgA. Others have proposed the option to repeat a positive serology after 3–6 months (while the patient remains on gluten), especially in patients with autoimmune conditions [50] or those with few or no symptoms, and where serological normalization is possible or will allow clearer evidence to proceed further. Some groups have audited their serology and found strong histological concordance at, for example, over 5X ULN and have proposed biopsy avoidance at this level [51]. All of these proposed alternative strategies need to be carefully and systematically evaluated to remain fully evidence based and secure. Finally, the utility of the "HLA-DQ-tetramer test" and where it fits into a diagnostic pathway for gluten-exposed individuals needs to be established [52, 53]. It will be an exciting prospect in the next few years to see what changes or proposals are suggested to safely amend current guidance.

The role of histology and its pitfalls

Histological examination of the intestinal mucosa is required to confirm CD diagnosis in approximately 50% of pediatric patients [1, 54].

Biopsies from the bulb (D1) as well as second (D2) and third (D3) part of the duodenum should be taken at upper gastrointestinal endoscopy usually under general anesthesia. The progressive injury of the intestinal mucosa is graded mostly using the Marsh-Oberhuber classification [55], as shown in Fig. 2. A minimum of a Marsh 2 lesion (increased intraepithelial lymphocytes and crypt hyperplasia but lacks villous atrophy) is generally accepted as consistent with CD in the context of positive autoantibodies [1].

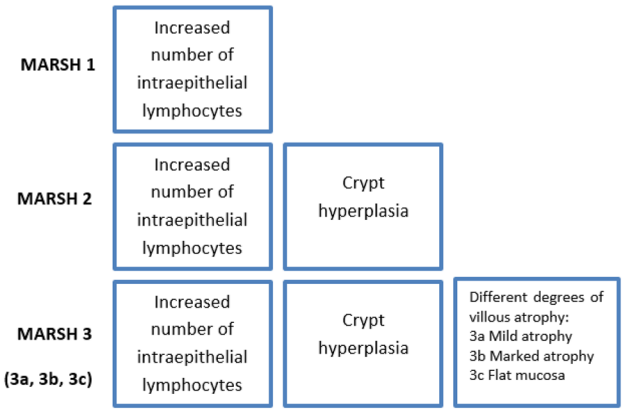

Fig. 2 Marsh-Oberhuber classification of intestinal mucosa lesions in celiac disease [55]. An increase of more than 25 IELs/100 enterocytes is considered abnormal [129]

However, clinicians should be aware of several pitfalls that may make a CD diagnosis less secure. One is not obtaining duodenal bulb samples that could lead to a false-negative result in cases where patchy lesions are limited to the bulb. Bulb mucosal samples are often difficult to interpret because of the characteristics of the area including mucosal damage by gastric acid and the presence of the Brunner's gland and lymphoid follicles impeding evaluations of the villous height [56]. Furthermore, the suboptimal orientation of duodenal samples is a major cause of misinterpretation of the lesions [57]. Whenever the histological interpretation is unclear, for example in cases with discordant results between serology and histology and/or poor sample orientation, reevaluation of new histological sections should be sought as this is the time point for a life-long diagnosis. Finally, the clinician must keep in mind that this histological appearance of the intestinal mucosa is not pathognomonic for CD (lesions mimicking CD may be found in food allergy, Crohn's disease, autoimmune enteropathy, common variable immunodeficiency and even severe malnutrition) [1]. The presence of TGA-IGA has proven to be highly predictive for CD, especially in high titers, where several studies showed strong correlation with clear architectural changes of the intestinal mucosa (villous atrophy) [54]. While the clinical consequences and diagnostic steps of a positive TGA-IGA are clear for most practitioners, a recent meta-analysis recommends caution in the interpretation of a negative TGA-IGA test. When verification bias was applied on the accuracy studies on TGA-IGA measurements, lower sensitivity of the test emerged resulting into possible false-negative results in clinical practice [58].

Potential coeliac disease

Potential CD (PCD) is defined by the presence of CD-specific antibodies in serum (TGA and EMA) in a patient with an architecturally normal duodenal mucosa. Most cases are first-degree relatives of CD patients or children with another autoimmune disease (for example: type I diabetes (T1D), autoimmune thyroiditis). The natural history of PCD is quite heterogeneous: one-third of children on a gluten-containing diet become seronegative; the other children remain seropositive with 40% of them developing villous atrophy during follow-up [59]. Major risk factors associated with the development of villous atrophy are: age at time of diagnosis (younger than 3 years, lowest risk), grade of intestinal inflammation (the higher the infiltration of γδ cells in the epithelium, the higher the risk to develop villous atrophy) and genetic profile (HLA and no HLA genes) [60].

The clinical management of these children is not yet standardized: the majority of cases are asymptomatic, and usually, they remain on a gluten-containing diet with periodically clinical and serological follow-up visits. However, PCD can also be associated with symptoms, even if only half of them, especially abdominal pain, diarrhea and vomiting, have been shown to be gluten-dependent [61]. Therefore, the start of a GFD can be considered with monitoring of symptoms. With all this in mind, prospective studies are needed in order to establish the best way of dealing with PCD and consultation with a coeliac expert is advised in individual patients.

Association with other autoimmune diseases

CD is known to occur more frequently in certain autoimmune diseases, especially T1D and autoimmune thyroid disease (AITD).

Studies focusing on the risk of developing CD in children with T1D estimated the prevalence of CD at 5.6% (range 2.5% to 16.4%) [62], with a few studies also observing a higher risk of T1D in individuals previously diagnosed CD [63, 64]. It was also found that T1D autoantibodies usually precede the development of celiac autoimmunity [65]. In the long run, CD seems to be a risk factor in T1D patients for developing thyroid disease [66, 67] and diabetic retinopathy [68]. It is also shown that growth can be affected for a prolonged time despite a strict GFD in patients with both T1D and CD [69].

Studies on the association of CD with AITD, such as Hashimoto thyroiditis and Graves-Basedow disease, found an increased CD prevalence in pediatric AITD ranging from 2% to 7.8% [70], with 6.2% CD prevalence [71].

Despite the fact that studies on the effect of gluten withdrawal on the development of other autoimmune diseases are controversial with some showing no effect and some claiming a reduction of the risk [64, 72–79], it is recommended to screen for CD in T1D and AITD, even in the absence of gastrointestinal symptoms [1], bearing in mind the possibility of transient increase of low-range positive celiac serology in T1D [50, 80]. In established CD, regular follow-up and evaluation for the possible occult endocrine disorder may also be recommended. A multidisciplinary approach with the cooperation between gastroenterologists and endocrinologists should always be encouraged to take care for patients with both CD and T1D or AITD [50].

Treatment with gluten-free diet

A lifelong GFD is the only effective and accepted treatment for children with CD. It requires complete gluten exclusion, a protein complex present in food and non-food products from wheat, rye, barley, oats, spelt, kamut or their hybridized strains. A product can be labeled "gluten free" if it contains less than 20 ppm gluten (20 mg/kg) [81]. The GFD should contain all the age-appropriate nutrients.

Strict adherence to a GFD is not easy as gluten can be hidden in many processed foods. It may negatively impact the quality of life due to concerns about inadvertent gluten contamination [82]; it might lead to deficiencies in vitamins, minerals and fiber [83, 84] and may perhaps increase the cardiovascular risk although this last issue is not clear [85]. Besides, adherence to dietary recommendations is reported to be lower compared to other health interventions including taking medication [86]. Therefore dietary counseling by a dietician with expertise in CD is an essential component of treatment, but this is time-consuming and requires experience. Specific questionnaires for children can be helpful [87] although short dietary questionnaires and serological markers may be insufficient to detect dietary transgressions [87–89].

Dietary adherence and mucosal healing is suggested by the resolution of symptoms, if the patient experienced any, and by the normalization of the CD-specific serology [90]. However, TGA can take 24 months to normalize after beginning GFD [91–93], and as GFD surrogate markers, they are not accurate enough to detect all possible transgressions during follow-up as they can be normal if only occasional gluten exposure occurs and only repeated gluten transgressions leading to histological damage can cause an increase in TGA levels [94, 95].

Current research on non-dietary treatments for CD

Many patients look for alternative treatments due to the significant burden of their diet [96]. In recent years, novel therapies have emerged aiming to allow coeliac patients to consume gluten safely, but most are still in the pre-clinical phase with only a few in phase 2b or 3 trials. The proposed strategies are: a) decreasing the immunogenicity of gluten by using genetically modified wheat grains [97, 98] and pre-treated flours [99] or by detoxifying gluten using oral proteases [100, 101]; b) sequestering gluten in the gut lumen before absorption [102, 103]; c) decreasing gut permeability and thereby preventing gluten peptides to elicit an immune response [41, 42]; d) using a selective oral transglutaminase 2 inhibitor [47]; e) dampening the downstream immune activation agonist IL-15 or IL-10 or using HLA-DQ2 blockers [104, 105]; and f) inducing immune tolerance to gluten though Hookworm infections [106], vaccines (Nexvax2) [43, 107] or nanoparticles [108].

Follow-up after diagnosis: what should be done?

Follow-up of children and adolescents with CD is necessary to assess symptoms, nutritional status, growth and the development of complications or other autoimmune diseases. Other general goals of coeliac follow-up are to ensure disease education and social support and to motivate the child and its family, reinforcing at each visit, the importance of dietary compliance.

Nowadays, follow-up of CD children is not standardized and based largely on expert opinions; therefor, a lot of variation is seen [109]. The chronic and systemic nature of CD makes a multidisciplinary team advantageous for the follow-up of the patients, including a pediatric gastroenterologist, dietitian-nutritionist, and in some cases, an immunologist, pathologist and psychologist. The first follow-up visit could be scheduled within or around 6 months after starting a GFD. Subsequent visits may be every 6 months until normalization of the IgA-TGA levels and every 12–24 months thereafter. The follow-up visits should include an evaluation of signs and symptoms associated with CD, monitoring of serology (which is expected to normalize within 18–24 months from starting GFD), dietary adherence, growth and pubertal evaluation in adolescents [91, 92, 110].

Other blood tests to monitor iron status, folate, vitamin B12, 25-OH vitamin D level, liver enzymes, especially if abnormal at the time of diagnosis, might be necessary, but evidence on how frequent this is necessary is lacking. This is also true for routine screening for thyroid disease and assessment of bone mineral density, hepatitis B antibody-titer monitoring and the need for specific additional treatments (lactose-free diet, iron supplementation). In order to address these issues, the ESPGHAN working group on CD is preparing a position paper on follow-up in pediatric CD to provide guidance for clinicians.

Future possibilities in follow-up care

Urine and fecal gluten-immunogenic peptides (GIP) have emerged as more sensitive tools to detect gluten ingestion than serological markers or dietary questionnaires as they can detect involuntary transgressions in patients with symptoms and they are also helpful in those cases in which TGA only slowly decreases to ensure correct diet adherence [89, 95, 111, 112]. However, GIPs have a short half-life and more data are needed in order to understand how GIPs should be implemented in clinical follow-up, how often and when (during week or weekend) they should be determined and how the results of this test should be interpreted. Their possible correlation with histological lesions in adults has been described but is still debated [113, 114].

Quality of life in pediatric CD

The health-related quality of life (HRQOL) in children and adolescents can be affected after CD diagnosis and the subsequent start of a GFD. Difficulties in accepting the diet, feeling different and upset about the need to comply to the GFD, especially during meals outside but also at home, are factors that can negatively impact emotions, social relationships and daily life.

When a CD-specific HRQOL questionnaire is used, CD children and adolescents show a poor to neutral HRQOL [115–119]. Conversely, when a generic HRQOL questionnaire is used, results are similar to healthy children [116, 118, 120–126]. Parents seem to underestimate the HRQOL of their children [115, 121, 127], whereas physicians were shown to overestimate the HRQOL of children and young adults with CD during follow-up [119]. Thus, relevant insight in HRQOL of coeliac children and adolescents during follow-up is best obtained by using CD-specific HRQOL questionnaires.

After childhood: the importance of transition of care

The transition between pediatric and adult care for young people with chronic illnesses, including CD, is often poorly organized [128], with a risk of loss of follow-up and may potentially have negative consequences on disease and quality of life. A systematic literature review on the transfer of

care in different chronic diseases suggested that the most common strategies in successful programs were patient education and specific transition clinics jointly staffed by pediatric and adult physicians or dedicated young adult clinics within adult services [129]. A transition letter written by the pediatrician may facilitate transition [130–132]. The transition letter should contain details on the basis of CD diagnosis and a summary of important follow-up information such as serology, growth data, comorbidities and dietary adherence. Follow-up in adults with CD can be done by gastroenterologists and general practitioners. Similar to pediatric follow-up care, there is no evidence regarding interval and issues that need to be addressed.

In conclusion, the incidence of childhood CD is still increasing, but the disease is still severely underdiagnosed. At the moment, only secondary preventive measures are available, encouraging medical professionals to diagnose CD as early as possible. The diagnosis in children can be established without duodenal biopsies in about 50% of selected cases. Follow-up practices need to be evidence based with special attention to the compliance to the GFD and HRQOL of our coeliac children.

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