ESPGHAN position paper on management and follow-up of children and adolescents with coeliac disease

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ABSTRACT

There is a need for consensus on the recommendations for follow-up of children and adolescents with coeliac disease.

Aim: To gather the current evidence and to offer recommendations for follow-up and management.

Methods: The Special Interest Group on Coeliac Diseases of the European Society of Paediatric Gastroenterology Hepatology and Nutrition formulated ten questions considered to be essential for follow-up care. A literature search (January 2010 - March 2020) was performed in PubMed or Medline. Relevant publications were identified and potentially eligible studies were assessed. Statements and recommendations were developed and discussed by all co-authors. Recommendations were voted upon: joint agreement was set as at least 85%.

Results: Publications (n=2775) were identified and 164 were included. Using evidence and/or expert opinion, 37 recommendations were formulated on: The need to perform follow-up, its frequency and what should be assessed, how to assess adherence to the gluten-free diet, when to expect catch-up growth, how to treat anaemia, how to approach persistent high serum levels of antibodies against tissue-transglutaminase, the indication to perform biopsies, assessment of quality of life, management of children with unclear diagnosis for which a gluten challenge is indicated, children with associated type 1 diabetes or IgA deficiency, cases of potential coeliac disease, which professionals should perform follow-up, how to improve the communication to patients and their parents/caregivers and transition from paediatric to adult health-care.

Conclusions: We offer recommendations to improve follow-up of children and adolescents with coeliac disease and highlight gaps that should be investigated to further improve management.

KEY WORDS: Coeliac disease, children and adolescents, follow-up, position paper

European Society of Paediatric Gastroenterology Hepatology and Nutrition (ESPGHAN)

What Is Known

There is a need for consensus on the methods regarding follow-up children and adolescents with coeliac disease.

What Is New

The Special Interest Group on Coeliac Diseases of the European Society of Paediatric Gastroenterology Hepatology and Nutrition (ESPGHAN) formulated ten questions considered to be essential for the follow-up care.

Based on the available evidence from the literature and/or on expert opinion, 37 recommendations to improve follow-up were formulated.

Gaps in knowledge were identified that should be investigated to further improve follow-up.

It is generally accepted that clinical follow-up of children and adolescents with coeliac disease (CD) is necessary to assess growth and development, resolution of their symptoms and possible complications and monitor compliance to the treatment with a gluten free diet (GFD). However, the current follow-up approach is largely based on local practice and opinion with lack of evidence-based approaches. The responses to an enquiry of the Special Interest Group (SIG) on CD of the European Society of Paediatric Gastroenterology Hepatology and Nutrition (ESPGHAN) among paediatricians and paediatric gastroenterologists across Europe showed significant variation in the methods of following-up their patients and offered scope for improvement (1).

The aim of this position paper was to therefore gather and evaluate the current evidence for the management and follow-up of CD in children and adolescents and offer recommendations on this topic.

METHODS

In 2019, ESPGHAN established a working group within the SIG on CD to develop a position paper on the management and follow-up of children and adolescents with CD. The working group consisted of paediatric gastroenterologists, a methodologist (PW), two adult gastroenterologists (CCi, AAT), a biologist (MR) and a representative of the Association of European Coeliac Societies (AOECS) (TK). During several group meetings, ten focused clinical questions considered to be essential for follow-up care were formulated (table 1). Smaller working groups, consisting of three to five co-authors, focused on each clinical question. All questions were then discussed jointly at two face-to-face meetings and at eight videoconferences.

Search for and Inclusion of Studies

Eligibility criteria: We searched in PubMed or in Medline for articles published in English from January 2010 to March 2020, relevant to children and adolescents (<18 years) diagnosed with CD according to the ESPGHAN criteria (2,3). However, if a paper published before or after these dates was considered particularly important for an individual question, it was also included and this information was specified in the corresponding search results for the question, both in the Summary Table of the Literature (Supplementary Appendix) and in the individual section of the question. The basic search strategy with emphasis on CD in children was shared by all groups and

broadening of the inclusion of publications was allowed according to the specific question. Full search strategies for each question are presented in the Summary Table of the Revised Literature (Supplementary Material). We excluded single case reports, commentaries, abstracts, non-systematic reviews of the literature such as narrative reviews and expert opinions and studies performed exclusively in adults. In particular, if a narrative review was considered especially important or if no paediatric studies were available, this information was also included and specified for the corresponding single question as well as in the Summary Table of the Revised Literature (Supplementary Material). Relevant papers were identified by review of their title and abstract contents. In case of potentially eligible studies, full texts were assessed. The final choice of studies was agreed upon by discussion and consensus. For each question, a short summary of the selected papers was provided, including study design (prospective or retrospective, cross-sectional or case-control), age of the study population, sample size, study objectives and main findings (Summary Table of the Revised Literature, Supplementary Material).

Strength of Recommendations

A recommendation was given for each (sub)question after an open discussion involving all co-authors, followed by a close individual voting. Agreement was set at 85% for each recommendation. When no agreement was reached, another round of discussions was performed to formulate a new recommendation upon which a final vote was taken. The recommendations are presented in Table 1.

Ethics and Regulations

All guideline members' conflicts of interest have been noted and registered on the ESPGHAN website. The development of the position paper was funded by ESPGHAN and was developed in collaboration with AOECS.

Results

Overall, 2775 publications were identified of which 164 informed these recommendations (Summary Table of the Literature, Supplementary Material).

Question 1: Is follow-up and management of CD needed?

A search was conducted in Medline using the search terms celiac, coeliac, children, adherence and follow-up. The search identified a total of 356 records, of which 12 were included for this question: 8 primary observational studies (7509 children) and 4 systematic reviews (640 studies). We included 1 study in both adults and children (Kurppa 2012), 1 systematic review

until the age of 20 years (Snyder 2016) and another one without an age specification (Valitutti 2017).

One goal of short-and medium-term follow-up is the monitoring of the improvement of symptoms after starting the GFD. In patients with inadequate improvement (symptoms, catch-up growth, serology) after short-medium-term adherence to the diet, it is necessary to investigate hidden sources of gluten in the diet and to consider the presence of other pathologies. Complications should be checked for. Another general goal is to ensure education on the condition and social support and to motivate the child with CD and their family (4,5), reinforcing at each visit the importance of dietary compliance which may vary between 45-90% (6-9). Strict adherence to GFD has a positive impact on the improvement of symptoms (10) and it may also allow prevention of CD-associated complications. Whether the risk for associated autoimmune diseases can be reduced by early diagnosis and treatment of CD remains controversial (11). During one of the first visits after the diagnosis, information on the increased risk of CD among first degree relatives and their indication of CD screening according to the ESPGHAN diagnostic guidelines (3), should be part of the family education. Information on new treatment avenues should also be given during follow-up.

Current recommendations on follow-up are largely based on expert opinion (12,13). Reports have emerged that may help shape the follow-up content of the follow-up visits (14). The chronic and systemic nature of CD makes a multidisciplinary team advantageous for follow-up, including a paediatric gastroenterologist, dietitian-nutritionist, and in some cases, an immunologist, pathologist and psychologist. Consultation with a paediatric gastroenterologist or a paediatrician with expertise in CD is recommended for diagnosing the disease. They should likewise be involved in the monitoring and adequate interpretation of the laboratory test results requested during follow-up, as well as in the identification and management of possible associated complications. During adolescence, the transfer to adult health-care is initiated and organized, depending on the patient's understanding of the condition, readiness and required maturity to transition into adult services (15).

Statement and Recommendation: We recommend follow-up for children and adolescents after the diagnosis of CD has been established. *100% Agreement.*

Q2. Who should do the follow-up of which patients and which is the role of the dietitian? What is the role of self-care and E-health?

A search was conducted in PubMed using the search terms celiac, coeliac, children, follow-up, gluten-free diet, paediatrician, paediatric expert in the field of celiac, general doctor, dietitian and e-health. The search identified a total of 111 records, of which 4 were included: 2 primary observational studies (381 children) and 2 randomized clinical trials (RTC) in both children and adults (Haas 2017, Vriezinga 2018) (365 patients <25 years).

Children with CD have traditionally been followed by paediatric gastroenterologists or paediatricians and sometimes after a period of a GFD by a dietitian (3). The indicated person to conduct the follow-up of children with CD differs substantially between countries and even regionally within countries applying the same health-care system. The general recommendation by most studies indicates that access to a dietitian and/or a physician with an interest in CD is important for adequate treatment and evaluation of adherence to the GFD (see question 1). There is, however, a paucity of studies that compare long-term effects of dietary compliance depending on who conducts the follow-up. The only study investigating compliance to the diet in children followed by a dietitian or a by a physician showed no differences in outcome, albeit dietitian-led visits being less expensive (16).

A cornerstone of successful treatment of children with CD is how they adapt to the GFD. Educating children, adolescents, parents and guardians (and extended family) about the GFD constitutes an important component of the follow-up visits (see question 9). Whether education in self-care of children with CD should be separated from physical follow-up visits may depend on local conditions and practices.

Communication over the internet offers new opportunities to connect to the patient and families and are under development. E-learning is defined as all forms of electronically mediated teaching. Electronic health technologies (E-health) is the use of information and communication technologies, such as smartphone applications, in support of health and disease management. Utilizing E-learning and E-health as a replacement for physical follow-up visits of children with CD has recently been evaluated. Three studies (of which two were RCTs (17,18) have investigated E-health in the follow-up of patients with CD. Haas et al. studied the influence of Text Message intervention in newly diagnosed children and young adults. Vriezinga et al. compared online consultation versus in-office outpatient visits. Both interventions positively affected self-management, QoL, patient satisfaction, and in one study reduced health-

care costs compared with conventional in-office standard of care. Another RCT by Connan et al. prospectively studied a small number of participants (n=33) and found an improvement in knowledge about CD by introducing interactive E-learning methods (19).

Statement.

2. There is evidence that the follow-up of children with CD should be performed by a physician and a dietitian with experience in managing and evaluating patients on a GFD. While a dietician-led follow-up of CD has shown promising results and may come at a lower cost, more research is needed before stating whether a dietitian, a physician, or both should conduct the long-term follow-up. E-health interventions seem promising tools in CD-care, which utilization and effectiveness in CD care should be further explored.

Recommendations.

2. The regular follow-up visits of children with CD are preferably carried out by a physician and/or a dietitian experienced in managing the disease. Local conditions and practices may determine how to apply these recommendations, but self-care treatment without access to adequate health-care and dietitians is not recommended.

93% Agreement.

Question 3: What should be the frequency of follow-up and what should be assessed?

A search was conducted in Pubmed using the search terms celiac, coeliac, children and follow-up. The search identified a total of 382 records, of which 30 were included for this question: 17 primary observational studies (1599387 children) and 13 reviews (772 studies). We included 1 guideline in adults (Al Toma 2019), one publication in adults and children (Husby & Murray 2019) and one systematic review (Zingone 2018) in adults. We also included 5 studies published before 2010 (Ansaldi 2003, Elfström 2008, Leonardi 2009, Meloni 2009 and Park 2007) and 1 after March 2020 (Lionetti 2021).

Current literature does not provide solid evidence on the optimal frequency of follow-up. Despite a lack of high-quality studies, a first follow-up visit scheduled 3-6 months after CD diagnosis is recommended, but with easy access to the coeliac service if earlier advice is needed and with earlier clinic review depending on family knowledge, concerns and difficulties with the diet, and importantly, if symptoms persist or worsen despite strict adherence to GFD, or if clinical presentation (e.g. malnutrition) or laboratory abnormalities at diagnosis require earlier follow up. Intervals for further

follow-up visits should also take the “above mentioned” issues under consideration, and be scheduled at a 6-12 months interval and every 12-24 months afterwards.

Paediatric patients on a strict GFD usually show rapid resolution of CD-related gastrointestinal symptoms, such as bloating, diarrhoea, abdominal pain, weight loss, as well as of extra-intestinal manifestations such as anaemia, delayed puberty and stomatitis (20). Inconsistent or no follow-up is associated with poor dietary adherence (10).

Normalization of serology is widely used during follow-up as a proxy for mucosal healing in children with high positive and negative predictive values (21-23). A significant reduction in levels of IgA against tissue-transglutaminase (TGA) is already seen after three months of GFD if measured with the same assay. However, TGA levels remained above 1x the upper level of normal (ULN) in 83.8% and above 10xULN in 26.6% of studied children after 3 months on GFD (24). Full normalization of both TGA levels and histopathology may take over two years, particularly in those with severe small bowel lesions and high TGA levels at diagnosis (25-27). IgG based tests and radio immune assay (RIA) based TGA measurements are not suitable for monitoring response to a GFD in IgA sufficient patients with CD.

Bone health may be compromised in CD patients (28) and in children bone disease is mostly asymptomatic and associated with decreased growth and bone quality (29). In contrast to that observed in adults (30), CD in children does not seem to be associated with an increased fracture risk (31). A reduced bone mineral density (BMD) may be present at CD diagnosis in children and adolescents (29, 32). Although a longer follow-up might be needed in some cases to ensure a proper BMD recovery (33), in most cases, one year on a strict GFD is sufficient to restore bone mass (12, 14, 28). Therefore, routine BMD testing is neither required nor cost-effective. When bone loss has been identified for clinical reasons serial bone-density tests should be conducted every 1 to 2 years until normalization (12).

Vitamin D levels have been investigated in CD children in several studies that are heterogeneous in their design and outcomes. Some of these demonstrate low vitamin D levels at diagnosis (12, 14, 34-36), but the impact of the GFD on vitamin levels remains uncertain. Although the evidence is not strong, assessment of vitamin D status, in case

of abnormal levels at CD diagnosis, and correction of any ongoing deficiency should be considered good patient care to optimize bone health.

The liver is a common site of extra-intestinal manifestations of CD, usually presenting with raised aminotransferases. Liver function should be monitored during follow-up if abnormal at diagnosis (12).

As CD children may present with micronutrient deficiencies, investigations for iron (commonest), folate, and vitamin B12 deficiencies are relevant at diagnosis and, if abnormal, these should be monitored until normalization, either via the GFD or supplementation in case of anaemia or depleted iron stores.

The risk of autoimmune thyroid disease is increased in CD patients as reported by a large population study (37) and several case-control studies (38-40). However, other studies show no added benefit of thyroid disease testing in CD children in the absence of symptoms (14). Based on the current literature, there is no evidence to advise whether assessment of thyroxin or thyroid stimulating hormone (TSH) blood levels should be monitored during follow-up, and in which frequency.

Concerning immunization, HBV vaccine has been shown to potentially have a reduced response, with 50% of patients with CD having a poor antibody response vs. 11% of controls in case of vaccination within the first 6 months of life (41-43). In addition, one study reported reduced protection after HAV vaccination (42). Whether this is related to genetic host susceptibility or to other factors has not been clarified. Based on the above, screening for HBV immunisation status has been suggested in newly diagnosed CD children (12). There is no current evidence indicating that response to HBV vaccine should be evaluated during follow-up. However, if a poor antibody response is detected, revaccination should be performed (43). A second dose effectively induces protective levels in those CD children (41-44). Several studies detected no differences between CD children and controls in the immune response to poliomyelitis, diphtheria, mumps, and pertussis (45), rubella, tetanus (45, 46), haemophilus influenzae type b (46) and measles (45, 47). There is therefore currently no evidence to support routine checking of vaccine response during follow-up.

The question about who should follow up the patient is the subject of question 2 in this paper. In general, and based on the resources available in each national system, a paediatric gastroenterologist or a paediatrician with special interest/experience in

paediatric gastroenterology or an experienced dietitian could follow the patient with CD.

Statements

1. The current literature does not provide evidence on the optimal frequency of follow-up or what should be assessed during visits.

2. Normalization of IgA-TGA levels is widely used as a proxy for mucosal healing in children.

3. Nutritional deficiencies may be present at the time of CD diagnosis.

4. Children with CD have an elevated risk of autoimmune thyroid diseases.

5. A reduced BMD may be present at CD diagnosis.

6. Vaccine responses in children with CD are identical to those of the general population, except for a moderate level of evidence of poor seroconversion in response to HBV vaccination.

Recommendations

3.1.The first follow-up visit should be scheduled 3-6 months after CD diagnosis, but with easy access to the coeliac service if earlier advice is needed, and sooner review if there are concerns regarding how the family is coping with the diet, if there are ongoing issues with growth or persistent symptoms or a need to repeat bloodwork earlier. Subsequent visits should be every 6 months until normalisation of the TGA levels, and every 12-24 months thereafter. *93% Agreement.*

3.2. During follow up patients should be evaluated for:

3.2.I. Gastro-intestinal and extra-intestinal signs and symptoms. *100% Agreement.*

3.2.II. Anthropometric measurements and growth parameters. *100% Agreement.*

3.2.III. IgA-TGA using the same assay (ELISA or EIA) as at diagnosis, as a surrogate marker for improvement/healing of the small bowel mucosa. IgG based tests and RIA based IgA-TGA measurements are not suitable for follow-up in IgA sufficient patients. IgA insufficient patients with CD should be followed with IgG based tests. *100% Agreement.*

3.2.IV. A complete blood cell count, micro-nutritional status (e.g., haemoglobin, iron, vitamin B12, and vitamin D levels) and ALT measurements, should be performed after clinical evaluation at time of diagnosis. Any abnormality should be followed and deficiencies corrected until normalization. If abnormalities persist additional diagnoses should be considered and appropriately investigated. *91% Agreement.*

3.2.V. Screening for thyroid disease with TSH and thyroxine (and autoantibodies if indicated) may be considered during follow-up after clinical evaluation at the discretion of the clinician. *91% Agreement.*

3.2.VI. Routine bone density screening is not recommended . *93% Agreement.*

3.2.VII. HBV antibody levels may be measured in previously immunized patients if this is considered important in the population. A booster dose should be given if inadequate levels are present. *91% Agreement.*

Question 4. Adherence to the gluten-free diet.

4.1. Should the adherence to the diet be assessed during follow-up and if so, how?

A search was conducted in Medline using the search terms celiac, coeliac, children, adherence, follow-up, gluten-free diet, dietitian, teenagers, questionnaires, score, E Health/App. The search identified a total of 54 records, of which 9 were included for this question: 6 primary observational studies (306 children) and 3 systematic reviews (15470 studies). We included 2 studies in adults and children (Comino 2016, Moreno 2017) and 2 in adults (Down 2018 and Harder 2020). We included Harder et al. published after March 2020.

There is general consensus about the need to assess adherence to the GFD during the follow up of CD patients (48-50). Despite the absence of a gold standard to assess dietary compliance, a dietary evaluation by a trained dietitian is considered the best method, as it is the cornerstone of dietitians to asses and manage diets, but this is time-consuming and requires expert personnel. Short dietary questionnaires and TGA determinations in serum fail to detect dietary transgressions in children and adolescents with CD, showing poor sensitivity to identify all patients who consume gluten (51-53). There is a limited range of questionnaires specific for children. Long questionnaires specific for children may be useful to assess diet compliance, especially in settings with no dietitian consultation available (51).

In spite of the wide use of determination of specific CD antibodies, especially TGA in serum as a surrogate marker of GFD adherence, negative TGA results do not correlate well with dietary compliance (21, 54).

Further development of E-Health resources for assessment of adherence to the GFD are needed, as most available CD smartphone apps lack clinical validation (55).

Statement

The assessment of adherence to the GFD is one of the primary goals of CD follow-up.

Recommendation

4.1. Since a gold standard method is still missing, adherence to the GFD should be assessed multi-dimensionally through a careful evaluation of symptoms, dietary interview and/or dietary questionnaires and laboratory tests. *100% Agreement.*

4.2. What is the role of detection of Gluten Immunogenic Peptides (GIPs) in the assessment of compliance to the gluten-free diet?

A search was conducted in Medline using the search terms celiac, coeliac, children, adherence, follow-up, gluten immunogenic peptides, gluten free diet, compliance, adherence, diet, monitor, aftercare, secondary care and health-care. The search identified a total of 28 records, of which 7 were included: 5 primary observational studies (1 in children, 2 in both adults and children and 2 in adults) (129 children) and 2 systematic reviews (990 publications). We included studies in adults (Stefanolo 2021 and Sylvester 2020) and in both adults and children (Comino 2016 and 2019 and Moreno 2017). We included Silvester 2020 and Stefanolo 2021 published after March 2020.

A small fraction of ingested gluten peptides is excreted in urine and in stools, thereby revealing recent gluten exposure. Measurement of GIPs in stool or urine has been introduced as a tool to detect gluten ingestion in patients adhering to a GFD (53, 54, 56-58). GIPs may be detected using specific monoclonal antibodies, A1 or G12, recognizing gluten epitopes by lateral flow immunochromatography (LFIA) (stool or urine) or ELISA (stool). Compared with other methods to evaluate adherence, GIP testing disclosed the lowest adherence rate to the GFD (75%), suggesting that this assay is more sensitive than others to detect cases occasionally exposed to inadvertent gluten ingestion (9). Repeated GIP positivity over a span of multiple days has been reported to correlate with intestinal mucosa damage (49, 54). Now that GIPs are available for use in clinical settings and for disease self-managing by the patient, some questions remain to be answered, as the indication for urine or stool testing, the latency between gluten exposure and appearance in stool/urine, the relationship between the quantity of ingested vs eliminated gluten in stool/urine and the role of these tests in the assessment of long-term adherence to GFD.

Statement and Recommendation

4.2. Further data are needed before a recommendation on stool/urinary GIPs determination to assess compliance to the GFD in clinical practice can be formulated. *93% Agreement.*

Question 5. Common issues during follow-up and management of CD. 5.1. When to expect catch-up growth? 5.2. Is a lactose-free diet necessary? 5.3. Chronic tiredness in

well-controlled CD. 5.4. Irritable bowel syndrome (IBS) in CD? 5.5. How to treat anaemia and/or sideropenia?

A search was conducted in Medline using the search terms celiac, coeliac, children, follow-up, catch up, growth and development, lactose intolerance, chronic tiredness, fatigue, irritable bowel syndrome, anaemia and iron deficiency. The search identified a total of 58 records, of which 18 were included: all primary observational studies (1590861 children). Two papers on adults and children were included (Jericho 2017, Burger 2018).

5.1. When to expect catch up growth?

Four original studies were included (29, 59-61-). All studies but one were retrospective and with a limited sample size. Only one study assessed the correlation between recovery of growth velocity and decrease in CD antibody levels (61). Maximum catch-up growth in weight and (in the pre-pubertal child) also in height, is expected within the first six months on a GFD (61) and it can continue for 2-3 years, at which time the child is predicted to reach the expected height. Age at diagnosis may influence final/target height (59) , but it is controversial whether it is possible to prevent permanent height reduction by early dietary treatment. Negative TGA is associated with a rapid weight recovery but does not seem to have the same long-term effect on catch-up of height (29, 59, 60).

Statement

5.1. In a child with impaired growth at the time of CD diagnosis, catch-up growth in weight and height is usually expected within six months after starting the GFD, after which, depending on the patient's age and continuance of the diet for 1-2 years, expected height is reached.

Recommendation

5.1. In the pre-pubertal/pubertal child, if significant catch-up growth in height is not reached within 1 year after initiating GFD, despite strict dietary adherence, additional investigations and consultation with a paediatric endocrinologist are recommended to rule out other causes of short stature. *93% Agreement.*

5.2. Is a lactose-free diet necessary?

Untreated CD may cause secondary lactose intolerance due to villous damage, but this is not a consistent finding. The prevalence of genotypes predisposing to adult-onset primary hypolactasia in CD patients is comparable to the rate within the general population (62, 63).

Statement

5.2. CD patients may develop primary lactose intolerance over time, similar to the general population. Patients can also have secondary lactase deficiency due to villous damage, but are usually lactose-tolerant and there is no evidence of the benefits of temporary lactose-free diet on top of the GFD, unless clinical symptoms are highly suggestive of concomitant lactose intolerance (such as ongoing diarrhoea, abdominal pain and/or gassiness after starting GFD).

Recommendation

5.2. We recommend a trial with lactose-reduced diet only in CD patients with symptoms suggestive of lactose intolerance (such as ongoing diarrhoea, abdominal pain and/or gassiness) despite adhering to the GFD. *93% Agreement.*

5.3. Chronic tiredness in well- controlled coeliac disease?

Only two papers (64, 65) were found, both reporting that children had greater and more significant improvements of chronic tiredness on a GFD compared to adults with CD. Fatigue improved significantly in 81% of children on a strict GFD and only 3 of the 40 children had persistent chronic fatigue after one year on the diet.

Statement

5.3. CD children on GFD have a significant improvement in chronic fatigue.

Recommendation

5.3. There are no specific recommendations for chronic fatigue in CD except to follow a GFD. *97% Agreement.*

5.4. Irritable Bowel Syndrome (IBS) in coeliac disease?

Similar prevalence of abdominal pain and functional gastrointestinal disorders have been demonstrated in CD on a GFD for at least six months vs. controls on a regular diet (66). In both CD patients and in controls, the most common functional gastrointestinal disorder was IBS.

Statement

5.4. No increased frequency of IBS has been demonstrated in children with CD on a GFD.

Recommendation

5.4. IBS in children with CD on a GFD should be treated similarly as in children without CD. *93% Agreement.*

5.5. Anaemia and/or sideropenia

Seventeen studies were evaluated and ten paediatric studies were included (14, 37, 64, 67-73). Only one study was prospective (71). Anaemia is a frequent finding (12-24%) in children with untreated CD (64, 67-70). It is usually caused by iron deficiency, but also vitamin B12 and folate deficiencies and anaemia of chronic disease may contribute. In one large nationwide study, anaemia, regardless of the underlying aetiology, was significantly more common in adolescents with CD compared to controls (37). However, prevalence of subclinical iron deficiency is rarely reported during follow-up. In most cases (84%-96%) anaemia improves or recovers on a GFD (14, 64, 67, 70, 72). Poor compliance to GFD may hamper recovery (70, 73). Evidence is lacking regarding the incremental benefit of routinely adding iron supplementation.

Statement

5.5. CD is a common cause of anaemia and associated nutritional deficiencies in children. Abnormal values should be monitored until normalization on a GFD. An adequate response can be expected within one year from initiating GFD, although more prospective evidence is needed. Poor dietary compliance and/or reduced nutritional iron-content predispose to non-recovery of anaemia.

Recommendation

5.5. Young children with anaemia due to iron, folate or vitamin B12 deficiency should receive supplementation in addition to the GFD, since improvement over time may take too long in these in children in a critical period of brain development and rapid catch-up growth. A low threshold for supplementation may also be considered for older children. The disappearance of anaemia should be confirmed in all cases, adherence to the GFD should be checked, and other causes for anaemia should be excluded in children who do not recover despite a strict GFD. Concerning sideropenia without anaemia, an expectant attitude may be appropriate on the GFD as long as there is improvement in iron stores without supplementation. *95% Agreement.*

Question 6. Specific issues during follow-up and management.

61. How to approach persistent high TGA levels during follow-up?

A search was conducted in PubMed using the search terms celiac, coeliac, children, follow-up, persistent or elevated transglutaminase, antibody and gluten-free diet. The search identified a total of 167 records, of which 17 were included: all primary observational studies (2128 children). We included one article published after March 2020 (Sansotta 2020).

Although CD serology markers (IgA-TGA and endomysial autoantibodies (EmA)) work very well for diagnosis, these are less accurate for dietary monitoring (74, 75). Dynamics of CD antibodies after diagnosis may vary according to the adherence to the GFD, the timeframe of testing, type of antibodies, age at diagnosis, coexisting diseases (IgA deficiency, type-1 diabetes), antibody levels at diagnosis, and by assays used (25, 26, 76-83).

During follow-up, continuous decreasing levels of IgA-TGA, until values below cut-off of normality (CON) are reached, and a negative EmA cautiously reflects sufficient dietary compliance (84, 85). On a GFD, IgA-TGA levels decrease over time and are expected to normalize by 18-24 months after starting the diet (84) depending on the serology kit used. No data are available on how slightly elevated IgA-TGA at follow-up should be addressed. However, it is reasonable to suspect that persistently slightly elevated IgA-TGA levels imply inadequate dietetic compliance in most patients with CD.

Different methods are available to detect CD antibodies in serum: enzyme-linked immunosorbent assay (ELISA); chemiluminescence; radioimmunoassay (RIA). For decades, the most widely used CD serology assessment method has been ELISA and the majority of clinical evidence available has been addressed by this technique. Persistent positivity of chemiluminescence IgA TGA should be interpreted with caution since it has a slower decrease over time (26) and should be better integrated with ELISA assay since more follow-up data are available on this latter technique with regards to dietary monitoring. Nevertheless, it should be clear that CD-specific antibody measurement does not suffice to evaluate compliance to a GFD and to establish complete recovery of mucosal healing. Gastrointestinal symptoms, with or without slightly elevated CD antibodies, may persist in a small percentage of children claiming optimal dietary adherence (86, 87) (see also question 6.2).

Statements:

6.1. IgA-TGA levels are expected to normalize by 18-24 months following the start of a strict GFD.

Recommendation:

6.1. Lack of decreasing IgA-TGA levels after 6-12 months on a GFD or persistently positive IgA-TGA levels should be assessed by carefully reviewing dietary compliance and testing IgA-TGA using the same test from the same manufacturer. *93% Agreement.*

6.2. When is it necessary to (re)biopsy?

A search was conducted in PubMed using the search terms celiac, coeliac, children, follow-up, repeated, biopsy and follow-up biopsy. The search identified a total of 225 records, of which 8 were included: 6 primary observational studies (592 children) and 2 systematic reviews (87 studies). We included 3 studies in both adults and children (Osman 2014, Sylvester 2017 and Szakács 2017).

After CD diagnosis, duodenal biopsies to assess mucosal healing may be considered as an ultimate option to discuss thoroughly with the family and to dismiss any further doubt about compliance and responsiveness to the GFD. This may be of clinical value even in those asymptomatic children whose parents claim strict dietary adherence but with still, mostly slightly, elevated IgA-TGA after 24 months on a GFD. Following this path, in the case of normal duodenal mucosa (Marsh 0 and Marsh 1) the family can be reassured (75). In case of persisting major mucosal abnormalities (i.e. Marsh 2 (crypt hyperplasia) and/or Marsh 3 (villous atrophy)), better dietary compliance should be encouraged.

In the scarce literature regarding persisting villous atrophy in CD children on a GFD, we found a prevalence of 2%-19% at 1-3 years after CD diagnosis (75, 85-89). The discrepancy in frequencies is possibly due to the heterogeneity in study design of the different studies, including the inclusion criteria, duration of the GFD and methods of assessment of dietary compliance. A meta-analysis demonstrated that children had higher frequency of complete histological recovery (65%) and regression of abnormal villous/crypt depth ratio (74%) than adults (24% and 58%, respectively) (90). Moreover, younger age at diagnosis was related to less severe initial histologic damage; and male gender predisposed for achieving mucosal recovery. Vécsei et al. concluded that antibody tests are of limited value in predicting the mucosal status in the early post-diagnosis years but that they perform better after a longer period of time on GFD. The study also found that negative EmA most reliably predicts mucosal healing (85). These results are in accordance with a prospective longitudinal study performed in Australia in which no persistent villous atrophy was found in 97 negative IgA-TGA CD children with a median time to re-biopsy of 1.4 years on a GFD (range 1.0 – 12.4 years) (75). However, in the retrospective study performed by Leonard et al., serology as predictor of Marsh 3 histology at repeat biopsy was poor (86). A recent meta-analysis concluded that IgA-TGA

has low sensitivity in detection of persistent villous atrophy, but the authors did not specify the levels of antibodies (only positive or negative) (21).

Statements:

6.2.1. There are few and heterogeneous studies addressing the question "if and when" to perform (re)biopsy.

6.2.2. Slightly elevated IgA-TGA levels in CD children on a GFD are unlikely to be correlated with mucosal injury.

Recommendation:

6.2. Routine assessment of mucosal healing by small bowel biopsies is not recommended in children with CD following a GFD. We recommend considering (re)biopsy only in selected CD cases; based on specific clinical grounds, for example, when doubts about the original diagnosis or suspicion of occurrence of an additional condition. *100% Agreement.*

6.3. Refractory coeliac disease in children: does it exist?

A search was conducted in PubMed using the search terms celiac, coeliac, children, follow-up, unresponsive, refractory, non-responsive and nonresponsive. The search identified a total of 69 records, of which 7 were included: 6 observational studies (252 children) and 1 systematic review (5 studies in children). We included studies in both adults and children (Jericho 2017, Schmitz 2013, Silvester 2017 and Van Leeuwen 2013).

Refractory coeliac disease is defined by persistent or recurrent villous atrophy and malabsorptive symptoms in CD patients despite adherence to a strict GFD. Although well described and characterized in adults, the occurrence of refractory CD in children is very rare. Our search did not find any report on refractory CD in children in 6 of the 7 papers (21, 56, 64, 91-93). Only one paper (94) described 3 cases of coeliac children "not responding to the GFD." However, 2 of the patients were negative at immunohistochemistry for CD3 changes consistent with refractory CD and in addition they eventually responded to a strict GFD. In the 3rd patient, who was apparently permanently non-responsive, specific immunochemical testing for refractory CD was not performed. The paucity of these challenging cases underline the importance of referring suspected child/adolescent cases to tertiary care centres (with available expert pathologists) and the duty of reporting cases of paediatric refractory CD in the medical literature.

Statement

6.3. There is very poor evidence for the existence of refractory CD in children.

Recommendation

6.3. We recommend properly investigating other causes of an apparent "refractory CD" in children, including ongoing inadvertent ingestion of gluten and other possible concomitant enteropathies, such as Crohn's disease, autoimmune enteropathy, small bowel bacterial overgrowth, cow's milk protein allergy and pancreatic insufficiency. *100% Agreement.*

Question 7. Should the quality of life (QOL) be assessed during follow-up and if so, how?

A search was conducted in Medline using the search terms celiac, coeliac, children, follow-up and quality of life/QoL. The search identified a total of 89 records, of which 18 were included: 16 primary observational studies (16043 children) and 2 systematic reviews (39 studies). The study from Nikniaz 2020, published after March 2020, was also included.

Most of the included studies assessed the health-related quality of life (HRQOL) in CD during follow-up after starting treatment with a GFD (4, 82, 95-109). Ten studies used generic HRQOL questionnaires: SF-12; KIDSSCREEN-52, Nowicki-Strickland Locus of Control Scale, KINDL, Pediatric QoL Inventory Test, PedsQL, Kidscreen , EQ-5D test, General Purpose HRQOLScale for Children, Inventory of Life Quality in Children and Adolescents; Berner Subjective Well-being Inventory. Nine of these studies found similar HRQOL in children with CD as in control children (4, 82, 95, 96, 99, 100, 102, 103, 106). However, five of the six studies using CD-specific HRQOL questionnaires (CDDUX, CDQL, CDQOL Scale-KINDL, CDPQOL) found that the HRQOL of children and adolescents with CD was poor or neutral (82, 96, 100, 105, 109). A model of a questionnaire for assessment of CD-specific HRQOL is provided in annex 1 (Supplementary Material). Parents gave lower HRQOL scores as compared to their children (96, 97). These findings are in agreement with those from studies reported in a recent systematic review and meta-analysis of the literature (110). Food situations at school, meals at home and meals outside home are factors repeatedly found to have a negative impact on emotions, social relationships and management of the daily life of CD children and adolescents. These factors include feeling different at times, feeling unhappy when eating, feeling angry about having to follow a GFD and in general difficulties in accepting the diet. In the only study on the subject, physicians were found to overestimate the HRQOL of children and young adults with CD during follow-

up (109). While a little-studied area of CD care, when indicated, one can consider it as good clinical practice to refer to a psychologist, preferably with knowledge of CD and coping strategies.

Statement

7. When assessed by CD specific questionnaires, the HRQOL of children and adolescents with CD on a GFD is reported to be neutral or poor.

Recommendation

7. We recommend assessing the HRQOL of children and adolescents with CD during follow-up by means of validated, CD-specific HRQOL questionnaires. 87% Agreement. These questionnaires may be administrated during or before the follow-up consultations, either on paper or by e-consultation. The results should be interpreted by the physician together with the parents/care givers, and if age adequate, also with the child.

Question 8. Should follow-up of children with special situations be different from the one in the average CD patient?

8.1 In cases of uncertain diagnosis: when and how to perform gluten-challenge?

A search was conducted in Pubmed using the search terms celiac, coeliac, children, follow-up and gluten-challenge. The search identified a total of 850 records, of which 20 were included: 9 RCT (1 in children: 23 children) and 8 primary observational studies (2 in children: 194 children). We included 14 studies in adults (Daveson 2020, Goel 2020, Kelly 2020, Lahdeaho 2011, Lahdeaho 2014, Lahdeaho 2019, Leffler 2012, Leffler 2013, Mansikka 2019, Sankari 2020, Sarna 2018, Taavela 2019, Tye-Din 2019, Leonard 2021) and 2 studies in both adults and children (Husby 2020 and Van Overbeek 1997). We included 4 studies published before 2010 (Van Overbeek 1997, Korponay-Szabo 1997, Holm 2006 and Kurppa 2008) and 1 after March 2020 (Leonard 2021).

In situations where a GFD was started before the diagnosis was completed, the reintroduction of gluten into the diet, or the so-called gluten-challenge is currently the only method to secure the diagnosis.

Due to its high negative predictive value, HLA-DQ2 and DQ8 typing is the most reliable test to select those children in which the CD diagnosis is extremely unlikely (3). However, in HLA-DQ2 and/or DQ8 positive children, the uncertain diagnosis may be assessed by gluten reintroduction, followed by monitoring of symptoms, measurements of CD-specific antibodies and small-bowel mucosal biopsy in selected cases. ESPGHAN 2012 CD diagnosis guidelines provided indications on how to perform a gluten challenge (2).

However, the amount of gluten to be used and the appropriate duration of the challenge remains a matter of debate. In general, the amount of gluten in one slice of bread is about 3-5 g and the regular daily gluten intake has been estimated to be 10-20 g/day in adults and about 5-15 g/day in children, depending on the age (2, 111, 112). In practice, 10-15 g/day of gluten followed by first clinical and serological assessment after 3 months of challenge is usually used for CD diagnosis. As a rule, CD may be considered less probable in children without specific CD antibodies in serum and normal small bowel mucosa after up to 2 years of gluten-challenge. However, cases of children relapsing after gluten-challenge as long as 19 years after the challenge have been reported (113). Gluten-challenge studies in children using a gluten amount of 5-10 g/day resulted in serological relapse in 66% of 134 CD children after 3 months and in 89,9% after 6 months. The challenge duration for histological relapse was about 6 months (114). One study reported 71% of 41 CD children developing gastrointestinal symptoms after a gluten-challenge with 1-3 slices of wheat bread per day during 3 consecutive days (115). A previous study demonstrated duodenal mucosal deterioration and positive coeliac autoimmunity in 10 long-term treated CD children after a challenge with 14 g gluten/day for 3-12 months (112).

As CD causes malabsorption and attenuated growth, gluten-challenge is usually avoided in toddlers and adolescents. In adults, randomized blinded gluten-challenges were performed as part of several CD pharmaceutical trials. Different amounts of gluten were given, concluding that 2 g of daily gluten ingested for 6 weeks induced small bowel injuries and symptoms in most of the patients, and that 2-4 g of daily gluten for 10 weeks induces symptoms as well as serological and histological relapse in the majority of CD patients (116-119). Even shorter challenges of 2-10 weeks with 2,4 g or 3 g of gluten /day have been proposed (120, 121). However, it has been argued that short gluten-challenges of 2 weeks are prone to false negative conclusions when only conventional histology is used for the mucosal assessment (122).

Statements:

8.1.I. Gluten-challenge is indicated in children suspected of CD but in whom a GFD was initiated before the CD diagnosis was certain. Challenge should be avoided during periods of accelerated growth. The gluten-challenge should be performed under the supervision of a paediatric gastroenterologist.

8.1.II. Gluten ingestion of 10-15 g/day for 3-6 months is expected to induce small bowel abnormalities in the majority of CD children.

8.1.III. The optimal amount of daily gluten intake and the shortest time for an effective gluten-challenge are still unknown.

Recommendations:

8.1. In cases of uncertain CD diagnosis, HLA typing should be performed before gluten-challenge in order to detect children in whom the occurrence of CD is unlikely. *100% Agreement.*

8.1.1. How to perform a gluten challenge?

8.1.1.I. In children with HLADQ2 and/or DQ8 positivity with an indication for gluten-challenge, intestinal biopsies before starting the challenge may be considered at the discretion of the clinician and in dialogue with the patient/caregivers. 77% *Agreement. As this recommendation did not reach threshold for agreement (85%) it is not included in the recommendations in this paper (table 1).*

8.1.1.II. To avoid unnecessary exposure to gluten in CD children with an early response to the challenge serum IgA-TGA determination may be considered 1 month after starting, and this should be measured every 3 months during daily ingestion of 10-15 g of gluten for 12 months. Earlier evaluation is recommended in case of suggestive symptoms. *100% Agreement.*

8.1.1.III. In case of symptoms suggestive of CD and/or specific CD-antibodies, small bowel biopsies should be performed. 82% *Agreement. As this recommendation did not reach threshold for agreement (85%) it is not included in the recommendations in this paper (table 1).*

8.1.1.IV. In the absence of symptoms and/or specific CD-antibodies after 1 year of formal gluten-challenge, the child should be allowed to have a normal gluten-containing diet and follow-up visits with measurement of specific CD-antibodies should be offered annually or every other year. Earlier evaluation is recommended in case of suggestive symptoms. *93% Agreement.*

8.2. Follow up of patients with CD and T1D

A search was conducted in PubMed using the search terms celiac, coeliac, children, follow-up and diabetes. The search identified a total of 151 records, of which 10 were included: 7 studies in children (3295 children) and 3 studies in both adults and children (Kurien 2016, Molazadegan 2013, Reilly 2016).

There are few studies focusing on the follow-up of children with CD and T1D, and they are mostly retrospective in nature. Most of the authors compared outcomes in patients with T1D and CD to patients with T1D only (123-127). Few compared patients with both diseases to patients with CD only (79, 128, 129). Some studies are nationwide, multicentric, registry-based focusing on a single country (123-126); others are single-centre studies (130). The number of patients in most of the studies is low. Most patients with CD and T1D are detected through screening and are usually asymptomatic, with some having potential CD. Data on long-term follow-up of patients with both diseases show that they have an increased risk of thyroid pathology compared to isolated T1D (124) or to isolated CD (128) and of diabetic retinopathy compared to isolated T1D (123). It has also been shown that growth can be affected for a prolonged time despite strict GFD (126). On the other hand, the risk of fractures and nephropathy was not found to be higher in patients with both CD and T1D compared to isolated T1D (125, 128, 131). The long-term outcome of CD in T1D patients is similar to the one in CD without T1D in terms of compliance with the GFD and achieving remission of CD (129, 130). However, some patients who perceived themselves to be asymptomatic had more problems with compliance with a GFD, warranting a stricter follow-up in selected cases (79).

Recommendations

8.2.I. We recommend the same frequency and follow-up tests in children with CD and T1D as in children with isolated CD, with (additional) special attention to test for thyroid involvement and diabetic retinopathy. *93% Agreement.*

8.2.II. We recommend developing the follow-up plan in conjunction with an endocrinologist/diabetologist and a dietitian, also considering the need for psychological and social support. *100% Agreement.*

8.3 Follow up of patients with CD and IgA deficiency

A search was conducted in PubMed using the search terms celiac, coeliac, children, follow-up and IgA deficiency. The search identified a total of 24 records, of which 2 were included: 2 primary observational studies (191 children), one of them prospective. We included 1 article published after March 2020 (López 2020).

Selective IgA deficiency is the most prevalent primary immunodeficiency in the general population (1:300–700). Children with selective IgA deficiency are at a 10- to 15-fold higher risk of developing CD. Limited data on the follow-up of children with CD and

selective IgA deficiency is available, with low number of affected children (88). Studies show prolonged recovery time of serological and mucosal changes after the introduction of GFD during follow-up, with half of IgA deficient CD patients having elevated serum IgG specific CD antibodies after two years on a GFD (132). No other findings were found to be specific during follow-up of selective IgA deficient CD patients.

Statement

8.3. Data from the literature on patients with selective IgA deficiency indicate a longer recovery time for serum IgG CD antibodies after starting a GFD.

Recommendation

8.3.I. We recommend the same follow-up practice in IgA deficient children with CD than in IgA sufficient children with CD. *93% Agreement.*

8.3.II. At follow-up visits CD specific IgG antibodies (TGA, EMA or DGP) should be assessed. *100% Agreement.*

8.4. Potential Coeliac Disease

A search was conducted in PubMed using the search terms celiac, coeliac, children, follow-up and potential celiac disease. The search identified a total of 80 records, of which 9 were included: 8 performed in children (835 children) and 1 in both adults and children (Kondola 2016).

Potential CD is defined as the presence of CD specific antibodies and compatible HLA, but normal duodenal architecture. It can either be asymptomatic or symptomatic. The patient may or may not develop villous atrophy later. Once diagnosed, the most important decision to be taken is whether to treat it with a GFD or not. That decision depends on the predictable evolution, the alleviation of possible symptoms by GFD and the possible risk inherent to a long-term regular diet, including bone health, because the presence of alterations may represent a valid reason to start a GFD, otherwise not prescribed if the subject is asymptomatic. Bone health should be monitored by assessment of serum levels of calcium, phosphate, alkaline phosphatase, vitamin D and eventually mineralometry performed at the discretion of the physician. The first two issues find some evidence in the literature (133-140). All studies but one (133) indicate that the evolution to villous atrophy occurs in a minority (5-20%) of the cases with a cumulative incidence of approximately 50%. The majority remain as “potential CD,” with a significant percentage of those normalizing their CD antibodies ,

which is frequently observed in younger children. Factors predicting evolution to villous atrophy are genetic profile, intraepithelial lymphocytic infiltration and intestinal CD antibodies deposits (138). A GFD does not always improve symptoms (141). No information is available on the long-term risks if left on a regular gluten-containing diet.

Statement

8.4. In the literature there is insufficient data for evidence-based management of patients with potential CD.

Recommendation

8.4.I. In the presence of symptoms attributable to gluten, a trial of a GFD should be discussed with the family. *90% Agreement.*

8.4.II. If left on a regular diet, we recommend annual follow-up visits, with attention towards growth and nutritional status, including bone health. *97% Agreement.*

8.4.III. Duodenal biopsies should be performed in case of appearance of symptoms and/or of increased elevation of the CD antibody levels. In other cases with persistent serological positivity, on an individual basis and in dialogue with the patient/caregivers, duodenal biopsies may be considered during follow-up. *95% Agreement.*

Question 9. How to improve communication: To parents? To patients?

A search was conducted in Medline using the search terms celiac, coeliac, children, follow-up, gluten-free diet, communication, patient satisfaction, caregivers/education, education, consultants/education, consultants/organization and administration. The search identified a total of 46 records and 14 publications were included:12 primary observational studies (638 children) and 2 literature reviews (34 studies). We included 4 studies in adults (Halmos 2018, Paganizza 2019, Ukkola 2011 and Ukkola 2012), 1 in both adults and children (Sainsbury 2018) and 2 published before 2010 (Gardiner 1999 and Cahill 2007).

Communication between the caring physician and other health-care professionals with the parents and patients includes much more than providing information on the disease. Communication shapes the patient's/parent's relationship with the caring medical team and the trust in evidence-based medicine. Communication in paediatrics is generally triadic and should be addressed towards both the parents and the child with language appropriate to the age of the child (142). How the physician communicates the initial diagnosis to the patient/parents affects the degree of acceptance of the diagnosis and may influence the impact of the disease on the intra-family relationship. In adults with

CD, it has been shown that negative perceptions of having CD were associated with dissatisfaction with the quality of doctor-patient communication (143).

9.1 Communication of diagnostic certainty to parents and children

The information at all times, but most importantly at the time of the diagnosis, should be given to the patient/family in lay terms in a relaxed atmosphere. It should include explanations of the results of the diagnostic work-up and the implications of the lifelong disease for the patient's life and the family. The documentation of confirmed diagnosis is important, particularly if the child was diagnosed early in life, to avoid later doubt by the patient and future caring physicians. Ideally, a coeliac passport should be used for documentation (in Germany free available from the German Celiac Society DZG: https://www.dzg-online.de/der-zoeliakiepass.1074.0.html). If the diagnostic criteria were not fulfilled, and there is doubt about the diagnosis, the physician should not name it as "CD," but as "suspected CD," and action should be taken to confirm or reject the diagnosis.

Statement

9.1. Communication and documentation of the CD diagnosis based on evidence-based guidelines are crucial to avoid later doubts about the diagnosis, both by the patient or other caring physicians.

Recommendations

9.1. The paediatric gastroenterologist/paediatrician should communicate to the patient and the parents/caregivers that the CD diagnosis is made with certainty and according to current evidence-based guidelines. All results (serology, histopathology, HLA if done) with dates of performance should be provided in writing for later proof of CD diagnosis.

97% Agreement.

9.2 Patient empowerment at diagnosis and during follow up

The diagnosing physician should communicate the benefits of an early diagnosis in childhood as compared to undiagnosed and untreated disease until adulthood in a structured way. To patients with symptoms affecting their QoL, this is obvious (immediate benefit). For screening-detected persons with minor or no symptoms (144, 145) or those who do not remember their symptoms due to young age at diagnosis, the motivation to adhere to a GFD is based on internalizing the risks / possible consequences to later health (146) and enduring beliefs of being spared negative consequences (146).

Knowledge about the disease may be provided using different tools, including information leaflets, web-based documentation, or E-learnings (19, 147). A modular E-learning tool for patients and their household members has been developed within an EU-funded project and is freely available in 6 languages: https://celiacfacts-onlinecourses.eu/?lang=en. Although children diagnosed early in life usually accept the GFD as normal, they need to be informed, reassured and empowered for autonomy and taking responsibility for their CD, particularly during adolescence (148). A well-informed patient is more likely to adhere to the GFD and to reconstruct normality (149, 150). Better knowledge of the risks and benefits of the disease may also reduce anxiety. Informed patients with trust in evidence-based medicine are less likely to follow unproven, sometimes risky treatments and intervention or spend money on these treatments or diagnostics of unproven value.

Statements and recommendations

9.2.I. The paediatric gastroenterologist/paediatrician and dietitian should communicate the need for a lifelong GFD and regular monitoring and facilitate access to professional dietary counselling knowledgeable on GFD. *100% Agreement.*

9.2.II. We recommend providing education using oral and written information (leaflets, E-learnings etc.) about the disease and benefits of adhering to the diet. Later health risks should be brought into perspective without inducing fear or anxiety considering the patient's age and complications at the time of diagnosis and compliance with dietary recommendations. *97% Agreement.*

9.3 Emotional and social support

Patients and parents should be informed about the value of the national or local coeliac patients' associations where they can meet families, participate in different programs and collect valuable and updated information about the disease, gluten-free products or even practical hints on reorganizing the household. Members of CD patients' associations may benefit by receiving psychosocial support by peer groups, which in turn may ensure better adherence to the diet and outcome (10). The CD patients' organizations in Europe usually are members of the AOECS: http://aoecs.org/members and encourage to name the condition in the social environment as something, which is "quite common," and "most people are aware of CD" (151). In their daily life, many individuals suffering from a chronic disease may not like to be considered a "patient,"

but as a person affected with a certain disease or condition. This is particularly true for CD, as the GFD reverts the enteropathy and alleviates most, if not all, signs and symptoms that may be present at the time of diagnosis. Children in particular may be sensitive to the word "patient" which implies feeling "sick." Therefore, the wording used should be carefully chosen and may be mutually decided upon with the affected child, including the wording she/he will use describing CD to their friends, peers and other social contacts in their daily life. Particularly, some screening identified adolescents perceive the change of their lifestyle (GFD) more as a burden than as potential benefit (152). This feeling of stigmatization and social isolation needs to be addressed in the patient-physician communication and requires particular attention and support (107).

Statements and recommendations

9.3.I. Emotional and practical support from personal contact with other individuals with CD (Coeliac /parent support groups, patient organizations, etc.) should be provided to reduce eventual feelings of social isolation. *97% Agreement.*

9.3.II. Patients, especially adolescents, perceiving lifestyle changes related to CD diagnosis, including the GFD and emotionally coping, as difficult warrant particular attention and support. *100% Agreement.*

Question 10. How to organize the transition from paediatric care to adult health-care?

A search was conducted in PubMed using the search terms celiac, coeliac, children, follow-up, childhood celiac and transition of care. The search identified a total of 85 records, of which 7 were included: 4 primary observational studies (17172 children) and 3 reviews/guidelines (Crowley 2011 (10 studies), Ludvigsson 2016 and Nagra 2015). Two studies on adults were included (Kivelä 2020 and Reilly 2020).

The transition between paediatric and adult care for young people with chronic illness, including CD, is often poorly organised, with potential negative consequences on the QoL. There is a general agreement that adolescent services need to be improved. Still, there is little empirical data on which policies can be used (153). The organization of transition from the paediatric to adult care for individuals with CD is necessary to prevent gaps in management (15).

Studies on the transition process in CD are scarce. We identified nine relevant original papers, several of which were performed in young adults after transition. These provided only retrospective, descriptive data without any long-term follow-up. Importantly, there are gaps in follow-up care after transition. Dietary compliance tends

to be low in young adults and surprisingly, there are suggestions that follow-up care is not associated with a higher compliance and good quality of health (154). Moreover, the transition of care in CD appears often to be inconsistent, particularly among asymptomatic patients (155).

A systematic review of the literature on the transfer of care among different chronic diseases suggested that the most commonly used strategies in successful programmes were patient education and specific transition clinics jointly staffed by paediatric and adult physicians or dedicated young adult clinics within adult services (156). The paediatrician should write a transition letter to facilitate care transition, (15, 35, 157). 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.

Young adults should have the chance to trust and improve their own abilities to cope with their disease burden and the necessary dietary restrictions (153). Furthermore, although there is little evidence, as for other diseases, building a good relationship between the young adult and the treating medical team may be relevant to ensure good management of the disease (153).

There is no evidence in the literature about the exact age to start the transition process in paediatric coeliac patients. Physician organizations from the USA had suggested that the transition be commenced at age 12–13 years, developing a transition plan at age 14–15 years, with the actual transfer taking place at ≥18 years of age (158). This proposed timeline is based on expert opinion, as the quality indicators and metrics used to evaluate transition outcomes are still being developed. The transition should start according to the general healthcare organization in a given country, taking into consideration the adolescent's physical, mental, psychosocial development and other factors such as the level of disease activity, dietary adherence, and the patient's autonomy in disease management.

Statements

10.1. There are no prospective studies on the transfer of care from paediatric to adult medical care in CD.

10.2. Retrospective data show that the transition to adult care is inconsistent, particularly among asymptomatic patients.

10.3. There is no evidence in the literature about the age to start the transition process in paediatric coeliac patients.

Recommendation

10. Even though current data is insufficient, we recommend a formal transfer of medical care of an adolescent with CD to facilitate the transition to adult care. The transfer should be structured and, as a minimum, include a transition letter or "coeliac passport" providing data on the basis of diagnosis, follow-up, anthropometric data, possible comorbidities and dietary adherence level. *93% Agreement.*

Discussion

In this paper we present a summary of the literature on the follow-up of children and adolescents with CD and we provide recommendations on how to approach it. Although the searched and identified literature encompass an impressive representation of the paediatric population with CD, most of the included studies are observational and retrospective, as shown in the Summary Table of the Revised Literature (Supplemental Material). In addition, the exclusion of case reports by the methods may have had an impact on the underestimation of refractory CD, which is such a rare event in paediatrics. For this reason we stress the importance of referring suspected cases to specialized centres and of reporting cases in the medical literature.

Although some of the provided recommendations have been based on available evidence (Table 1: 1; 3.2.II-VI; 4.1; 4.2; 5.1-5,4; 6.1-6.3, 7; 8.1, 8.2.1, 8.2.II, 8.3.I, 8.3.II, 9.2.I; 9.3.1), others have been based on expert opinion (Table 1: 2; 3.1, 3.2.IV,V,VII; 5.5, 8.1.1.II, 8.1.1.IV, 8.4.I-8.4.III;9.1, 9.2.II, 9.3,I; 10). Nevertheless, upon voting, agreement was present for 95% of the 39 statements and 37 recommendations were formulated.

Gaps in knowledge were identified indicating fields for future prospective research.

These include the frequency of follow-up visits and the laboratory tests that should be performed, including vitamin D determinations and control of thyroid disease. Also, how to treat sideropenia and how to address persistent slightly elevated levels of serum IgA-TGA in children adhering to the GFD are knowledge gaps that were addressed based on expert opinion and available evidence. The need for a reliable method to assess adherence to the GFD was identified, as well as the importance of studying the performance of GIPs determinations in clinical practice.

Although some evidence supports the assessment of QOL during follow-up, it remains unknown what the frequency of assessments should be, taking into account the time-consuming and economic aspects of follow-up.

Although three recommendations are provided on how to perform a gluten-challenge in children with uncertain diagnosis of CD adhering to a gluten-free diet (Table 1: 8.1, 8.1.1.II and 8.1.1.IV), these are mainly based on expert opinion, since there is little evidence on this topic. This was also the reason to avoid formulating a recommendation on the quantity of gluten that should be ingested during a gluten-challenge, even if, as stated, gluten ingestion of 10-15 g/day for 3-6 months is expected to induce small bowel abnormalities in the majority of CD children. In addition, no consensus was reached on whether intestinal biopsies should be performed before starting and/or after the gluten challenge (8.1.1.I and 8.1.1.III), since a substantial number of the co-authors found that serum IgA-TGA levels >= 10x ULN should be enough to confirm a relapse of CD after gluten challenge. All these reasons make future prospective research on gluten-challenge in children necessary. Surrogate biomarkers of CD-specific small bowel damage, such as cytokines and gliadin specific T-cells recruited in peripheral blood after short-time gluten exposure, are promising tools to develop less invasive forms of gluten-challenge. This may involve new immunohistochemical markers of morphological changes of the mucosa such as APOA4:Ki67 ratios (159, 160), detection of the HLA-DQ-gluten tetramer and increase in IL2 in peripheral blood (122) and/or changes in gut-homing CD8T-cells, HLA-DQ restricted gluten-specific CD4 T-cells, all proposed as markers of T-cell response in CD patients after short-term gluten intake (161-165).

Similarly, there is little information available on how to follow children with potential CD and long-term studies on this topic are needed. In addition, there is a paucity of studies that compare long-term effects on dietary compliance depending on who does the follow-up and more studies are warranted to evaluate if physical follow-up visits can be replaced by E-health services.

Finally, there are few studies on the effect of communication between the physician and the patient/parents/caregivers on the long-term health status of CD children and no prospective studies on the transfer of care from paediatric to adult medical care in CD.

In conclusion, we present here an update of the present knowledge on the follow-up of children and adolescents with CD and provide recommendations accordingly.

Furthermore, we have identified and highlighted gaps in knowledge that warrant more research to improve further follow-up of CD children and adolescents.

DISCLAIMER: ESPGHAN is not responsible for the practices of physicians and provides guidelines and position papers as indicators of best practice only. Diagnosis and treatment is at the discretion of physicians.

References

1. Wessels M, Dolinsek J, Veenvliet A, et al on behalf of the ESPGHAN Special Interest Group on Celiac Disease**. Follow-up practices for children and adolescents with celiac disease: Results of an international survey. Eur J Pediatr 2021; Nov 24. doi: 10.1007/s00431-021-04318-2. Online ahead of print. PMID: 34817672.
2. Husby S, Koletzko S, Korponay-Szabó IR, et al; ESPGHAN Working Group on Coeliac Disease Diagnosis; ESPGHAN Gastroenterology Committee; European Society for Pediatric Gastroenterology, Hepatology, and Nutrition. European Society for Pediatric Gastroenterology, Hepatology, and Nutrition guidelines for the diagnosis of coeliac disease. J Pediatr Gastroenterol Nutr 2012;54(1):136-60.
3. Husby S, Koletzko S, Korponay-Szabó I, et al. European Society Paediatric Gastroenterology, Hepatology and Nutrition Guidelines for Diagnosing Coeliac Disease 2020. J Pediatr Gastroenterol Nutr 2020;70(1):141-56.
4. Bellini A, Zanchi C, Martelossi S, et al. Compliance with the gluten-free diet: the role of locus of control in celiac disease. J Pediatr 2011;158(3):463-6.
5. Rimárová K, Dorko E, Diabelková J, et al. Compliance with gluten free diet in a selected group of celiac children in the Slovak republic. Cent Eur J Public Health 2018;26(Suppl): S19–24.
6. Kurppa K, Lauronen O, Collin P, et al. Factors Associated with Dietary Adherence in Celiac Disease: A Nationwide Study. Digestion 2012; 86:309–14.
7. Charalampopoulous D, Panayiotou J, Chouliaras G, et al. Determinants of adherence to gluten-free diet in Greek children with coeliac disease: A cross-sectional study. Eur J Clin Nutr 2013;67(6):615-9.
8. Tapsas D, Fälth-Magnusson K, Högberg L, et al. Swedish children with celiac disease comply well with a gluten-free diet, and most include oats without reporting any adverse effects: a long-term follow-up study. Nutr Res 2014;34(5):436-41.
9. Myléus A, Reilly NR, Green PHR. Rate, Risk Factors, and Outcomes of Nonadherence in Pediatric Patients With Celiac Disease: A Systematic Review. Clin Gastroenterol Hepatol 2020;18(3):562-73.
10. Barnea L, Mozer-Glassberg Y, Hojsak I, et al. Pediatric celiac disease patients who are lost to follow-up have a poorly controlled disease. Digestion 2014;90(4):248-53.
11. Hagopian W, Lee HS, Liu E, et al; TEDDY Study Group. Co-occurrence of Type 1 Diabetes and Celiac Disease Autoimmunity. Pediatrics 2017;140(5): e20171305.
12. Snyder J, Butzner D, DeFelice AJ, et al. Evidence-Informed Expert Recommendations for the Management of Celiac Disease in Children. Pediatrics 2016;138: e20153147.
13. Valitutti F, Trovato CM, Montuori M, et al. Pediatric Celiac Disease: Follow-Up in the Spotlight. Adv Nutr 2017;8(2):356-61.
14. Wessels M, van Veen II, Vriezinga SL, et al. Complementary Serologic Investigations in Children with Celiac Disease Is Unnecessary during Follow-Up. J Pediatr 2016; 169:55-60.
15. Ludvigsson JF, Agreus L, Ciacci C, et al. Transition from childhood to adulthood in coeliac disease: the Prague consensus report. Gut 2016;65(8):1242-51.
16. Johansson K, Malmberg Hard af Segerstad E, Martensson H, et al. Dietitian visits were a safe and cost-effective form of follow-up care for children with celiac disease. Acta Paediatr 2019;108(4):676-680.
17. Haas K, Martin A, Park KT. Text Message Intervention (TEACH) Improves Quality of Life and Patient Activation in Celiac Disease: A Randomized Clinical Trial. J Pediatr 2017; 185: 62–67.
18. Vriezinga S, Borghorst A, van den Akker-van Marle E, et al. E-Healthcare for Celiac Disease—A Multicenter Randomized Controlled Trial. J Pediatr 2018;195: 154-160.

19. Connan V, Marcon M.A, Mahmud F.H, et al. Online education for gluten-free diet teaching: Development and usability testing of an e-learning module for children with concurrent celiac disease and type 1 diabetes. Pediatric Diabetes 2019;20: 293–303.
20. Sansotta N, Amirikian K, Guandalini S, et al. Celiac Disease Symptom Resolution: Effectiveness of the Gluten-free Diet. J Pediatr Gastroenterol Nutr 2018;66(1):48-52.
21. Silvester JA, Kurada S, Szwajcer A, et al. Tests for Serum Transglutaminase and Endomysial Antibodies Do Not Detect Most Patients With Celiac Disease and Persistent Villous Atrophy on Gluten-free Diets: a Meta-analysis. Gastroenterology 2017;153(3):689-701.
22. Husby S, Bai JC. Follow up of coeliac disease. Gastroenterol. Clin N Am 2019;48(1):127-36.
23. Husby S, Murray JA, Katzka DA. AGA Clinical practice update on the diagnosis and monitoring of celiac disease: changing utility of serology and histologic measures: expert review. Gastroenterology 2019;156(4):885-9.
24. Petroff D, Wolf J, Richter T, et al. Antibody Concentrations Decrease 14-Fold in Children With Celiac Disease on a Gluten-Free Diet but Remain High at 3 Months. Clin Gastroenterol Hepatol 2018;16(9):1442-9.
25. Gidrewicz D, Trevenen CL, Lyon M, et al. Normalization Time of Celiac Serology in Children on a Gluten-free Diet. J. Pediatr Gastroenterol Nutr 2017; 64(3):362-7.
26. Sansotta N, Alessio MG, Norsa L, et al. Trend of Antitissue Transglutaminase Antibody Normalization in Children With Celiac Disease Started on Gluten-free Diet: A Comparative Study Between Chemiluminescence and ELISA Serum Assays. J Pediatr Gastroenterol Nutr 2020;70(1):37-41.
27. Blansky B, Hintze Z, Alhassan E. Lack of Follow-up of Pediatric Patients With Celiac Disease. Clin Gastroenterol Hepatol 2019;17(12):2603-4.
28. Mager DR, Qiao J, Turner J. Vitamin D and K status influences bone mineral density and bone accrual in children and adolescents with celiac disease. Eur J Clin Nutr 2012;66(4):488-95.
29. Tuna Kirsaçlioğlu C, Kuloğlu Z, Tanca A, et al. Bone mineral density and growth in children with coeliac disease on a gluten free-diet. Turk J Med Sci 2016;46(6):1816-21.
30. Al Toma A, Volta U, Auricchio R, et al. European Society for the Study of Coeliac Disease (ESsCD) guideline for coeliac disease and other gluten-related disorders. United European Gastroenterol J 2019; 7:583-13.
31. Canova C, Pitter G, Zanier L, et al. Risk of Fractures in Youths with Celiac Disease - A Population-Based Study. J Pediatr 2018; 198:117-20.
32. Fouda MA, Khan AA, Sultan M, et al. Evaluation and management of skeletal health in celiac disease: Position statement. Can J Gastroenterol 2012;26(11):819-29.
33. Usta M, Urganci N. Does Gluten-Free Diet Protect Children with Celiac Disease from Low Bone Density? Iran J Pediatr 2014;24(4):429-34.
34. Deora V, Aylward N, Sokoro A, et al. Serum Vitamins and Minerals at Diagnosis and Follow-up in Children With Celiac Disease. J Pediatr Gastroenterol Nutr 2017;65(2):185-9.
35. Zingone F, Ciacci C. The value and significance of 25(OH) and 1,25(OH) vitamin D serum levels in adult coeliac patients: A review of the literature. Dig Liver Dis 2018;50(8):757-760.
36. Lionetti E, Galeazzi T, Dominijanni V, et al. Lower Level of Plasma 25-Hydroxyvitamin D in Children at Diagnosis of Celiac Disease Compared with Healthy Subjects: A Case-Control Study. J Pediatr 2021; 228:132-7.
37. Assa A, Frenkel-Nir Y, Tzur D, et al. Large population study shows that adolescents with celiac disease have an increased risk of multiple autoimmune and non-autoimmune comorbidities. Acta Paediatr 2017;106(6):967-72

38. Ansaldi N, Palmas T, Corrias A, et al. Autoimmune thyroid disease and celiac disease in children. J Pediatr Gastroenterol Nutr 2003;37(1):63-6.
39. Meloni A, Mandas C, Jores RD, et al. Prevalence of autoimmune thyroiditis in children with celiac disease and effect of gluten withdrawal. J Pediatr 2009;155(1):51-5.
40. Diamanti A, Ferretti F, Guglielmi R, et al. Thyroid autoimmunity in children with coeliac disease: a prospective survey. Arch Dis Child 2011;96(11):1038-41.
41. Rousseff T, Claeys T, Vande Vijver E, et al. Hepatitis B virus vaccination and revaccination response in children diagnosed with coeliac disease: a multicentre prospective study. Acta Gastroenterol Belg 2019;82(1):27-30.
42. Urganci N, Kalyoncu D. Response to Hepatitis A and B Vaccination in Pediatric Patients With Celiac Disease. J Pediatr Gastroenterol Nutr 2013;56(4):408-11.
43. Anania C, Olivero F, Spagnolo A, et al. Immune response to vaccines in children with celiac disease. World J Gastroenterol 2017;23(18):3205-13.
44. Heshin-Bekenstein M, Turner D, Shamir R, et al. Hepatitis B Virus Revaccination With Standard Versus Pre-S Vaccine in Previously Immunized Patients With Celiac Disease. J Pediatr Gastroenterol Nutr 2015;61(4):400–3.
45. Leonardi S, Spina M, Spicuzza L, et al. Hepatitis B vaccination failure in celiac disease: Is there a need to reassess current immunization strategies? Vaccine 2009;27(43):6030–3.
46. Park SD, Markowitz J, Pettei M, et al. Failure to respond to hepatitis B vaccine in children with celiac disease. J Pediatr Gastroenterol Nutr 2007;44(4):431-5.
47. Zanoni G, Contreas G, Valletta E, et al. Normal or defective immune response to Hepatitis B vaccine in patients with diabetes and celiac disease. Hum Vaccin Immunother 2015;11(1):58-62.
48. Ludvigsson JF, Leffler DA, Bai JC, et al. The Oslo definitions for coeliac disease and related terms. Gut 2013;62(1):43-52.
49. Ludvigsson JF, Ciacci C, Green PH, et al. Outcome measures in coeliac disease trials: the Tampere recommendations. Gut 2018;67(8):1410-24.
50. Harder G, Schiepatti A, Biagi F, et al. Optimising the follow-up of adult coeliac disease with a clinical-based score to identify patients in need of a histological reassessment: a retrospective single centre study. Br J Nutr 2020;123(10):1159-64.
51. Wessels M, Te Lintelo M, Vriezinga SL, et al. Assessment of dietary compliance in celiac children using a standardized dietary interview. Clin Nutr 2018;37(3):1000-4.
52. Gerasimidis K, Zafeiropoulou K, Mackinder M, et al. Comparison of Clinical Methods With the Faecal Gluten Immunogenic Peptide to Assess Gluten Intake in Coeliac Disease. J Pediatr Gastroenterol Nutr 2018;67(3):356-60.
53. Comino I, Fernández-Bañares F, Esteve M, et al. Fecal Gluten Peptides Reveal Limitations of Serological Tests and Food Questionnaires for Monitoring Gluten-Free Diet in Celiac Disease Patients. Am J Gastroenterol 2016;111(10):1456-65.
54. Moreno ML, Cebolla Á, Muñoz-Suano A, et al. Detection of gluten immunogenic peptides in the urine of patients with coeliac disease reveals transgressions in the gluten-free diet and incomplete mucosal healing. Gut 2017;66(2):250-7.
55. Dowd AJ, Jackson C, Tang KTY, et al. MyHealthyGut: development of a theory-based self-regulatory app to effectively manage celiac disease. Mhealth 2018; 4:19.
56. Comino I, Segura V, Ortigosa L, et al. Prospective longitudinal study: use of faecal gluten immunogenic peptides to monitor children diagnosed with coeliac disease during transition to a gluten-free diet. Aliment Pharmacol Ther 2019; 49(12):1484-92.
57. Stefanolo JP, Tálamo M, Dodds S, et al. Real-World Gluten Exposure in Patients With Celiac Disease on Gluten-Free Diets, Determined From Gliadin Immunogenic Peptides in Urine and Fecal Samples. Clin Gastroenterol Hepatol. 2021;19(3):484-91.

58. Silvester JA, Comino I, Rigaux LN, et al. Exposure sources, amounts and time course of gluten ingestion and excretion in patients with coeliac disease on a gluten-free diet. Aliment Pharmacol Ther 2020 Nov;52(9):1469-79.
59. Comba A, Çaltepe G, Yüce O, et al. Effects of age of diagnosis and dietary compliance on growth parameters of patients with celiac disease. Arch Argent Pediatr 2018;116(4):248-55
60. Soliman AT, Laham M, Jour C, et al. Linear growth of children with celiac disease after the first two years on gluten- free diet: a controlled study. Acta Biomed 2019;90(8-S):20-7.
61. Zung A, Kori M. Lack of association between seroconversion and catch-up growth in children with celiac disease. J Pediatr Endocrinol Metab 2012; 25 (1-2):131-7.
62. Basso MS, Luciano R, Ferretti F, et al. Association between celiac disease and primary lactase deficiency. Eur J Clin Nutr 2012;66(12):1364-5.
63. Kuchay RA, Thapa BR, Mahmood A, et al. Lactase genetic polymorphisms and coeliac disease in children: a cohort study. Ann Hum Biol 2015;42(1):101-4.
64. Jericho H, Sansotta N, Guandalini S. Extraintestinal manifestations of celiac disease: effectiveness of the gluten-free diet. J Pediatr Gastroenteol Nutr 2017 Jul;65(1):75-9.
65. Terrone G.Parente I, Romano A, et al.The Pediatric Symptom Checklist as screening tool for neurological and psychosocial problems in a paediatric cohort of patients with coeliac disease. Acta Paediatr 2013;102(7): e325-8.
66. Saps M, Sansotta N, Bingham S, et al. Abdominal Pain-Associated Functional Gastrointestinal Disorder Prevalence in Children and Adolescents with Celiac Disease on Gluten-Free Diet: A Multinational Study. J Pediatr 2017; 182:150-4.
67. Burger JPW, van der Laan JJH, Jansen TA, et al. Low yield for routine laboratory checks in follow-up of coeliac disease. J Gastrointestin Liver Dis 2018; 27:233-23.
68. Çatal F, Topal E, Ermistekin H, et al. The hematologic manifestations of pediatric celiac disease at the time of diagnosis and efficiency of gluten-free diet. Turk J Med Sci 2015; 45:663-7.
69. Kivelä L, Kaukinen K, Huhtala H, et al. At-risk screened children with celiac disease are comparable in disease severity and dietary adherence to those found because of clinical suspicion: a large cohort study. J Pediatr 2017; 183:115-21.
70. Rajalahti T, Repo M, Kivelä L, et al. Anemia in pediatric celiac disease: association with clinical and histological features and response to gluten-free diet. J Pediatr Gastroenterol Nutr 2017; 64:1-6.
71. Repo M, Lindfords K, Mäkki M, et al. Anemia and iron deficiency in children with potential celiac disease. J Pediatr Gastroenterol Nutr 2017; 64:56-62.
72. Radlović N, Mladenovic M, Lokovic Z, et al. Effect of gluten-free diet on the growth and nutritional status of children with coeliac disease. Srp Arh Celok Lek 2009; 137:632-7.
73. Nestares T, Martin-Masot R, Labella A, et al. Is a gluten-free diet enough to maintain correct micronutrients status in young patients with celiac disease? Nutrients 2020; 12:844.
74. Mehta P, Pan Z, Riley MD, et al. Adherence to a Gluten-free Diet: Assessment by Dietitian Interview and Serology. J Pediatr Gastroenterol Nutr 2018;66(3): e67-70.
75. Bannister EG, Cameron DJ, Ng J, et al. Can celiac serology alone be used as a marker of duodenal mucosal recovery in children with celiac disease on a gluten-free diet? Am J Gastroenterol 2014;109(9):1478-83.
76. Webb C, Myléus A, Norström F, et al. High adherence to a gluten-free diet in adolescents with screening-detected celiac disease. J Pediatr Gastroenterol Nutr 2015;60(1):54-9.
77. Bufler P, Heilig G, Ossiander G, et al. Diagnostic performance of three serologic tests in childhood celiac disease. Z Gastroenterol 2015;53(2):108-14.
78. Lund F, Hermansen MN, Pedersen MF, et al. Decrease by 50% of plasma IgA tissue transglutaminase antibody concentrations within 2 months after start of gluten-free diet

in children with celiac disease used as a confirming diagnostic test. Scand J Clin Lab Invest 2016;76(2):128-32.
79. Isaac DM, Rajani S, Yaskina M, et al. Antitissue Transglutaminase Normalization Postdiagnosis in Children With Celiac Disease. J Pediatr Gastroenterol Nutr 2017;65(2):195-99.
80. Dahlbom I, Korponay-Szabó IR, Kovács JB, et al. Prediction of clinical and mucosal severity of coeliac disease and dermatitis herpetiformis by quantification of IgA/IgG serum antibodies to tissue transglutaminase. J Pediatr Gastroenterol Nutr 2010;50(2):140-6.
81. Candon S, Mauvais FX, Garnier-Lengliné H, et al. Monitoring of anti-transglutaminase autoantibodies in pediatric celiac disease using a sensitive radiobinding assay. J Pediatr Gastroenterol Nutr 2012;54(3):392-6.
82. Benelli E, Carrato V, Martelossi S, et al. Coeliac disease in the ERA of the new ESPGHAN and BSPGHAN guidelines: a prospective cohort study. Arch Dis Child 2016;101(2):172-6.
83. Chow MA, Lebwohl B, Reilly NR, et al. Immunoglobulin A deficiency in celiac disease. J Clin Gastroenterol 2012;46(10):850-4.
84. Hogen Esch CE, Wolters VM, Gerritsen SA, et al. Specific celiac disease antibodies in children on a gluten-free diet. Pediatrics 2011;128(3):547-52.
85. Vécsei E, Steinwendner S, Kogler H, et al. Follow-up of pediatric celiac disease: value of antibodies in predicting mucosal healing, a prospective cohort study. BMC Gastroenterol 2014; 14:28.
86. Leonard MM, Weir DC, DeGroote M, et al. Value of IgA tTG in Predicting Mucosal Recovery in Children With Celiac Disease on a Gluten-Free Diet. J Pediatr Gastroenterol Nutr 2017;64(2):286-91.
87. Ghazzawi Y, Rubio-Tapia A, Murray JA, et al. Mucosal healing in children with treated celiac disease. J Pediatr Gastroenterol Nutr 2014;59(2):229-31.
88. Belei O, Dobrescu A, Heredea R, et al. Histologic recovery among children with celiac disease on a gluten-free diet. A long-term follow-up single-center experience. Arch Med Sci 2018;14(1):94-100.
89. Osman M, Taha B, Al Duboni G. Assessment of the response to gluten-free diet in an Iraqi population with coeliac disease. A histological and serological follow-up study. Arch Med Sci 2014;10(2):294-9.
90. Szakács Z, Mátrai P, Hegyi P, et al. Younger age at diagnosis predisposes to mucosal recovery in celiac disease on a gluten-free diet: A meta-analysis. PLoS One 2017;12(11): e0187526.
91. Salvestrini C, Lucas M, Lionetti P, et al. Matrix expansion and syncytial aggregation of syndecan-1+ cells underpin villous atrophy in coeliac disease. PLoS One 2014;9(9): e106005.
92. Schmitz F, Tjon JM, Lai Y, et al. Identification of a potential physiological precursor of aberrant cells in refractory coeliac disease type II. Gut 2013;62(4):509-19.
93. Van Leeuwen MA, du Pré MF, van Wanrooij RL, et al. Changes in natural Foxp3(+) Treg but not mucosally-imprinted CD62L(neg)CD38(+) Foxp3(+) Treg in the circulation of celiac disease patients. PLoS One 2013;8(7): e68432.
94. Janczyk W, de Roo JH, Schweizer J, et al. Coeliac disease not responding to a gluten-free diet in children: case studies and literature review. Dev Period Med 2015;19(2):162-6.
95. Altobelli E, Paduano R, Gentile T, et al. Health-related quality of life in children and adolescents with celiac disease: survey of a population from central Italy. Health Qual Life Outcomes 2013; 11:204.
96. Barrio J, Román E, Cilleruelo M, et al. Health-Related Quality of Life in Spanish Children With Coeliac Disease. Eur J Pediatr 2016;62(4):603-8.

97. Barrio J, Cilleruelo ML, Román E, et al. Health-related quality of life in Spanish coeliac children using the generic KIDSCREEN-52 questionnaire. Eur J Pediatr 2018;177(10):1515-22.
98. Biagetti C, Naspi G, Catassi C. Health-related quality of life in children with celiac disease: a study based on the Critical Incident Technique. Nutrients 2013;5(11):4476-85.
99. Biagetti C, Gesuita R, Gatti S, et al. Quality of life in children with celiac disease: A paediatric cross-sectional study. Dig Liver Dis 2015;47(11):927-32.
100. Mager DR, Marcon M, Brill H, et al. Adherence to the Gluten-free Diet and Health-related Quality of Life in an Ethnically Diverse Pediatric Population With Celiac Disease. J Pediatr Gastroenterol Nutr 2018;66(6):941-8.
101. Meyer S, Rosenblum S. Development and Validation of the Celiac Disease-Children's Activities Report (CD-Chart) for Promoting Self-Management among Children and Adolescents. Nutrients 2017;9(10):1130.
102. Myléus A, Petersen S, Carlsson A, et al. Health-related quality of life is not impaired in children with undetected as well as diagnosed celiac disease: a large population based cross-sectional study. BMC Public Health 2014; 14:425.
103. Nordyke K, Norström F, Lindh L, et al. Health-related quality of life in adolescents with screening-detected celiac disease, before and one year after diagnosis and initiation of gluten-free diet, a prospective nested case-referent study. BMC Public Health 2013;1 3:142.
104. Simsek S, Baysoy G, Gencoglan S, et al. Effects of Gluten-Free Diet on Quality of Life and Depression in Children With Celiac Disease. J Pediatr Gastroenterol Nutr 2015; 61:303-6.
105. Skjerning S, Hourihane J, Husby S, et al. A comprehensive questionnaire for the assessment of health-related quality of life in coeliac disease (CDQL) Included for different instruments available to assess QoL in CD in children. Qual Life Res 2017; 26:2831–50.
106. Wagner G, Zeiler M, Berger G, et al. Eating Disorders in Adolescents with Celiac Disease: Influence of Personality Characteristics and Coping. Eur Eat Disorders Rev 2015;23: 361–70.
107. White LE, Bannerman E, Gillett PM. Coeliac disease and the gluten-free diet: a review of the burdens; factors associated with adherence and impact on health-related quality of life, with specific focus on adolescence. J Hum Nutr Diet 2016; 29(5):593–606.
108. Wolf RL, Lebwohl B, Lee AR, et al. Hypervigilance to a Gluten-Free Diet and Decreased Quality of Life in Teenagers and Adults with Celiac Disease. Digestive Diseases and Sciences 2018; 63:1438–48.
109. Vriezinga SL, Farih N, van der Meulen-de Jong AE, et al. Comparison of Patients' and Doctors' Reports on Health-related Quality of Life in Celiac Disease. J Pediatr Gastroenterol Nutr 2017;64(5):737-41.
110. Nikniaz Z, Abbasalizad Farhangi M, Nikniaz L. Systematic Review With Meta-analysis of the Health related Quality of Life in Children With Celiac Disease. J Pediatr Gastroenterol Nutr 2020;70: 468–77.
111. Van Overbeek FM, Uil-Dieterman IG, Mol IW, et al. The daily gluten intake in relatives of patients with coeliac disease compared with that of the general Dutch population. Eur J Gastroenterol Hepatol 1997 Nov;9(11): 1097-9.
112. Holm K, Maki M, Vuolteenaho N, et al. Oats in the treatment of childhood coealic disease: a 2 -year controlled trial and a long-term clinical follow-up study. Aliment Pharmacol Ther 2006;23(10)L1463-72.
113. Kurppa K, Koskinen O. Collin P, et al. Changing phenotype of celiac disease after long-term gluten exposure. J Peditr Gastroenterol Nutr 2008;47(4):500-3.

114. Korponay-Szabo IR, Kovacs JB, Lorincz M, et al. Prospective significance of antiendomysium antibody positivity in subsequently verified celiac disease. J Pediatr Gastroenterol Nutr 1997 Jul;25(1):56-63.
115. Hardy MY, Girardin A, Pizzey C, et al. Consistency in polyclonal T-cell responses to gluten between children and adults with celiac disease. Gastroenterology 2015 ;149(6):1541-1552.
116. Lähdeaho ML, Mäki M, Laurila K et al. Small-bowel mucosal changes and antibody responses after low- and moderate-dose gluten challenge in celiac disease. BMC Gastroenterol. 2011; 11:129.
117. Lähdeaho ML, Kaukinen K, Laurila K et al. Glutenase ALV003 attenuates gluten-induced mucosal injury in patients with celiac disease. Gastroenterology 2014 ;146(7):1649-58.
118. Lähdeaho ML, Scheinin M, Vuotikka P, Taavela J, Popp A, et al. Safety and efficacy of AMG 714 in adults with coeliac disease exposed to gluten challenge: a phase 2a, randomised, double-blind, placebo-controlled study. Lancet Gastroenterol Hepatol 2019 ;4(12):948-959.
119. Kelly CP, Green PH, Murray JA et al. Larazotide acetate in patients with coeliac disease undergoing a gluten challenge: a randomised placebo-controlled study. Aliment Pharmacol Ther 2013 ;37(2):252-262.
120. Leffler D, Schuppan D, Pallav K et al. Kinetics of the histological, serological and symptomatic responses to gluten challenge in adults with coeliac disease. Gut. 2013 ;62(7):996-1004.
121. Leffler DA, Kelly CP, Abdallah HZ et al. A randomized, double-blind study of larazotide acetate to prevent the activation of celiac disease during gluten challenge. Am J Gastroenterol. 2012 ;107(10):1554-1562.
122. Sarna VK, Skodje GI, Reims HM, et al. HLA-DQ:gluten tetramer test in blood gives better detection of coeliac patients than biopsy after 14-day gluten challenge. Gut. 2018 ;67(9):1606-1613.
123. Mollazadegan K, Kugelberg M, Montgomery SM, et al. A population-based study of the risk of diabetic retinopathy in patients with type 1 diabetes and celiac disease. Diabetes Care 2013;36(2):316-21.
124. Kurien M, Mollazadegan K, Sanders DS, et al. Celiac Disease Increases Risk of Thyroid Disease in Patients With Type 1 Diabetes: A Nationwide Cohort Study. Diabetes Care 2016 ;39(3):371-5.
125. Reilly NR, Lebwohl B, Mollazadegan K, et al. Celiac Disease Does Not Influence Fracture Risk in Young Patients with Type 1 Diabetes. J Pediatr 2016; 169:49-54.
126. Craig ME, Prinz N,Boyle CT, et al. Prevalence of Celiac Disease in 52,721 Youth With Type 1 Diabetes: International Comparison Across Three Continents. Diabetes Care 2017 ;40(8):1034-1040.
127. Williams KV, Cristaldi CL, Miller RG, et al. Celiac Autoimmunity Is Associated With Lower Blood Pressure and Renal Risk in Type 1 Diabetes. J Clin Endocrinol Metab 2018;103(10):3828-3836.
128. Tsouka A, Mahmud FH, Marcon MA. Celiac Disease Alone and Associated With Type 1 Diabetes Mellitus. J Pediatr Gastroenterol Nutr 2015 ;61(3):297-302.
129. Laitinen AU, Agardh D, Kivelä L, et al. Coeliac patients detected during type 1 diabetes surveillance had similar issues to those diagnosed on a clinical basis. Acta Paediatr 2017 ;106(4):639-646.
130. Kivelä L, Popp A, Arvola T, et al. Long-term health and treatment outcomes in adult coeliac disease patients diagnosed by screening in childhood. United European Gastroenterol J 2018 6(7):1022-1031.
131. Gopee E, van den Oever EL, Cameron F, et al. Coeliac disease, gluten-free diet and the development and progression of albuminuria in children with type 1 diabetes. Pediatr Diabetes 2013 ;14(6):455-8.

132. López RV, Cid CM, García GR, et al. Influence of the 2012 European Guidelines in Diagnosis and Follow-up of Coeliac Children With Selective IgA Deficiency. J Pediatr Gastroenterol Nutr 2020 ;71(1):59-63.
133. Kurppa K, Ashorn M, Iltanen S, et al. Celiac disease without villous atrophy in Children: a prospective study. The Journal of Pediatrics 2010; 157:373-80.
134. Tosco A, Salvati VM, Auricchio R, et al. Natural history of potential celiac disease in children. Clinical Gastroenterology and Hepatology. 2011; 9:320-25.
135. Lionetti E, Castellaneta S, Pulvirenti A, et al. Prevalence and natural history of potential celiac disease in at- family-risk infants prospectively investigated from birth. The Journal of Pediatrics 2012;161(5):908-14.
136. Auricchio R, Tosco A, Piccolo E, et al. Potential celiac children: 9-year follow-up on a gluten diet. Am J Gastroenterol 2014; 109: 913-921.
137. Kondola R, Puri AS, Banka AK, et al. Short-term prognosis of potential celiac disease in Indian patients. United European Gastroenterol Journal 2016; 4:275-80
138. Auricchio R, Tosco A, Piccolo E, et al. Progression of Celiac Disease in Children With Antibodies Against Tissue Transglutaminase and Normal Duodenal Architecture. Gastroenterology 2019; 157:413-20.
139. Fernández S, Borrell B, Cilleruelo ML, et al. Prevalence of celiac Disease in a long-term study of a Spanish at genetic-risk cohort from the general population. J Pediatr Gastroenterol Nutr 2019; 68:364-70.
140. Lionetti E, Castellaneta S, Francavilla R, et al. Long-Term Outcome of Potential Celiac Disease in Genetically at-Risk Children: The Prospective CELIPREV Cohort Study. J Clin Med 2019 ;8(2):186.
141. Mandile R, Discepolo V, Scapaticci S, et al. The effect of gluten-free diet on clinical symptoms and the intestinal mucosa of patients with potential celiac disease. J Pediatr Gastroenterol Nutr 2018; 66:654-56.
142. Cahill P, Papageorgiou A. Triadic communication in the primary care paediatric consultation: a review of the literature. Br J Gen Pract 2007;57(544):904-11.
143. Ukkola A, Maki M, Kurppa K, et al. Patients' experiences and perceptions of living with coeliac disease - implications for optimizing care. J Gastrointestin Liver Dis 2012;21(1):17-22.
144. Kinos S, Kurppa K, Ukkola A, et al. Burden of illness in screen-detected children with celiac disease and their families. J Pediatr Gastroenterol Nutr 2012;55(4):412-6.
145. Ukkola A, Maki M, Kurppa K, et al. Diet improves perception of health and well-being in symptomatic, but not asymptomatic, patients with celiac disease. Clin Gastroenterol Hepatol 2011;9(2):118-23.
146. Nordyke K, Rosen A, Emmelin M, et al. Internalizing the threat of risk--a qualitative study about adolescents' experience living with screening-detected celiac disease 5 years after diagnosis. Health Qual Life Outcomes 2014; 12:91.
147. Gardiner PV. Evidence based patient information. Doctors should be encouraged to develop information resources on the internet. BMJ 1999;318(7181):461.
148. Sainsbury K, Halmos EP, Knowles S, et al. Maintenance of a gluten free diet in coeliac disease: The roles of self-regulation, habit, psychological resources, motivation, support, and goal priority. Appetite 2018; 125:356-66.
149. Paganizza S, Zanotti R, D'Odorico A, et al. Is Adherence to a Gluten-Free Diet by Adult Patients With Celiac Disease Influenced by Their Knowledge of the Gluten Content of Foods? Gastroenterol Nurs. 2019;42(1):55-64.
150. Halmos EP, Deng M, Knowles SR, et al. Food knowledge and psychological state predict adherence to a gluten-free diet in a survey of 5310 Australians and New Zealanders with coeliac disease. Aliment Pharmacol Ther 2018;48(1):78-86.

151. Germeni E, Vallini I, Bianchetti MG, et al. Reconstructing normality following the diagnosis of a childhood chronic disease: does "rare" make a difference? Eur J Pediatr 2018;177(4):489-95.
152. Rosen A, Ivarsson A, Nordyke K, et al. Balancing health benefits and social sacrifices: a qualitative study of how screening-detected celiac disease impacts adolescents' quality of life. BMC Pediatr 2011; 11:32.
153. McManus MA, Pollack LR, Cooley WC, et al. Current status of transition preparation among youth with special needs in the United States. Pediatrics 2013; 131: 1090–1097.
154. Kivelä L, Hekkala S, Huhtala H, et al. Lack of long-term follow-up after paediatric-adult transition in coeliac disease is not associated with complications, ongoing symptoms or dietary adherence. United European Gastroenterol J 2020;8(2):157-166.
155. Reilly NR, Hammer ML, Ludvigsson JF, et al. Frequency and Predictors of Successful Transition of Care for Young Adults With Childhood Celiac Disease. J Pediatr Gastroenterol Nutr 2020 ;70(2):190-194.
156. Crowley R, Wolfe I, Lock K, et al. Improving the transition between paediatric and adult healthcare: a systematic review. Arch Dis Child 2011; 96 (6):548-553.
157. Nagra A, McGinnity PM, Davis N, et al. Implementing transition: Ready Steady Go. Arch Dis Child Educ Pract Ed 2015; 100(6):313-320.
158. Cooley WC, Sagerman PJ, American Academy of Pediatrics, et al. Supporting the health care transition from adolescence to adulthood in the medical home. Pediatrics 2011 ;128(1):182-200.
159. Sankari H , Hietikko M, Kurppa K et al. Intestinal TG3- and TG2-Specific Plasma Cell Responses in Dermatitis Herpetiformis Patients Undergoing a Gluten Challenge. Nutrients. 2020 ;12(2):467
160. Mansikka E, Hervonen K, Kaukinen K et al. Gluten Challenge Induces Skin and Small deBowel Relapse in Long-Term Gluten-Free Diet-Treated Dermatitis Herpetiformis. J Invest Dermatol. 2019 ;139(10):2108-2114.
161. Leonard MM, Silvester JA, Leffler D, et al. Evaluating responses to gluten challenge: a randomized double-blind 2 dose gluten challenge trial. Gastroenterology 2021 feb;160(3):720-733.
162. Taavela J , Viiri K , Popp A et al. Histological, immunohistochemical and mRNA gene expression responses in coeliac disease patients challenged with gluten using PAXgene fixed paraffin-embedded duodenal biopsies. BMC Gastroenterol. 2019 ;19(1):189.
163. Tye-Din JA , Daveson AJM, Hooi C Ee et al. Elevated serum interleukin-2 after gluten correlates with symptoms and is a potential diagnostic biomarker for coeliac disease. Aliment Pharmacol Ther. 2019 ;50(8):901-910.
164. Daveson AJM, Tye-Din JA, Goel G et al. Masked bolus gluten challenge low in FODMAPs implicates nausea and vomiting as key symptoms associated with immune activation in treated coeliac disease. Aliment Pharmacol Ther 2020; 51(2):244-252.
165. Goel G, Daveson AJM, Hooi CE et al. Serum cytokines elevated during gluten-mediated cytokine release in coeliac disease. Clinical and Experimental Immunology 2020, 199: 68–78.

Table 1. Questions and Recommendations on the Follow-up of Children and Adolescents with Coeliac Disease
Questions and *Recommendation*s
1. Is follow-up and management of coeliac disease needed? *We recommend follow-up for children and adolescents after the diagnosis of CD has been established.*
2. Who should do the follow-up of which patients and which is the role of the dietitian? What is the role of self-care and E-health? *The regular follow-up visits of children with CD are preferably carried out by a physician and/or a dietitian experienced in managing the disease. Local conditions and practices may determine how to apply these recommendations, but self-care treatment without access to adequate health care and dietitians is not recommended.*
3. What should be the frequency of follow-up and what should be assessed?
3.1. *The first follow-up visit should be scheduled 3-6 months after CD diagnosis, but with easy access to the coeliac service if earlier advice is needed, and sooner review if there are concerns regarding how the family is coping with the diet, if there are ongoing issues with growth or persistent symptoms or a need to repeat bloodwork earlier. Subsequent visits should be every 6 months until normalisation of TGA levels, and every 12-24 months thereafter.*
3.2. During follow up patients should be evaluated for: *3.2. I. Gastro-intestinal and extra-intestinal signs and symptoms.* *3.2.II. Anthropometric measurements and growth parameters.* *3.2.III. IgA-TGA using the same assay as at diagnosis as a surrogate marker for improvement/healing of the small bowel mucosa. IgG based tests and RIA based IgA-TGA measurements are not suitable for follow-up in IgA sufficient patients. IgA insufficient patients with CD should be followed with IgG based tests.* *3.2.IV. A complete blood cell count, micro-nutritional status (e.g., haemoglobin, iron, vitamin B12 and vitamin D levels) and ALT measurements, should be performed after clinical evaluation at time of diagnosis. Any abnormality should be followed and deficiencies corrected until normalisation. If abnormalities persist, additional diagnoses should be considered and appropriately investigated.* *3.2.V. Screening for thyroid disease with TSH and thyroxine (and autoantibodies if indicated) may be considered during follow-up after clinical evaluation at the discretion of the clinician.* *3.2.VI. Routine bone density screening is not recommended .* *3.2.VII. HBV antibody levels may be measured in previously immunized patients if this is considered important in the population. A booster dose should be given if inadequate levels are present.*
4. Adherence to the gluten-free diet
4.1. Should the adherence to the diet be assessed during follow-up and if so, how? *Since a gold standard method is still missing, adherence to the GFD should be assessed multi-dimensionally through a careful evaluation of symptoms, dietary interview and/or dietary questionnaires and laboratory tests.* 4.2. What is the role of detection of Gluten Immunogenic Peptides (GIPs) in the assessment of the compliance to the gluten-free diet? *Further data are needed before a recommendation on stool/urinary GIPs determination to assess compliance to the GFD in clinical practice can be formulated.*
5. Common issues during follow-up and management of CD
5.1. When to expect catch-up growth? *In the pre-pubertal/pubertal child, if significant catch-up growth in height is not reached within 1 year after initiating the GFD, despite strict dietary adherence, additional investigations, and consultation with a paediatric endocrinologist are recommended to rule out other causes of short stature.* 5.2. Is a lactose-free diet necessary?

We recommend a trial with lactose-reduced diet only in CD patients with symptoms suggestive of lactose intolerance (such as ongoing diarrhoea, abdominal pain and/or gassiness) despite adhering to the GFD.

5.3. Chronic tiredness in well- controlled coeliac disease?

There are no specific recommendations for chronic fatigue in CD except to follow a GFD.

5.4. Irritable bowel syndrome (IBS) in coeliac disease?

IBS in children with CD on a GFD should be treated similarly as in children without CD.

5.5. How to treat anaemia and/or sideropenia?

Young children with anaemia due to iron, folate or vitamin B12 deficiency should receive supplementation in addition to the GFD, since improvement over time may take too long in these children in a critical period of brain development and rapid catch-up growth. A low threshold for supplementation may also be considered for older children. The disappearance of anaemia should be confirmed in all cases. Adherence to the GFD should be checked, and other causes for anaemia should be excluded in children who do not recover despite a strict GFD. Concerning sideropenia without anaemia, an expectant attitude may be appropriate on GFD as long as there is improvement in iron stores without supplementation.

6. Specific issues during follow-up and management

6.1. How to approach persistent high serum levels of antibodies against tissue transglutaminase (TGA)?

Lack of decreasing IgA-TGA levels after 6-12 months on a GFD or persisting positive IgA-TGA levels should be assessed by carefully reviewing dietary compliance and testing IgA-TGA using the same test from the same manufacturer.

6.2. When is it necessary to (re)biopsy?

Routine assessment of mucosal healing by small bowel biopsies is not recommended in children with CD following a GFD. We recommend considering (re)biopsy only in selected CD cases; based on specific clinical grounds, for example, when doubts about the original diagnosis or suspicion of occurrence of an additional condition.

6.3. Refractory coeliac disease in children: does it exist?

We recommend properly investigating other causes of an apparent "refractory CD" in children, including ongoing inadvertent ingestion of gluten and other possible concomitant enteropathies, such as Crohn's disease, autoimmune enteropathy, small bowel bacterial overgrowth, cow's milk protein allergy and pancreatic insufficiency.

7. Should the quality of life (QOL) be assessed during the follow-up and if so, how?

We recommend assessing the HRQOL of children and adolescents with CD during follow-up by means of validated, CD-specific HRQOL questionnaires. These questionnaires may be administrated during or before the follow-up consultations, either on paper or by e-consultation. The results should be interpreted by the physician together with the parents/care givers, and if age adequate, also with the child.

8. Should follow-up of children with special situations be different from the one in the average CD patient?

8.1. In cases of unclear diagnosis

In cases of uncertain CD diagnosis, HLA typing should be performed before gluten-challenge in order to detect children in whom the occurrence of CD is unlikely.

8.1.1. How to perform a gluten-challenge?

8.1.1.II. To avoid unnecessary exposure to gluten in CD children with an early response to the challenge serum IgA-TGA determination may be considered 1 month after starting and this should be measured every 3 months during daily ingestion of 10-15 g of gluten for 12 months. Earlier evaluation is recommended in case of suggestive symptoms.

8.1.1.IV. In the absence of symptoms and/or specific CD-antibodies after 1 year of formal gluten challenge, the child should be allowed to have a normal gluten-containing diet and follow-up visits with measurement of specific coeliac-antibodies should be offered annually or every other year. Earlier evaluation is recommended in case of suggestive symptoms.

8.2. In children with associated type 1 diabetes (T1D)?

8.2.I. We recommend the same frequency and follow-up tests in children with CD and T1D as in

children with isolated CD, with (additional) special attention to test for thyroid involvement and diabetic retinopathy.

8.2.II. We recommend developing the follow-up plan in conjunction with an endocrinologist/diabetologist and a dietitian, also considering the need for psychological and social support.

8.3. In children with associated IgA deficiency?

8.3.I. We recommend the same follow-up practice in IgA deficient children with CD than in IgA sufficient children with CD.

8.3.II. At follow-up visits CD specific IgG antibodies (TGA, EMA or DGP) should be assessed.

8.4. In cases of potential CD?

8.4.I. In the presence of symptoms attributable to gluten, a trial of a GFD should be discussed with the family.

8.4.II. If left on a regular diet, we recommend annual follow-up visits, with attention towards growth and nutritional status, including bone health.

8.4.III. Duodenal biopsies should be performed in case of appearance of symptoms and/or of increased elevation of the CD antibody levels. In other cases with persistent serological positivity, on individual basis and in dialogue with the patient/caregivers, duodenal biopsies may be considered during follow-up.

9. How to improve communication: To parents? To patients?

9.1. Communication of diagnostic certainty to parents and children

The paediatric gastroenterologist/paediatrician should communicate to the patient and the parents/caregivers that the CD diagnosis is made with certainty and according to current evidence-based guidelines. All results (serology, histopathology, HLA if done) with dates of performance should be provided in writing for later proof of CD diagnosis.

9.2.Patient empowerment

9.2.I. The paediatric gastroenterologist/paediatrician and dietitian should communicate the need for a lifelong GFD and regular monitoring and facilitate access to professional dietary counselling knowledgeable on GFD.

9.2.II. We recommend providing education using oral and written information (leaflets, E-learnings etc.) about the disease and benefits of adhering to the diet. Later health risks should be brought into perspective without inducing fear or anxiety considering the patient's age and complications at the time of diagnosis and compliance with dietary recommendations.

9.3. Emotional and social support

9.3.I. Emotional and practical support from personal contact with other individuals with CD (Coeliac /parent support groups, patient organizations, etc.) should be provided to reduce eventual feelings of social isolation.

9.3.II. Patients, especially adolescents, perceiving lifestyle changes related to CD diagnosis, including the GFD and emotional coping, as difficult warrant particular attention and support.

10. How to organize the transition from paediatric care to adult health-care?

Even though current data is insufficient, we recommend a formal transfer of medical care of an adolescent with CD to facilitate the transition to adult care. The transfer should be structured and, at minimum, include a transition letter or "coeliac passport" providing data on the basis of diagnosis, follow-up, anthropometric data, possible comorbidities and dietary adherence level.

CD = coeliac disease; GFD = gluten-free diet; GIPs = gluten immunogenic peptides; HLA = human leukocyte antigen; HRQOL = health related quality of life; IBS = irritable bowel syndrome; RIA = radio immune assay; TGA = antibodies against tissue transglutaminase; T1D = type 1 diabetes.

Summary Table of the Revised Literature

ESPGHAN position paper on the management and follow-up of children and adolescents with coeliac disease.

Supplementary material

Question 1. Is follow-up and management of CD needed?

A search was conducted in Medline using the search terms celiac, coeliac, children, adherence and follow-up. The search identified a total of 356 records, of which 12 were included for this question: 8 primary observational studies (7509 children) and 4 systematic reviews (640 studies). As there were insufficient studies in children only, we included 1 study in both adults and children (Kurppa 2012), 1 systematic review until the age of 20 years (Snyder 2016) and another one without an age specification (Valitutti 2017).

Author, country (year)	Study type/ description	Age (years)	Sample size	Objectives	Main findings
Barnea, Israel (2014)	Case-control	Mean diagnosis 6.4 lost to follow up (LTFU) 5.96 controls	50 CD children 52 CD children with LTFU	To characterize LTFU population, and identify compliance barriers to gluten- free diet (GFD) and follow-up.	LTFU is associated with non-adherence to GFD and positive serology.
Bellini, Italy (2011)	Case-control	6-16	156 cases, 353 controls	To determine locus-of-control in coeliacs compared to healthy.	No difference between locus-of-control, to test for adherence to the GFD, in the two groups.
Charalampopoulous, Greece (2013)	Cohort	2-18	90 CD children	To characterize compliance to GFD.	Low compliance rate (44%), worse with age. Parents' education is important.
Hagopian, US/Europe (2017)	Cohort	4.5 months-15	5891 CD children	To determine timing, extent of co-occurrence, and associated genetic and demographic factors.	Early type 1 diabetes (T1D) and coeliac disease (CD) autoimmunity occur together more than expected.

Kurppa, Finland (2012)	Interview	<18 ->18	94 CD children 749 CD adults	To assess adherence to GFD.	88% Adherence. Younger age at diagnosis, being currently a teenager, and current symptoms were associated with non-adherence to diet.
Ludvigson, Sweden (2016)	Systematic review	Not available (N/A)	190 studies	To propose recommendations for the management in adolescents and young adults, and how to facilitate the transition to adult healthcare.	Diagnosis to be re-evaluated when made outside current European Society of Paediatric Gastroenterology Hepatology and Nutrition (ESPGHAN) or North American Society for Pediatric Gastroenterology, Hepatology and Nutrition (NASPGHAN) recommendations or when the patient questions his/her diagnosis.
Myléus, Sweden (2020)	Systematic review	<20	49 studies	To assess adherence to GFD.	Adherence 78% (range 23-98%). Studies varied in design and quality.
Rimárová, Slovakia (2018)	Cross-sectional	9-15	Caregivers to 325 children	To assess adherence to GFD.	Adherence is higher among girls. Younger children and children with family history of CD had significantly higher compliance. Children of parents (especially of mothers) with higher education had better adherence.
Snyder, US (2016)	Systematic review	6 months – 20	N/A	To assess the available evidence in 6 categories associated with CD to develop a set of best practices.	Quality of the data available was often insufficient to provide unequivocal best practices. Using the available data and the clinical experience of the panel, a practical framework for the management of children with CD was created.
Tapsas, Sweden (2014)	Cohort	<1	316 children	To assess adherence to GFD and intake of oats.	97% Adherence, but 83% had occasional transgressions.
Valitutti, Italy (2017)	Systematic review	N/A	401 studies	To summarize the available studies on follow-up of CD in children.	The “best practice” and evidence-based recommendations for follow-up in patients with CD are still awaited. A yearly follow-up visit is advised as the safest approach for children with CD.

Wessels, Netherlands (2016)	Cohort	Mean at diagnosis 6.3	182 CD children	To determine the frequency of nutritional deficiencies and thyroid dysfunction in children with CD at diagnosis and during follow-up after initiation of a GFD.	Investigations for iron, folate, and vitamin B12 deficiencies are relevant at the time of diagnosis. However, ordering these tests at follow-up visits may be questionable because only mild deficiencies occurred in a minority of the children.

Question 2. Who should do follow-up of which patients and which is the role of the dietician? What is the role of self-care including E-health?

A search was conducted in PubMed using the search terms celiac, coeliac, children, follow-up, gluten-free diet, paediatrician, paediatric expert in the field of celiac, general doctor, dietitian and e-health. The search identified a total of 111 records, of which 4 were included for this question: 2 primary observational studies (381 children) and 2 randomized clinical trials (RTC) in both children and adults (Haass 2017, Vriezinga 2018) (365 patients <25 years).

Author, country (year)	Study type/ Description	Age (years)	Sample size	Objectives	Main findings
Connan, Canada (2019)	Prospective	Mean 13.5±4.5	18 CD children	To design, develop and refine an interactive E-learning module to educate CD patients/families regarding implementation of a GFD.	Interactive E-learning module is effective in knowledge retention. Mean satisfaction post-module completion was high. Knowledge test scores increased significantly from pre- to post- module completion.
Haas, USA (2017)	RCT	12-24	61 CD children/adults	To determine the impact of Text message intervention on GFD adherence, QoL and patient activation.	Comparing enrolment and three-month follow-up significant improvement in patient activation and QoL in the TEACH intervention group. No statistically significant difference in GFD adherence.

Johansson, Sweden (2019)	Retrospective cohort	Median at diagnosis 7	363 CD patients	To investigate the outcome of different follow up protocols of CD led by either paediatricians or dietitians.	Non-compliance: no difference in prevalence between the different follow-up protocols. anti-tTG IgA reversed equally over time between the three clinics. Total mean cost per patient was less by visits led by dietitian.
Vriezinga, The Netherlands (2018)	RCT multicentre	<25	304 CD children and adults	To evaluate the efficacy of online consultation compared with outpatient clinic follow-up.	Health problems were detected more frequently using online consultation. Results indicate that online consultations for children and young adults with CD are cost saving, increase CD-specific HRQOL, and are satisfactory for the majority.

Question 3: What should be the frequency of follow-up and what should be assessed?

A search was conducted in Pubmed using the search terms celiac, coeliac, children and follow-up. The search identified a total of 382 records, of which 30 were included for this question: 17 primary observational studies (1599387 children) 12 reviews (772 studies) and 1 guideline. As there were insufficient studies in children only, we included 1 guideline in adults (Al Toma 2019), one publication in adults and children (Husby & Murray 2019) and one systematic review (Zingone 2018) in adults. We also included 5 studies published before 2010 (Ansaldi 2003, Elfström 2008, Leonardi 2009, Meloni 2009 and Park 2007), 1 after March 2020 (Lionetti 2021) and 1 narrative review (Anania 2017) since they were considered especially informative.

Author, country (year)	Study type/ description	Age (years)	Sample size	Objectives	Main findings
Al Toma, Europe (2019)	United European Gastroenterology (UEG) adult guidelines	Adults	N/A	To address the management of gluten-related disorders including CD.	Bone density measurement (DEXA) should be measured in those at high risk of osteoporosis. At diagnosis or not later than the age of 30–35 years and then repeated at 5-year intervals. A shorter interval (2–3 years) in case of low bone density, evidence of ongoing villus atrophy or poor dietary adherence.
Anania, Italy (2017)	Narrative Review	4-17	N/A	A review of vaccination status in CD patients.	Current evidence supports a good immunogenicity of most vaccines with the exception of hepatitis B virus (HBV), that elicits a lower response in CD patients compared to the general population. An evaluation of the response to HBV vaccine should be routinely assessed in newly diagnosed CD children and adolescents who were previously vaccinated for HBV.

Ansaldi, Italy (2003)	Cohort	17 months-17	343 CD cases, 230 controls	To establish the prevalence of autoimmune thyroid involvement in a large series of paediatric patients with CD.	The high frequency of autoimmune thyroid disease found among patients with CD, even on a GFD, may justify a thyroid status assessment at diagnosis and at follow-up evaluation of children with CD.
Assa, Israel (2017)	Cross-sectional	Mean 17.1	7145 CD cases, 1580896 controls	To investigate the association of a diagnosis of CD with various comorbidities in late adolescence.	Autoimmune diseases were significantly more common in subjects with CD, including insulin dependent diabetes, inflammatory bowel disease, arthritis, thyroid diseases, and psoriatic skin disorders. Further associations included asthma, bile stones, migraine, anaemia and menstrual abnormalities.
Barnea, Israel (2014)	Retrospective case-control	Mean at diagnosis 6.4 in LTFU and 5.96 in control	50 cases (CD with LTFU) 52 controls (CD with FU)	To assess utility of follow up and consequences of not being followed up.	LTFU is associated with non-adherence to GFD and positive serology. Risk factors for LTFU should be identified and addressed in order to improve patient care.
Blansky, USA and Canada (2019)	Retrospective chart review	Mean at diagnosis 9.7	250 CD	To evaluate adherence to guidelines for dietitian consultation and follow-up for children with CD.	Most subjects (83%) consulted a dietitian, with 31% attending both a dietitian-led class and an individual visit. One-fourth of children were lost to follow-up within a year of diagnosis, and 22 (9%) had no gastrointestinal (GI) visits after their diagnostic biopsy. Children lost to follow-up within the first year were older at diagnosis than those who adhered to follow-up for longer.
Canova, Italy, Sweden, and USA (2018)	Longitudinal population-based	0-17	1233 CD cases 6167 controls	To examine the risk of any fracture in CD children compared with references individually using the	22 Individuals with CD and 128 reference individuals experienced a fracture, giving an overall HR (hazard ratio) of 0.87 (95% ci 0.55-1.37). There is no evidence of an increased risk of fractures during childhood and youth.

				regional medical birth register.	
Deora, Canada (2017)	Retrospective chart review	Median 7.8	140 CD	To examine the prevalence of micronutrient deficiencies at diagnosis, 6 and 18 months following the start of GFD.	Vitamin D is the most common deficient vitamin at diagnosis and should be checked as a part of the annual assessment for these children. Serum ferritin was subnormal in 34.5% with zinc in 18.6% children, but only 10.9% children had iron deficiency anaemia.
Diamanti, Italy (2011)	Cohort	1.9–24	545 cases, 622 controls	To evaluate, in children and adolescents with CD on GFD the prevalence of autoimmune thyroiditis	There was no significant difference in autoimmune thyroiditis prevalence between patients with CD on a GFD (10%) and controls (8.2%).
Fouda, Saudi Arabia and Canada (2013)	Systematic review Position paper	N/A	N/A	To provide recommend-dations on screening, diagnosis, treatment and follow-up of low bone mineral density (BMD) in CD patients.	Current evidence does not support the screening of all CD patients for BMD at diagnosis. Follow-up BMD assessment should be performed 1-2 years after initiation of a GFD.
Gidrewicz, Canada (2017)	Cross-sectional	Mean 10.4	228 CD children	To characterize the normalization of the tissue transglutaminase antibody (TGA) and EMA in children on a strict GFD	In children with the highest serology at diagnosis, 79.7% had an abnormal TGA 12 months after diagnosis. At 2 years, an abnormal TGA persisted in 41.7%. In contrast, only 35% of children with the lowest serology at diagnosis displayed abnormal TGA at 12 months.

Heshin-Bekenstein, Israel (2015)	RCT	1-18	82 CD children	To assess two vaccines, a new pre-s vaccine compared to standard hepatitis b (engerix b) in CD patients.	Good response to two vaccinations for hepatitis B in CD patients. Single booster dose sufficient to raise abs in all. Vaccine response for HBV appears good.
Husby, Denmark and Argentina (2019)	Systematic review	Adults and children	N/A	Review and update on CD.	The follow-up should be problem oriented based on symptoms and signs, rather than a routine screening of malabsorption parameters. Guidelines suggest that patients should be controlled by a multidisciplinary team each 3 to 6 months from diagnosis to stabilization. After substantial improvement, annual evaluation is recommended.
Husby & Murray Denmark and USA (2019)	Systematic review American Gastroenterological Association (AGA)	Adults and children	N/A	To define key modalities in the diagnosis and monitoring of CD in adults as well as in children and adolescents.	The usefulness of serology at follow-up is limited for adults and better for children. A refinement of the TG2-IgA determination utilizing the detectable levels below the upper normal limit may be added in the identification of CD patients with mucosal healing.
Leonardi, Italy (2009)	Retrospective	N/A	60 CD patients	To study if CD patients are less able to respond to the hepatitis B vaccine	CD patients have a lower percentage of response to hepatitis B vaccination than healthy subjects.
Lionetti, Italy (2021)	Case-control	Range 5-11	131 CD cases 131 controls	To evaluate vitamin D status of children with newly diagnosed CD by a large case-control study.	Plasma vitamin D levels were significantly lower in patients than in control subjects. The percentage of children with vitamin D deficiency (<20 ng/ml) was significantly higher in CD children as compared to controls.

Mager, Canada (2012)	Registry	3-17	54 CD children	To determine the relationships between vitamin K/D status and lifestyle variables on BMD in CD children at diagnosis and after 1-year GFD.	43% had suboptimal vitamin D status and 25% had suboptimal vitamin K status at diagnosis all resolved after 1 year. Children CD are at risk for suboptimal bone health likely due in part to suboptimal vitamin D/K status. Strategies to optimize vitamin K/D intake may contribute to improved BMD in CD.
Meloni, Italy (2009)	Retrospective	10 months -18	324 CD children	To study the prevalence of autoimmune thyroiditis in children with CD and the effects of a GFD on thyroid function.	A high prevalence of autoimmune thyroiditis among children with CD (10.5%), compared with the Sardinian paediatric background population (2.92%), was found, and appears to be gluten independent.
Park, USA (2007)	Case-control	9.2 cases, 10.4 controls	26 CD cases, 18 controls	To determine whether children with CD fail to show a response to HBV vaccine more frequently than children without CD.	More than 50% of children with CD do not show a response to standard vaccination regimens for HBV. Given the large number of children with CD throughout the world, this observation suggests that there is a large HBV-susceptible population despite widespread vaccination. Current immunization strategies may need to be reassessed to protect this population and achieve the goal of universal protection.
Petroff, Germany (2018)	Cohort	Mean 8.6	345 CD children	To determine if antibody test could provide valuable information about GFD success after 3 months.	The mean concentration TGA-IgA decreased by a factor of 14 at 3 months of follow-up but remained above 1-fold the upper limit of normal (ULN) in 83.8% of patients.

Rousseff, Belgium (2018)	Multicentre prospective	Mean diagnosis 6.0 Currently Mean 7.3	133 CD children	To evaluate HBV vaccination response in children with CD. Response in initial non-responders after a single booster vaccination as well as factors influencing HBV vaccination response were evaluated.	A single intramuscular booster vaccination is able to induce a serologic response in two thirds of the initial non-responders. Control of HBV vaccination response has to become part of the follow-up in CD patients.
Sansotta, Italy (2020)	Retrospective chart review	Mean at diagnosis 5.1	260 CD children	To compare the performance of TGA by chemiluminescence immunoassay (CLIA) to the standard enzyme-linked immunosorbent assay (ELISA) methods in monitoring CD children after the start of GFD	At 30 months follow-up children tested by CLIA are less likely to normalize TGA levels compared to those tested by ELISA. Younger age at diagnosis and lower baseline TGA are predictors of earlier TGA normalization, regardless of the adopted assay.
Sansotta, USA (2017)	Retrospective chart review	1.28-17.89	260 CD children	To compare the performance of TGA by CLIA to the ELISA methods in monitoring CD children after the start of GFD.	The percentage and the time of the TGA normalization in CD children on GFD should be interpreted according to the utilized assay: at 30 months' follow-up children tested by CLIA are less likely to normalize TGA levels compared to those tested by ELISA. Younger age at diagnosis and lower baseline TGA are predictors of earlier TGA normalization, regardless of the adopted assay.

Snyder, USA (2016)	Systematic review	6 months-20	N/A	To assess the available evidence in 6 categories associated with CD to develop a set of best practices.	Routine screening for bone health at 1 year, alanine aminotransferase (ALT) and aspartate aminotransferase (AST), anaemia if previously abnormal, measure 25-OH vitamin D level if previously abnormal. Routinely obtain complete blood cells (CBC), screening for thyroid disease at follow-up, testing with tTG-IgA antibodies at periodic intervals and assessment of anthropometric measures.
Tuna Kirsaçlioğlu, Turkey (2016)	Retrospective chart review	1.25–16	37 CD cases, 143 controls	To evaluate changes in growth and bone metabolism during GFD.	The BMD of patients was significantly lower than that of control subjects at time of diagnosis, but not after 1 year of follow-up. In the first year of GFD, BMD, BMD z-score, height-for-age z-scores, and weight-for-age z-scores were significantly increased compared with the baseline.
Urganci, Turkey (2013)	Case-control	1-15	30 CD cases, 50 controls	To evaluate the response to hepatitis A and B vaccinations in paediatric patients with CD.	The rate of seroconversion to the hepatitis B virus- and hepatitis A virus (HAV) vaccine is lower in patients with CD than in healthy controls.
Usta, Turkey (2014)	Cohort	Mean 13.2	63 CD	To assess the effect and duration of GFD on bone health in children with CD.	Dietary compliance is important for bone health, and the time needed to normalize the BMD is not known. Patients with positive EMA, poor dietary history and history of bone pain should be evaluated with dual-energy x-ray absorptiometry (DXA) during follow-up.
Wessels, The Netherlands (2016)	Cohort. Retrospective	Median at diagnosis 6.3□4.3	182 CD	To determine the frequency of nutritional deficiencies and thyroid dysfunction in children with CD and during follow-up after initiation of a GFD.	Complementary blood investigations are relevant at the time of diagnosis of CD but have little diagnostic yield during follow-up visits once the patient is placed on a GFD.

Zanoni, Italy (2015)	Case-control	1-18 T1D 1-37 CD 1-43 HC	69 T1D 42 CD 79 HC	To analyse the serological response to HB vaccine and measles-containing vaccines in T1D, patients with CD and healthy control (HC) subjects.	HC subjects showed protective anti-HBs antibodies after vaccination, with no statistically significant difference. A lower statistically significant difference was found in the mean antibodies to Hepatitis B surface antibody (HBsAb) level of T1DM subjects when compared with the other two groups. No correlation between Human Leukocyte Antigen (HLA) DQ2 expression in T1DM and vaccine response was detected.
Zingone Italy (2018)	Systematic review	N/A	328 studies Adults	To examine the data from existing studies in which vitamin D has been assessed in CD patients.	Most of the studies on vitamin D in adult CD report a 25 (OH) vitamin D deficiency at diagnosis that disappears when the patient goes on a GFD, independently of any supplementation. When the active 1,25 (OH) vitamin D form was evaluated, it resulted in the normal range at the time of CD diagnosis. A strict and lifelong GFD can help recover vitamin D level without any supplementation

Question 4. Adherence to the gluten-free diet.

Q4.1. Should the adherence to the GFD be assessed during follow-up and if so, how?

Q4.2. What is the role of detection of Gluten Immunogenic Peptides (GIPs) in the assessment of the compliance to the gluten-free-diet?

Q4.1. Should the adherence to the diet be assessed during follow-up and if so, how?

A search was conducted in Medline using the search terms celiac, coeliac, children, adherence, follow-up, gluten-free diet, dietitian, teenagers, questionnaires, score, E Health/App. The search identified a total of 54 records, of which 9 were included for this question: 6 primary observational studies (306 children) and 3 systematic reviews (15470 studies). As there were insufficient studies in children only, we included studies in adults and children (Comino 2016, Moreno 2017) and in adults (Down 2018 and Harder 2020). We included Harder 2020 published after March 2020 since it was considered especially informative.

Author, country (year)	Study type/ description	Age (years)	Sample size	Objectives	Main findings
Comino, Spain (2016)	Cohort	1-72 CD cases	N/A	To evaluate the measurement of GIP in stools as a	No association was found between faecal GIP and dietary questionnaire or TGA.

				marker of GFD adherence in CD patients and compare it with traditional methods of GFD monitoring.	
Dowd, Canada (2018)	Prospective	Mean 39.25	118 CD adults	To design, develop and pilot test a smartphone app to promote effective self-management of CD and promote gut health.	MyHealthyGut is the first evidence-based app that may be helpful in empowering users to effectively self-manage CD and promote general gut health.
Gerasimidis, Scotland (2018)	Prospective	New diagnosed 10 Previously diagnosed 9.3	90 CD children	Recent gluten intake measured by GIP in children with CD and compared to routine clinical measures to evaluate GFD compliance.	Compared to GIP, the Biagi score, TGA, and clinical assessment presented sensitivity of 17%, 42%, and 17%, respectively. A combination of methods did not improve identification of patients who were noncompliant and more than 50% of the patients noncompliant on GFD still remained undetected. Interestingly, the specificity and positive predictive validity of TGA was very low.
Harder, Italy (2020)	Retrospective	Adults	273 CD adults	To develop a scoring system to stratify CD patients on a GFD according to their risk of having persistence of villous atrophy (VA).	A four-level score (0·5, 1·5, 3, 4) was obtained. Patients on a strict GFD and with good clinical conditions (4) have a very low risk of persistence of VA. Conversely, the risk is very high in patients with poor adherence to a GFD and unsatisfactory clinical response (0·5). A score of 1·5 is linked with a high risk. Risk is intermediate in patients scoring 3 (strict GFD and no/partial clinical improvement).
Ludvigsson, Sweden (2018)	Systematic review	N/A	10062 CD	To review the literature on CD therapeutic trials and issue recommendations for outcome measures.	Careful evaluation and reporting of outcome measures will increase transparency and comparability of CD therapeutic trials, and will benefit patients, healthcare and the pharmaceutical industry.

Ludvigsson, Sweden (2013)	Systematic review	N/A	N/A	To review the literature on the use of terms related to CD and gluten.	This paper presents the Oslo definitions for CD-related terms.
Moreno, Spain (2017)	Case-control	3-64 CD cases 3-57 controls	65 children, 69 adults 58 CD cases, 76 controls	To develop a method to determine gluten intake and monitor GFD compliance in patients with CD and to evaluate its correlation with mucosal damage.	GIPs are detected in urine after gluten consumption, enabling a new and non-invasive method to monitor GFD compliance and transgressions. The method was sensitive, specific and simple enough to be convenient for clinical monitoring of patients with CD as well as for basic and clinical research applications including drug development.
Silvester, Canada (2017)	Systematic review	N/A	26 studies	To assess the sensitivity and specificity of TG IgA and serum EMA immunoglobulin A (IgA) assays in identifying patients with CD who have persistent villous atrophy despite a GFD.	In a meta-analysis of patients with biopsy-confirmed CD undergoing follow-up biopsy on a GFD, we found that tests for serum TG IgA and EMA IgA levels had low sensitivity in detection of persistent villous atrophy. We need more-accurate non-invasive markers of mucosal damage in children and adults with CD who are following a GFD.
Wessels, The Netherlands (2018)	Cohort	Mean 11.3 Mean at diagnosis 4.9	151 children and young adults	To compare GFD compliance in CD children, measured by a short dietary questionnaire against a long questionnaire similar to a dietary interview and correlation between both questionnaires and CD antibodies and identifying variables predicting noncompliance.	Compared to the long questionnaire, short dietary questionnaires and TG2 antibodies serology failed to detect dietary transgressions in CD children, wherein adolescents were shown to be at highest risk. Long questionnaires specific for children may be useful to assess diet compliance, especially in settings with no dietitian consultation available.

Q4.2. What is the role of detection of Gluten Immunogenic Peptides (GIPs) in the assessment of the compliance to the gluten-free diet?

A search was conducted in Medline using the search terms celiac, coeliac, children, adherence, follow-up, gluten immunogenic peptides, gluten free diet, compliance, adherence, diet, monitor, aftercare, secondary care and health-care. The search identified a total of 28 records, of which 7 were included for this question: 5 primary observational studies (1 in children, 2 in both adults and children and 2 in adults) (129 children) and 2 systematic reviews (990 publications). As there were insufficient studies in children only, we included studies in adults (Stefanolo 2021 and Sylvester 2020) both adults and children (Comino 2016 and Moreno 2017) and children (Comino 2019). We included Silvester 2020 and Stefanolo 2021 studies published after March 2020 since they were considered especially informative.

Author, country (year)	Study type/ description	Age (years)	Sample size	Objectives	Main findings
Comino, Spain (2016)	Multicentre prospective	1–72 cases, 0–66 controls	188 CD cases 84 controls	To evaluate the measurement of GIP in stools as a marker of GFD adherence in CD patients and compare it with traditional methods of GFD monitoring.	Detection of GIP in stools reveals limitations of traditional methods for monitoring GFD in CD patients. The GIP ELISA enables direct and quantitative assessment of gluten exposure early after ingestion and could aid in the diagnosis and clinical management of nonresponsive CD and refractory CD.
Comino, Spain (2019)	Multicentre prospective	Median 4	64 CD children	To evaluate the usefulness of faecal GIP to support the diagnosis and to determine the adherence to the GFD in CD children.	Faecal GIP testing may guide treatment of CD prior to diagnosis and during the assessment diet adherence. Further studies could determine if early identification of gluten exposure reduces the need for expensive/invasive investigations for non-responsive CD.
Ludvigsson, Sweden (2018)	Systematic review	N/A	10062 CD	To review the literature on CD therapeutic trials and issue recommendations for outcome measures.	A strong correlation has been demonstrated between the absence of GIP in urine and healing of the intestinal epithelium.
Myléus, Sweden (2020)	Systematic review	N/A	49 studies, 7850 children	To investigate the rate of adherence to a GFD in children with CD, risk factors that affect adherence, and	The GIP assays reported the lowest adherence rate, suggesting that it also finds those with occasional involuntary gluten exposure. The highest median adherence was found for biopsies, followed by self-report, structured dietary interview, and serology test.

				outcomes of non-adherence.	
Moreno, Spain (2017)	Prospective	3–64 CD cases 3–57 controls	69 adults 65 children 58 CD cases 76 controls	To develop a method to determine gluten intake and monitor GFD compliance in patients with CD and to evaluate its correlation with mucosal damage.	GIPs are detected in urine after gluten consumption, enabling a new and non-invasive method to monitor GFD compliance and transgressions. The method was sensitive, specific and simple enough to be convenient for clinical monitoring of patients with CD as well as for basic and clinical research applications including drug development.
Stefanolo, Argentina (2021)	Prospective cohort	Median 46 (IQR 34-55)	53 CD adults	To evaluate how often patients who are on GFD are still exposed to gluten.	Patients with CD on a long-term GFD still frequently are exposed to gluten. Assays to detect GIP in stool and urine might be used to assist dietitians in assessment of GFD compliance.
Silvester, Canada (2020)	Prospective	Mean 41	18 CD adults	To detect gluten in food ingested and stool and urine excreted by CD patients endeavouring to follow a strict GFD.	8% of food samples from 9 participants with detectable gluten had a median concentration of 11 ppm, 40% contained >20 ppm, and 20% contained >200 ppm. GIPs were detected in 30 urine samples from 8 participants and 8 stool samples from 5 participants. Two thirds of those with a positive sample result had persistent VA.

Question 5. Common issues during follow-up and management of CD

Q5.1. When to expect catch-up growth? Q5.2. Is a lactose-free diet necessary? Q5.3. Chronic tiredness in well controlled in coeliac disease? Q5.4. Irritable bowel syndrome (IBS) in CD? Q5.5. How to treat anaemia and/or sideropenia?

A search was conducted in Medline using the search terms celiac, coeliac, children, follow-up, catch up, growth and development, lactose intolerance, chronic tiredness, fatigue, irritable bowel syndrome, anaemia and iron deficiency. The search identified a total of 58 records, of which 18 were included for this question: all primary observational studies (1590861 children). We included studies in children (Comba 2018, Soliman 2019, Tuna Kirsaclioglu 2016, Zung 2012, Basso 2012, Terrone 2013, Saps 2017, Assa 2017, Çatal 2015, Kivelä 2017, Nestares 2020, Radlović 2009, Rajalaht 2017 and Wessels 2016). Two especially informative papers on adults and children were also included (Jericho 2017, Burger 2018).

Q5.1. When to expect catch-up growth?

Author, country (year)	Study type/description	Age (years)	Sample size	Objectives	Main findings

Comba, Turkey (2018)	Retrospective cohort	2-17	73 CD	To evaluate the relation between age at diagnosis and adherence to the GFD on growth in children with CD.	Late CD diagnosis (> 6 years) negatively affected both the height and weight and BMI. Adherence to a GFD was shown to have significantly positive effects on weight and BMI z scores. No difference was found between the two groups in terms of height z-scores.
Soliman, Qatar (2019)	Case-control	7,4 ± 2,6 cases and controls	30 CD cases 30 controls	To evaluate the effect of GFD on growth of children with CD on long-term GFD (>2 years).	The change in the Ht-SDS was significantly higher in the CD group. 50% of children with CD on GFD were still increasing their Ht-SDS even after an average of 2 years or more after the beginning of GFD. No difference in Ht-SDS between CD children on GFD and normal controls. Daily weight gain was significantly lower in the control versus CD children on a GFD.
Tuna Kirsaclioglu, Turkey (2016)	Retrospective cohort	8.8 ± 4.6	37 CD	To evaluate changes in growth and bone metabolism during GFD in children with CD.	Significant improvements in WAZs and HAZs after 1 year on a GFD. 21.4% of the patients remained short statured after 3 years on a GFD. All patients with low weight at presentation had normal weight ranges after 2 years on a GFD. No difference in WAZ, HAZ and lab data due to adherence to the GFD.
Zung, Israel (2012)	Retrospective cohort	4,5 ± 2,4	55 CD	To assess the significance of seroconversion in predicting height and weight gain during the first year of GFD in children with CD.	Early catch-up growth occurs without seroconversion: mean Ht-SDS and Wt-SDS after 6 months GFD were higher than those at baseline, both in seropositive TGA and seronegative patients. No difference in Ht-SDS and Wt-SDS between those who reversed to seronegative TGA and those who remained seropositive.

Q5.2. Is a lactose-free diet necessary?

Author, country (year)	Study type/description	Age (years)	Sample size	Objectives	Main findings
Basso, Italy (2012)	Case-control	Mean 11,8 cases 13.5 controls	92 CD cases 188 controls	To evaluate the association of Primary Lactase Deficiency (PLD) and CD by comparing the prevalence of PLD in CD subjects and in a control population.	More than 70% of all subjects positive for the cytosine (C)/C polymorphism at C/Thymine (T)-13910 and for the Guanosine (G)/G polymorphism at G/Adenine (A)-22018 (genetic markers of hypolactasia), without significant differences between CD patients and controls.
Kuchay, India (2015)	Case-control	5-10	52 CD cases 102 controls	To assess the association between CD and SNPs leading to adult type hypolactasia (AtH) in children.	No significant correlation between C/T -13910 or G/A -22018 SNPs of AtH and CD. Children with C/C or G/G genotype of AtH may not be at greater risk of CD.

Q5.3. Chronic tiredness in well-controlled in coeliac disease?

Author, country (year)	Study type/description	Age (years)	Sample size	Objectives	Main findings
Jericho, USA (2017)	Retrospective cohort	Median 8.8	157 CD children	To characterize prevalence of extraintestinal symptoms at time of diagnosis and after GFD.	Children had greater improvements on a GFD as compared to adults. Chronic fatigue improved in 81% of children on strict GFD.
Terrone, Italy (2013)	Prospective cohort	Median 10.2	139 CD: 54 newly diagnosed, 54 in remission after GFD, 45 potential CD.	To screen for neurological and behavioural disorders in a paediatric cohort of patients with CD to detect possible	Statically significant decrease of chronic fatigue at remission in comparison to diagnosis. GFD had a positive impact on neuropsychiatric symptoms.

				differences related to adherence to GFD.	

Q5.4. Irritable bowel syndrome (IBS) in CD?

Author, country (year)	Study type/description	Age (years)	Sample size	Objectives	Main findings
Saps, Italy and USA (2017)	Case- control	4-18	96 CD cases, 97 unrelated controls.	To test the hypothesis that CD children on a GFD are at risk of abdominal pain (AP) and abdominal pain related functional GI disorders (AP-FGDI).	Subjects with CD and controls (8,2%) have a similar prevalence of chronic AP and AP-FGIDs.

Q5.5. How to treat anaemia and/or sideropenia?

Author, Country (year)	Study type/description	Age (years)	Sample size	Objectives	Main findings
Assa, Israel (2017)	Case-control	Mean 17.1 cases and controls	7145 CD cases, 1580896 controls	To investigate the associations between CD and various medical conditions.	Anaemia was significantly more common in subjects with CD (OR = 1.7, 95% CI 1.5–1.9, p <0.0001) than in controls.
Burger, The Netherlands (2018)	Retrospective cohort	9	250 CD children and adults	To evaluate the yield of routine laboratory tests and DEXA scans in CD.	At diagnosis: anaemia in 24.4%, iron deficiency in 38% of all 250 patients. All deficiencies recovered within 2 years of GFD with or without supplements. Data on children not presented separately.
Çatal, Turkey (2015)	Retrospective cohort	8.1 ± 4.21	91 CD	To determine the hematologic manifestations at diagnosis and the effects of a GFD.	Anaemia is 24.2% at diagnosis. Anaemia was less common in patients on a strict GFD (5.8% vs 25.6%).

Jericho, USA (2017)	Retrospective cohort	8.8	157 CD	To characterize prevalence of extra-intestinal symptoms at diagnosis and recovery on GFD.	12% Anaemia at diagnosis. It improved in 84% after 24 months on a GFD, including 1 patient who received a blood transfusion.
Kivelä, Finland (2017)	Retrospective cohorts	Screen-detected 7.0 Clinically detected 8.0	504 CD	To compare the baseline and follow-up characteristics of patients detected by screening and due to clinical suspicion.	Anaemia present in 22.9% (P < .001) of clinically detected patients and 7.1% of screen-detected patients (p<0.001); low MCV 10.6% vs 13.4%, ferritin 20.5% vs 20.0% and increased TfR 31.3% vs 22.2%. Clinical response was similar in both groups? 97.5% vs 96.2%, (P = .766).
Nestares, Spain (2020)	Case-control	Mean 8.5 cases 10.3 controls	68 CD cases 43 controls	To assess whether the use of a GFD is sufficient for maintaining correct iron status in children with CD.	CD children on a GFD had lower iron intake and nutritionally less balanced diet than the controls.
Radlović, Serbia (2009)	Retrospective cohort	0.5-7.5	90 CD	To evaluate the effect of GFD on the nutritional status of children with the classical form of CD. Sub-analysis about the effects of the GFD duration and the patients' compliance.	86 (95.56%) Had normal Hb values and 4 anaemia on a GFD after a median of 3.03 (range 1.08-8.75) years.
Rajalahti, Finland (2017)	Retrospective cohort	Anaemic 8.5 Non-anaemic 7.4	455 CD	To compare clinical, serological, and histological manifestations between CD children with and without anaemia at diagnosis.	Anaemia in 18.0% at diagnosis. Children with anaemia had higher values for TGA, were less often screen-detected and had more severe histological damage 92% Recovered from anaemia after a median of 1 year on a GFD, but Hb remained lower compared with the non-anaemic group.

Repo, Finland (2017)	Prospective cohorts	Potential CD with partial or subtotal villous atrophy (P/SVA), CD and controls, respectively: 6.3, 7.5, 6.1, 6.0	19 potential CD cases, 83 CD cases, 23 controls	To investigate the prevalence of anaemia and iron deficiency in children with potential and established CD.	Prevalence of anaemia in controls, potential CD, P/SVA, and TVA: 0%, 15%, 22%, and 63% respectively. Low ferritin 0%, 21%, 35%, and 87%. After a median of 7 months on a GFD.
Wessels, The Netherlands (2016)	Retrospective cohort	6.3 (±4.3)	182 CD	To determine the frequency of nutritional deficiencies in children with CD at diagnosis and during follow-up on a GFD.	At diagnosis: iron deficiency (28%) and anaemia (9%). At follow-up (mean 3.1 (±3.1 years): iron deficiency i8% and iron deficiency anaemia 2%.

Question 6. Specific issues during follow-up and management. Q6.1. How to approach persistent high serum levels of antibodies against tissue transglutaminase (TGA)? Q6.2. When is it necessary to (re)biopsy? Q6.3. Refractory coeliac disease in children: does it exist?

Q6.1. How to approach persistent high serum levels of antibodies against tissue transglutaminase (TGA)?

A search was conducted in PubMed using the search terms celiac, coeliac, children, follow-up, persistent or elevated transglutaminase, antibody and gluten-free diet. The search identified a total of 167 records, of which 17 were included for this question: all primary observational studies (2128 children). Since it was considered especially informative, we included one article published after March 2020 (Sansotta 2020).

Author, country (year)	Study type/ description	Age (years)	Sample size	Objectives	Main findings
Bannister, Australia (2014)	Retrospective cohort	Mean 7.5	150 CD	To evaluate the accuracy of anti-TGA-IgA and IgG against anti-deamidated gliadin peptide (DGP) during follow-up.	Sensitivity and specificity of combined TGA-IgA and DGP IgG was 75% and 85%, with positive predictive value (PPV) and a negative predictive value (NPV) of 22% and 98%, respectively.
Benelli, Italy (2016)	Prospective cohorts	Mean group 1 2.1. Mean group 2 2.4.	143 CD	To evaluate the clinical and laboratory response to GFD of patients	The percentage of children whose TGA IgA became negative after diagnosis was 51-55% at 6 months, 19-21% at 12 months, 5-6% at 24 months and 7% at 36 months.

				who received a diagnosis without a biopsy compared with those who underwent a biopsy.	
Bufler, Germany (2014)	Retrospective cohort	Mean 5.6	91 CD	To compare performance of DGP IgG, DGP IgA and TGA IgA during follow-up on a GFD.	DGP decreased sooner than TGA IgA. Non-adherence was best indicated by TGA IgA. At 18 months on GFD, 30% of children still showed positive TGA IgA for three different assay tests and 15%t for only one assay.
Candon, France (2012)	Retrospective cohort	Mean 6.6	80 CD	To compare the quantitative radio binding assay for TGA (RBA-TGA) to one of the second generation commercial ELISA at diagnosis and during follow-up.	RBA is likely responsible for higher TGA positivity rates during GFD than previously reported with ELISA. Decreasing trend in TGA levels rather than absolute levels may be used as a surrogate marker of adherence to GFD.
Chow, USA (2012)	Retrospective cohort	N/A	26 CD	To determine the prevalence and significance of IgA deficiency and partial deficiency in patients with CD.	In patients who are IgA deficient, IgG serologies may be persistently elevated despite histologic recovery.
Comino, Spain (2019)	Multicentre prospective cohort	Mean 4	64 CD	To evaluate TGA IgA, DPG IgA, GIP and dietary compliance at 6, 12 and 24 months after diagnosis.	Dietitian assessment was only moderately correlated with GIP detection but performed better in compliance evaluation than antibody assessment.
Dahlbom, Hungary-Sweden (2010)	Multicentre prospective cohorts	Group 1 52 children mean 1.6 Group 2 59 children mean 8.1	111 CD	To evaluate quantitative detection of IgA-TGA and IgG-TGA in serum for the prediction of the mucosal condition.	IgG-TGA declined slower than IgA-TGA. The initial levels of IgA-TGA correlated with the normalization time. Longer normalization time attains older children with milder clinical symptoms.

Ghazzawi, USA (2014)	Retrospective cohort	Mean 8.5	40 CD	To assess the rate of mucosal healing in treated children with CD within a median time on GFD of 24 months.	The mucosal healing rate was 64% in a selected group of treated children with mean time for follow-up biopsy of 24 months.
Gidrewicz, Canada (2017)	Retrospective cohort	Mean 10.4	228 CD	To characterize the normalization of the TGA and IgA EMA in children on a strict GFD.	Normalization of coeliac serology took >1 year in approximately 75% of GFD-compliant children with the highest coeliac serology or most severe mucosal injury at diagnosis.
Hogen Esch, The Netherlands (2011)	Retrospective multicentre cohort	Mean 5.6	129 CD	To determine the dynamics of TGA and EMA in children with CD after starting a GFD.	80% Will be seronegative for EMA and TGA after 2 years of GFD, and the mean concentration of TGA will show a 74% decrease after 3 months of diet.
Isaac, Canada (2017)	Retrospective cohort	Mean 9.3	487 CD	To evaluate time to normalization of TGA in the local paediatric CD population post diagnosis.	Good dietary compliance and lower anti-TG at diagnosis are predictors of earlier anti-TG normalization. Patients with T1DM are less likely to normalize anti-TG levels, with longer normalization time.
Leonard, USA (2017)	Retrospective cohort	Mean 10.6	103 CD	To determine whether IgA TGA correlates with mucosal damage at the time of a repeat endoscopy with duodenal biopsy in these patients.	19% Of paediatric patients treated with a GFD had persistent enteropathy. At the time of the repeat biopsy, TGA was elevated in 43% of cases with persistent enteropathy and 32% of cases in which there was mucosal recovery.
Lund, Sweden-Denmark (2016)	Multicentre retrospective cohort	Mean 9	34 CD	To measure the reduction of CD antibodies (IgA-TG and IgG DGP) in children with CD after initiation of GFD.	After 3.6 months on GFD 15% of children had normalized IgA-TG values and 26% had normalized IgG DGP values. After 7.6 months on GFD 39% had normalized IgA-TG values and 57% had normalized IgG DGP values.
Mehta, USA	Retrospective cohort	Mean 11	66 CD	To determine the association between	A negative TGA value was not associated with good adherence.

(2018)				serum TGA and dietitian-assessed adherence	
Sansotta, Italy (2020)	Retrospective cohort	Median ELISA 5.1 Chemiluminescence: 7.7	130 CD	Comparison of TGA IgA ELISA Vs Chemiluminescence titters during follow-up.	TGA normalization takes longer in children tested by chemiluminescence as compared to ELISA. Higher baseline TGA and older age at diagnosis predict a longer TGA normalization time.
Vécsei, Austria (2014)	Prospective cohort	Median: 7.8	53 CD	To compare the performance of up-to-date antibody tests in predicting mucosal status in children with untreated CD vs. children after GFD (18 months follow-up biopsy).	Only negative EMA had a likelihood ratio (LR) < 0.1 thus being an informative and clinically useful marker of mucosal healing in CD.
Webb, Sweden (2014)	Sub-study of a cross-sectional CD screening	Median: 13	193 CD	To evaluate GFD adherence after 1 year of follow-up in children with screening-detected CD in a general population.	After 1 year, 85% had normalized TG2-IgA levels. Those with the highest markers at diagnosis had the lowest proportion (75%) of normalized TG2-IgA levels after 1 year, but for most of them their initial values were more than halved.

Q6.2. When is it necessary to (re)biopsy?

A search was conducted in PubMed using the search terms celiac, coeliac, children, follow-up, repeated, biopsy and follow-up biopsy. The search identified a total of 225 records, of which 8 were included for this question: 6 primary observational studies (592 children) and 2 Meta-analysis (87 studies). As there were insufficient studies in children only, we included studies in both adults and children (Osman 2014, Sylvester 2017 and Szakács 2017).

Author, country (year)	Study type/ Instrument	Age (years)	Sample size	Objectives	Main findings
Bannister, Australia (2014)	Prospective longitudinal	Mean at diagnosis 7.5.	150 CD	To determine whether TGA IgA and anti-DGP IgG are sensitive and specific markers of mucosal recovery in	5.3% of follow-up duodenal biopsies had persistent villous abnormalities. The sensitivity and specificity of serology as a marker of significant mucosal pathology was 75 and 85%, PPV 22% NPV 98%.

				children with CD on a GFD for at least 12 months	
Belei, Romania (2018)	Prospective cohort	Mean age: 4.6	105 CD	To assess the rate and timing of histologic recovery among children with CD on a GFD.	86 children enrolled with Marsh type III lesions, histologic remission was observed in 81.4% after 1 year, 91.8% within 2–3 years and 97.6% in long-term follow up (≥ 3 years). Histologic recovery in CD after starting a GFD in children takes at least 1 year and might be incomplete in a small proportion of children, mainly associated with IgA immunodeficiency.
Ghazzawi, Minnesota (2014)	Retrospective cohort	Average at diagnosis 8.5	40 CD	To assess the rate of mucosal healing and indications for repeat small bowel (SB) biopsy in children with CD.	Histology on the second biopsy showed complete healing (n=25), intraepithelial lymphocytes (n=9), and persistent villous atrophy (n=6). Average time between biopsies was 24 months.
Leonard, USA (2017)	Retrospective cohort	Mean at diagnosis 10.6	103 CD	To determine the rate of mucosal recovery in paediatric patients with CD on a GFD. To determine whether IgA TGA correlates with mucosal damage at the time of a repeat endoscopy with duodenal biopsy.	5 CD children may have persistent enteropathy despite adherence to a GFD for at least 1 year. 45% of patients with persistent enteropathy were asymptomatic at the time of the repeat endoscopy. IgA TGA was a poor predictor of Marsh 3 histology at repeat biopsy as sensitivity 43%, specificity 68%, PPV 25%, and NPV was 83%. TGA IgA may not be an accurate marker of mucosal recovery in these patients.
Osman, Malaysia (2014)	Prospective cohorts	Mean 15	78 CD 46 children 32 adults	To assess the serological and histological recovery profiles of CD patients, in children and adults after commencing a GFD for at least 1 year ± 1 month.	Complete histological remission was seen in 29 of 46 treated CD children, 5 showed Marsh 3a changes and 2 showed Marsh 3b after GFD. After 1 year of follow-up, 15.2% of children patients with CD still had at least partial VA.
Silvester, USA	Systematic review	Children/Adults	26 studies	To assess the sensitivity and	Tests for serum TGA IgA and EMA IgA levels had low sensitivity in detection of persistent VA. Few studies

(2017)				specificity of TGA IgA and EMA IgA assays in identifying patients with CD who have persistent VA despite a GFD.	have specifically examined the relationship between serum antibody testing and mucosal damage in patients who are trying to follow a GFD.
Szakács, Hungary (2017)	Systematic review	Children/Adults	61 studies	To address the question whether CD children on a GFD display higher mucosal recovery ratios than adults.	Children show higher complete recovery and disappearance of VA ratios as compared to adults. There is considerable heterogeneity across studies concerning complete mucosal recovery ratios achieved by a GFD in CD. Younger age on diagnosis, less severe initial histologic damage and male gender predisposes for achieving mucosal recovery.
Vécsei, Austria (2014)	Prospective cohort	Mean 11.3	148 CD	To compare the performance of up-to-date antibody tests in predicting mucosal status in children with untreated CD vs. children on GFD.	Negative EMA most reliably predicts mucosal healing. In general antibody tests, especially DGP-IgA, are of limited value in predicting the mucosal status in the early years post-diagnosis but may be sufficient after a longer period of time.

Q6.3. Refractory coeliac disease in children: does it exist?

A search was conducted in PubMed using the search terms celiac, coeliac, children, follow-up, unresponsive, refractory, non-responsive and nonresponsive. The search identified a total of 69 records, of which 7 were included for this question: 6 observational studies (252 children) and 1 meta-analysis (5 studies in children). As there were insufficient studies in children only, we included studies in both adults and children (Jericho 2017, Schmitz 2013, Silvester 2017 and Van Leeuwen 2013).

Author, country (year)	Study type/ description	Age (years)	Sample size	Objectives	Main findings
Comino, Spain (2019)	Multicenter prospective cohort	Mean 4	64 CD	To evaluate the usefulness of faecal GIP to support the diagnosis and to determine the adherence to the GFD in CD children. Faecal GIP, IgA-TG and anti-DGP analysed at	97% Of the children had detectable GIP at diagnosis. On a GFD, the rate of GIP increased from 13% at 6 months to 25% at 24 months. Mean estimated gluten exposure dropped from 5543 mg/d at diagnosis to 144 mg/d at 6 months, then increased to 606 mg/d by 24 months. DGP normalized and only 20% had elevated TG by 24 months. The elevation of IgA-TG was more prolonged in patients with detectable GIP.

				diagnosis, and 6, 12 and 24 months thereafter.	
Janczyk, Poland/ The Netherlands (2015)	Case reports	Patients 1/ 2: 7 Patient 3: 1	3 CD	To describe clinical and laboratory data of children with biopsy-proven CD who did not respond to GFD.	Patient 1 showed no refractory CD, responded to Enteral Nutrition (EN) and on long-term follow-up symptoms, pathology and serology resolved completely on GFD. Patient 2 showed no refractory CD, responded to EN after 5 years of follow-up remains asymptomatic on GFD but with high EMA. Patient 3 did not respond to EN, partially responded to immunosuppressive treatment, had to remain indefinitely on total parenteral nutrition (TPN).
Jericho, USA (2017)	Retrospective cohorts	Children (≤18) and adults (>18) Mean diagnosis 8.8	328 CD 157 children	To assess the prevalence of extra-intestinal symptoms in children vs adults and the effect of the GFD on their resolution.	Extraintestinal manifestations of CD occur at similar rates in children and adults. However, children on a GFD resolve their symptoms more completely and faster than the adults. No refractory CD identified in the whole series.
Salvestrini, Italy and UK (2014)	Laboratory investigation	Children	23 5 archival jejunal biopsies 9 CD cases 9 controls	To verify if VA in CD represents a disorder of pathological matrix expansion. Staining for sulphated GAGs, heparan sulphate proteoglycans (HSPG), short-chain HSPG (D-HSPG) and the proteoglycan syndecan-1 (CD138), which is expressed on epithelium and plasma cells.	HSPG expression was lost in the epithelial compartment but contrastingly maintained within an expanded lamina propria. Matrix expansion, through syndecan-1+ cell recruitment and lamina propria GAG increase, underpins VA in CD. As in other matrix expansion disorders, IL-6 is upregulated and represents a target for immunotherapy in patients with CD refractory to GFD.

Schmitz, The Netherlands (2013)	Laboratory investigation	Children and adults	N/A	To identify the physiological counterpart of the aberrant intraepithelial lymphocytes (IELs) displaying an atypical $CD3^{-}CD7^{+}icCD3^{+}$ phenotype seen in refractory CD type II.	RCDII cell lines were transcriptionally distinct from T-cell receptor positive Intraepithelial lymphocytes (T-IEL) and expressed higher levels of multiple NK (Natural Killer) cell receptors. The authors speculate that this Interleukin-15 (IL-15) responsive population of cells represents the physiological counterpart of the aberrant T cells expressed in RCDII.
Silvester, USA (2017)	Systematic review	Children and adults	26 studies	To assess the sensitivity and specificity of TGA IgA and EMA IgA in identifying patients with CD who have persistent villous atrophy despite a GFD.	The analysis excluded subjects with refractory CD. TGA and EMA detected VA with specificity, respectively, of 0.83 and 0.91; sensitivity was 0.50 and 0.45. Thus, authors conclude that most persons with VA on a GFD had normal levels of TGA or EMA.
Van Leeuwen, The Netherlands (2013)	Laboratory investigation	Children and adults; Children mean 5.9	36 children	To find out whether alterations occur in the frequency of natural CD62L (+) transcription factor forkhead box P3 (Foxp3) (+) regulatory T cell (Treg) or mucosally-imprinted CD62L(neg) CD38(+) Foxp3(+) Treg in peripheral blood of CD patients, comparing children with adults.	In children, the percentages of peripheral blood CD4+ Foxp3+ Treg were comparable between CD patients and healthy age-matched controls. In adultS on GFD and in refractory CD, increased percentages of circulating natural CD62L+ Foxp3+ Treg, normal mucosally-imprinted CD62LnegCD38+ Foxp3+ Treg frequencies were observed. Significant numeric deficiency of mucosally-imprinted or natural Foxp3+ Treg could explain the effector responses in CD.

Question 7. Should the quality of life (QOL) be assessed during the follow-up and if yes, how?

A search was conducted in Medline using the search terms celiac, coeliac, children, follow-up and quality of life/QoL. The search identified a total of 89 records, of which 18 were included for this question: 16 primary observational studies (16043 children) and 2 systematic reviews (39 studies). As the study from Nikniaz 2020, published after March 2020, was considered especially informative, we have included it.

Author country year	Study type/ Instrument	Age (years)	Sample size	Objectives	Main findings
Altobelli, Italy (2013)	Cross-sectional	Mean 14.2	140 CD	To assess health-related quality of life (HRQOL) and effect of demographic, clinical characteristics and GFD adherence on perceived health status.	Only the mental component summary score (MCS12) was lower in CD patients. More than one third of CD reported feeling angry “always” or “most of the time” about having to follow the GFD, and nearly 20% reported feeling different from others and misunderstood because of the CD.
Barrio, Spain (2018)	Cross-sectional	Mean 12.4	434 CD	To assess the impact of CD in HRQOL.	CD had no substantial negative impacts on the children’s quality of life (QOL).
Barrio, Spain (2016)	Cross-sectional	Mean 12.4	480 CD	To assess HRQOL in CD.	Overall, both children and parents reported the HRQOL of the children as ‘‘neutral”. Significantly worse HRQOL scores were recorded in children showing a non-classical clinical presentation, in those not adhering to treatment and in those reporting difficulties in following the diet.
Bellini, Italy (2011)	Case-control	Mean Cases 10 Controls 12	156 CD cases, 353 controls	To verify whether subjects with CD have a different LoC compared with healthy subjects, and to evaluate the relationship with adherence to a prescribed GFD and QOL.	No difference in LoC values between patients with CD and controls. Good dietary compliance was associated with a more internal LoC. Patients with a satisfactory QOL had a more internal LoC.
Benelli, Italy (2016)	Prospective cohort	Mean 5.9	143 CD	To evaluate consequences on QOL of the application of the	Patients diagnosed according to the no-biopsy approach have the same QOL as patients diagnosed with duodenal biopsies.

				new ESPGHAN guidelines for the diagnosis of CD.	
Biagetti, Italy (2015)	Case-control	Mean Cases 8.7 Controls 9.5	73 CD cases, 143 controls	To investigate the impact of the GFD on the psycho-physical well-being of CD children.	No significant differences in QOL between CD patients and controls. Children with diet-difficulties or comorbidities (allergy, asthma and autoimmune thyroiditis) showed the lowest QOL scores.
Biagetti, Italy (2013)	Cross-sectional	Mean 8.7	76 CD	To investigate the impact of CD and the GFD on the HRQOL and the social and emotional world of children with CD.	Children with CD experience strong emotions related to the GFD, involving several aspects of everyday life. There were no significant differences between symptomatic and asymptomatic patients.
Mager, Canada (2018)	Case control multisite	Mean Cases 10.4 Controls 10.9	243 CD cases, 148 controls	To determine sociodemographic and socioeconomic factors influencing HRQOL.	Child-parent perceptions of HRQOL in a multi-ethnic population with CD are comparable to healthy reference populations, but significantly higher than in parent/child with mild gastrointestinal complaints (GI-CON). Adherence to the GFD in ethnically diverse youth with CD was related to GI symptoms, age of the child, and ethnicity of the parent-child.
Meyer, Israel (2017)	Development and validation of the CD Children's Activities Report (CD-Chart)	Mean 8.33	126 CD cases, 30 controls	To establish the CD-Chart's reliability and validity.	CD-Chart showed adequate internal consistency. CD group required significantly more pre-preparation for food-related activities than controls ($p < 0.001$).
Myléus, Sweden (2014)	Cross-sectional multicentre	12	328 CD cases, 12037 controls	To investigate QoL in 1. undetected CD; 2. diagnosed CD; 3. without CD.	HRQOL was similar in the 3 groups.
Nikniaz, Iran (2020)	Systematic review	<18	26 studies	To report the published data on HRQOL assessed by CD-specific and	Mean HRQOL score using CD-specific CDDUX was 58.81, which is neutral. The result using the generic PedsQL showed similar HRQOL in CD patients and in healthy

				by generic questionnaires.	controls. Parents reported the child‘s diet and communication scores lower than that of children.
Nordyke, Sweden (2013)	Cross-sectional	12 -13	103 CD cases 483 controls	To investigate QOL of adolescents with screening-detected CD before and one year after diagnosis and treatment.	QOL in CD was similar to the referents, both before and one year after, except in the dimension of pain at follow-up, in which fewer cases reported > problems than referents (12.6% and 21.9% respectively, adjusted odds ratio (OR) 0.50).
Simsek, Turkey (2015)	Case-control	Mean 11.84	25 CD cases, 25 controls	To assess QOL in children with newly diagnosed CD and in healthy controls, both at diagnosis and after 1 year on GFD.	Total scores and scores of the emotional well-being subscale were significantly lower in patients with CD compared with the control group. No differences in QOL were found between before and after GFD recommendations in children with CD, indicating a persistent decreased QOL the first year of follow-up.
Skjernin, Denmark (2017)	Enquiry	Mean 11.12	77 CD	To assess HRQOL in children/adolescents with mean CD duration 4.05 +/- 3.43 years and compare it with the one of 345 adults with CD (mean age 39.03 +/-13.75 years; mean CD duration 9.12+/- (11.88 years).	Respondents reported being mainly satisfied with their QOL when assessed by generic items. In comparison to adults, children perceived a larger burden of following a GFD and were more negatively affected by thoughts of desired gluten-containing food and by feelings of exclusion or difference from peers.
Vriezinga, The Netherlands (2017)	Prospective cohort	Mean 12.5	78 CD	Agreement between physician reported and patient reported HRQOL at a follow-up visit.	Reports were discrepant in 40 of 70 (self-reported a poor HRQOL & physicians good). Discrepancies occurred more frequently in patients with a disease duration <9 y and in females. Both factors were predictors of a poorer HRQOL.

				Patient variables predicting a discrepancy between reports, or a lower HRQOL.	
Wagner, Austria-Germany (2015)	Case-control	10–20	259 CD cases, 53 controls	To assess QOL and eating disorders (ED) in young females with CD adhering to GFD since at least 1 year. * ED assessed using Eating Disorder Inventory 2 and Eating Disorder Examination (EDE).	32 CD patients (15.5%) suffered from ED. HRQOL of CD patients without ED was similar to the one in healthy controls with a higher Joy of life. QOL was significantly lower in CD patients with ED, both in comparison to CD patients without CD disorders as in health controls. The authors suggest early identification of ED in patients with CD.
White, UK (2016)	Systematic review	N/A <18	Adolescents	To assess burdens associated with following a GFD and the factors associated with adherence.	Adolescents with CD face stigmatisation and feel isolated in social situations and at school. Additional burdens are a lack of knowledge regarding CD and GFD difficulties in interpreting food labels, as well as dissatisfaction with the organoleptic properties of GF products.
Wolf, USA (2018)	Prospective cohort	Mean 15.7	30	To examine the associations of QOL with adherence to GFD.	The overall mean CDPQOL score was 70.1 which corresponds to a good QOL without significant differences by level of dietary vigilance.

Q8. Should the follow-up of children with special situations be different from the one in the average CD patient? Q8.1 In cases of unclear diagnosis? Q8.1.1. How to perform a gluten-challenge? Q8.2 8.2. In children with associated type 1 diabetes (T1D)? Q8.3 In children with IgA deficiency? Q8.4 In cases of potential CD?

Q8.1 In cases of unclear diagnosis? Q8.1.1. How to perform a gluten-challenge?

A search was conducted in Pubmed using the search terms celiac, coeliac, children, follow-up and gluten-challenge. The search identified a total of 850 records, of which 20 were included for this question: 9 RCT (1 in children: 23 children) and 8 primary observational studies (2 in children: 194 children). As there were insufficient studies in children only, we included 14 studies in adults (Daveson 2020, Goel 2020, Kelly 2020, Lahdeaho 2011, Lahdeaho 2014, Lahdeaho 2019, Leffler 2012, Leffler 2013, Mansikka 2019, Sankari 2020, Sarna 2018, Taavela 2019, Tye-Din 2019, Leonard 2021) and 2 studies in both adults and children (Husby 2020 and Van Overbeek). We included 4 studies published before 2010 (Van Overbeek 1997, Korponay-Szabo 1997, Holm 2006 and Kurppa 2008) and 1 after March 2020 (Leonard 2021) since they were especially informative.

Author, country (year)	Study type/ description	Age (years)	Sample size	Objectives	Main findings
Daveson, Australia (2020)	RTC: 6g/day masked gluten challenge (GC) versus Sham challenge Time course: 4 hours	18-70	36 CD adults	To assess serum immunological markers Interleukin 2 (IL-2) as reaction to GC.	CD Patient Reported Outcome (CeD PRO) scores increased, mainly nausea. IL2 serum levels increase 4 hours after the GC median fold change of 20. No increase in IL2 serum levels in the sham challenge group.
Goel, Australia (2020)	Dietary intervention/ 6g/day gluten Time course: 6 hours	18-70	50 CD adults	To assess a wide spectrum of serum cytokines (IL2, IL6, Interferon gamma (IFNγ) ,tumor necrosis factor alpha (TNFα), chemokine ligand 9,8,20, Interleukin-22 (IL22), Interleukin-10 (IL10), C-C Motif Chemokine Ligand 2 (CCL2), amphiregulin) as response to short term GC.	Serum cytokine showed an increased level after short term GC, peak concentration 4 hours after GC. Serum cytokines were correlated with symptoms.

Hardy Italy, Australia, USA (2015)	Dietary intervention/ 1-3 slices of wheat bread/day	Median 9	41 CD children	To compare the T-cell response to gluten in children and adults.	GI symptoms in 71% of the patients after the gluten challenge. Isolation and measurement of T-cell clones in blood samples showed similar gluten-specific T-cell receptor (TRC) repertoires, similar clone response in children and adults.
Holm, Finland (2006)	Dietary intervention 14 g/day gluten, (range 7-19g/day)	Median 13	10 CD children	To assess the response to gluten and oats respectively	4 Patients had gastrointestinal symptoms concurrent with the duodenal mucosal deterioration. Both TGA and EMA showed elevated levels after one month of gluten challenge in all patients. Histological relapse was shown within 3-12 months after starting the GC.
Husby, Europe (2020)	Systematic review Evidence based guidelines	N/A	61 Studies Children and Adults	To guide physicians in accurately diagnosing CD and permit omission of duodenal biopsies in selected cases	CD diagnosis can be accurately established with or without duodenal biopsies if given recommendations are followed
Kelly, USA (2013)	Exploratory, RTC: 2.7g/day gluten (900 mg three times/day) vs placebo. Time course: 6 weeks	Median 50.3	43 CD adults	To assess gluten-induce response in symptoms, serology, urinary lactulose-mannitol ratio (LAMA).	GI symptoms increased in the first 3 weeks up to a mean of 0.3-0.4 units maintained in plateau in the last 3 weeks. Psychological General Well Being Index (PGWBI) lower scores in the last 2 weeks. Urinary LAMA ratio increased from 1.0 to 2.3-2.4 at 4 weeks of GC. 30% of the patients in the GC group seroconverted to positive antibodies (TGA-IgA).
Korponay-Szabo, Hungary (1997)	Dietary intervention gluten 5-10 g/day	Median: 5.09 3.31 8.63	153 CD children	To assess EMA accuracy	Serological relapse (EMA positivity) as early as 6 weeks; 66% of 134 pts at 3 months of challenge and 90% at 6 months respectively. Histological relapse at 6 months of gluten challenge

Kurppa, Finland (2008)	Case report/ N/A	6, 10 months 16 years	3 CD children	To evaluate if periods of gluten intake and gluten withdrawal may have an impact on disease expression, and the phenotype may vary in the same person over time	The phenotype of CD can change from intestinal disorder to extraintestinal manifestations over time.
Lahdeaho, Finland (2011)	Dietary intervention: Low amount GC (1-3 g/day) OR Moderate amount GC (3-5 g/day) Time-course: 12 weeks/84 days (Range 29-103)	Median 49	25 CD adults	To assess the amount and duration of GC intervention to produce SB mucosal deterioration.	1-3g/day Gluten for 12 weeks is proposed to induce measurable SB mucosal deterioration.

Lahdeaho, Finland (2014)	Dietary intervention: Low dose GC: 1.5g/day Medium dose GC: 3g/day High dose GC: 6g/day Time course: 6 weeks Part 2: 2g/day Gluten Time course: 6 weeks	Part 1 Low dose: Median 55 Medium dose: Median 52 High dose: Median 59 Part 2: Median 50	Part 1 47 CD adults Part 2 21 CD adults	To establish the optimal daily dose of gluten for a 6-week GC.	"Gluten dose optimization": 1.5g/day gluten induces mucosal deterioration, even if clinically tolerated, however the change of villous height/crypt ratio (VH:CrD) from baseline was not sufficiently consistent and was too close to the baseline readout. GC in the placebo drug arm: 2g/day gluten for 6 weeks-time course induces measurable, clear injury to the SBl mucosa.
Lahdeaho, Finland (2019)	Dietary intervention: 2-4 g/day gluten Time course of GC: 10 weeks	Median 55.8	19 CD adults Per protocol: 15 CD adults	To assess gluten-induce response in symptoms, serology, small bowel mucosal histology.	Worsening of symptoms (increase in mean weekly CeD PRO and Gastrointestinal Symptom Rating Scale (GSRS) scores). Seroconversion to positivity for TGA-IgA and DGP antibodies. 2-4 g/day Gluten induces clinical, serological and histological relapse in the majority of patients.
Leffler, USA (2012)	Dietary intervention: 2.4 g/day gluten (800 mg capsules- three times/day during meals) Time course:14 days	Median 46.3	14 CD adults	To assess gluten-induce response in the placebo arm in symptoms, serology, urinary lactulose-mannitol ratio.	GI symptoms according to GSRS increased in severity, especially "indigestion" 64.3% pts. Experienced symptoms of "gluten toxicity". Urinary LAMA ratios increased in the GC group, but not statistically significant'. Antibody titers with no significant mean changes from baseline to day 21.
Leffler, USA (2013)	RCT Low amount GC (3g/day gluten). High amount GC (7.5g/day gluten).	Median 43.3	20 CD adults	To assess duration of GC	GI symptoms increased by day 3 and returned to baseline by day 28. Antibody titers increased slightly from baseline to day 14 of GC but markedly by day 28. No changes in LAMA. Reduction in VH:CrD ratio and increase in intraepithelial lymphocyte (IEL) density. 3g/day for at least 2 and up to 8 weeks is proposed to obtain gluten-induced response in serology and histology.
Leonard USA	Dietary intervention	Adults	14 CD adults	Assessment of the response to	Significant changes in gut-homing CD8 T cells, enzyme-linked immune absorbent spot and HLA-DQ2 restricted

(2021)	RCT: Lower dose GC: 3g/day Higher dose GC: 10g/day Time course: 14 days			dose and duration of the GC, assessment of new biomarkers	gluten-specific CD4 T cells after higher dose (10 g Gluten/day) Symptoms and IL2 significant or near significant changes after lower dose (3g Gluten/day)
Sankari, Finland (2020)	Dietary intervention Case-control/ 200g/day commercially available wheat bread Time course: 3 days followed by the same amount for 1 year time course	Treated Dermatitis herpetiformis (DH) Median 58 Treated CD Median 48 Untreated CD Median 50	16 DH adults 15 CD adults 18 untreated CD adults	To assess the response to dose and duration of the GC in terms of clinical, serological and histological parameters.	Clinical, serological and histological remission (non-VA in the duodenal mucosa).12/16 developed Dermatitis Herpetiformis (DH) rash, 12/16 seroconverted to positive EMA, 14/16 and 10/16 showed positive serum anti transglutaminase 3 (TG3) and transglutaminasa 2 (TG2), decrease in VH:CrD ratio,10/16 showed presence of TG2-IgA deposits in SB mucosa, 10/16 showed TG3-IgA deposits in the skin.
Sarna, Norway, (2018)	Dietary intervention/ 5.7 g/day gluten Time course: 2 weeks	41.6	19 CD adults	To assess response to 2 weeks of GC in CD individuals.	2 weeks of GC is not enough to detect gluten induced histological changes by conventional histology. HLA-DQ: gluten tetramers detection by flow-cytometry is proposed as surrogate biomarkers after short gluten-challenge
Taavela, Finland (2019)	Dietary intervention/ 4g/day gluten. Time course: 10 weeks	N/A	15 CD adults	To assess SB deterioration in GC Assessment of new immunohistochemical (IHC) markers of SB mucosal response of GC; comparison of the studied IHC markers with	Marsh class worsened in 80% of cases. Good correlation coefficient between APOA4:Ki67 messenger RNA (mRNA) ration and crypt depth (VH:CrD) ratio. Good correlation coefficient between Apolipoprotein A4:Ki-67 protein (APOA4:Ki67) mRNA ratio with CD3+IELs densities. CD138+ lamina propria strongly increased during GC.

				morphometric measurements.	
Tye-Din, Australia (2019)	Dietary intervention Case-control/ 6g/day gluten Time course: 6 hours	N/A	25 CD adults 25 not CD adults	To assess serum immunological markers IL2 as reaction to GC.	IL2 serum levels increase after 2,4, and 6 hours of GC. Peak IL2 levels correlated with symptoms severity (mainly with vomiting and nausea). No increase in serum IL2 levels among the control group.
Van Overbeek The Netherlands, (1997)	Retrospective Questionnaires/ N/A	2-57	55 FDR children and adults	To investigate the pattern of gluten consumption in the general Dutch population for different age and sex groups and for different product groups, and to investigate the daily gluten intake of first-degree relatives of CD patients	The gluten intake of first-degree relatives (FDR) of CD patients was the same as that of the general population. A low gluten intake apparently does not explain the specific presentation and prevalence of CD in first-degree relatives of CD patients

Q8.2. In children with associated type 1 diabetes (T1D)?

A search was conducted in PubMed using the search terms celiac, coeliac, children, follow-up and diabetes. The search identified a total of 151 records, of which 10 were included for this question: all primary observational studies, 7 studies in children (3295 children) and 3 studies in both adults and children (Kurien 2016, Molazadegan 2013, Reilly 2016).

Author, country (year)	Study type/ description	Age (years)	Sample size	Objectives	Main findings
Craig, Australia	Multicentric, multi continent.	Median 8.1	1835 children	To analyse outcomes (Haemoglobin A1c	CD is a common comorbidity in youth with T1DM. Differences in CD prevalence may reflect international

(2017)	Cross sectional			(HbA1c), Ht-SDS, overweight/obesity) between T1DM and CD.	variation in screening and diagnostic practices, and/or CD risk. Although glycaemic control was not different, the lower Ht-SDS supports close monitoring of growth and nutrition in this population.
Gopee, Australia (2013)	Cohort children with T1DM and CD 1 year after GFD	N/A Children	24 children	Renal involvement in T1DM and CD	Lower degree of renal involvement in T1DM and CD compared to T1DM alone.
Isaac, Canada (2017)	Retrospective	Mean 9.3	487 CD children with T1DM	Follow-up of patients with T1DM and CD.	Seroconversion in patients with CD and T1DM is three times as long as in DC patients compliant with the diet. Compliance of T1DM and CD patients was lower than the one of patients with only CD.
Kivelä, Finland (2018)	Retrospective	Clinically detected 8.7 Screen detected 11.7	236 CD children	Long term outcomes of CD patients diagnosed in childhood.	Long term outcomes as measured by Psychological General Well-Being (PGWB) and GI symptoms GSRS, of screen-detected (including T1DM) patients do not differ from clinically detected cases, suggesting that there is no need to recommend different follow-up practices in these two groups.
Kurien, Sweden (2016)	Population based cohort	Median at diagnosis T1DM 9 Median at diagnosis CD 12 Adults/children	960 CD adults/children with T1DM	Development of thyroid disorders in T1DM and CD	CD patients with T1DM have an increased risk of developing autoimmune thyroid disease than isolated T1DM patients. Thyroid disorders should be actively assessed in T1DM and CD patients. Individuals diagnosed with T1DM early in childhood had lower risk for AI thyroid disease.
Laitinen, Finland (2017)	Retrospective	Mean 7.3	42 Children with T1DM	Clinical characteristic of CD detected by screening in T1DM and by diagnosis of clinical cases. Dietary adherence.	CD patients detected during T1DM surveillance have similar signs of malabsorption and mucosal damage as clinical cases. Similar recommendations on follow-up for screening detected CD in T1DM and clinical CD. The compliance is comparable in both groups; thus, no additional monitoring is suggested in screen-detected cases.

Mollazadegan, Sweden (2013)	Retrospective registry based	Adults /Children N/A	566 children with CD and T1DM 261 (age 10-20)	Diabetic retinopathy in T1DM and CD compared to T1DM alone.	Risk of retinopathy is not increased in T1DM and CD. It is lower within the first 0-5 and neutral within the 5-10 years of follow-up. Risk progressively increases after 10 years and is the highest after >=15 years of follow-up.
Reilly, Sweden (2016)	Nationwide registry	Median at T1DM diagnosis 9 Median at CD diagnosis 12 Adults/Children	958 adults/children with T1DM and CD	Fracture risk in T1DM and CD patients.	Compared to T1DM patients with T1DM and CD do not have increased fracture risk. This risk does not change with the follow-up time. HR for fracture is progressively increasing by time after CD diagnosis but it doesn't reach significant levels. Overall number of fractures are very low.
Tsouka, Canada (2015)	Retrospective	Median 8.83	41 CD children with T1DM	To evaluate complication screening and follow-up patterns in a population with T1DM/CD in relation to a matched cohort with CD.	Increased number of thyroid diseases after 2 years of follow-up in 15% of the T1DM and CD group. No differences in pathological findings between the two groups. Patients with both T1DM and CD had higher BMI, weight and height.
Williams, USA (2018)	Cohort	At T1DM diagnosis 8.1 strongly positive; 7.4 weakly positive	64 children with T1DM and CD	Long term renal involvement in patients with T1DM and CD autoimmunity	Patients with T1DM and CD have lower blood pressure (BP) and cholesterol levels at 25 years of diabetes duration. Risk of microalbuminuria in these patients is also lower in this group compared to T1DM only patients. Only 8 known CD patients. Conclusion coeliac autoimmunity in patients with T1DM does not increase the risk of renal disease.

Q8.3 In children with associated IgA deficiency?

A search was conducted in PubMed using the search terms celiac, coeliac, children, follow-up and IgA deficiency. The search identified a total of 24 records, of which 2 were included for this question: 2 primary observational studies (191 children), one of them prospective. Since it was especially informative, we used one article published after March 2020 (López 2020).

Author, country (year)	Study type/ description	Age (years)	Sample size	Objectives	Main findings
Belei, Romania (2018)	Prospective cohort	Mean 4.6 +/- 1.2.	105 CD children; 2 with IgA deficiency	Histology recovery after one year of GFD in children.	Incomplete recovery of intestinal mucosa might take longer in patients with IgA deficiency. Only two such patients.
López, Spain (2020)	Multicentric retrospective cohort	Biopsy group median 4.4 No biopsy group 4.2	86 CD children with IgA deficiency	Diagnosis and follow-up practices in IgA deficient patients after 2012 ESPGHAN guidelines.	After 2 years half of patients with IgA deficiency remain seropositive. Substantial number of patients diagnosed with no-biopsy approach in IgA deficient patients, which is not in accordance with the 2012 guidelines.

Q8.4. In cases of potential CD?

A search was conducted in PubMed using the search terms celiac, coeliac, children, follow-up and potential celiac disease. The search identified a total of 80 records, of which 9 were included for this question: 8 performed in children (835 children) and 1 in both adults and children (Kondola 2016).

Author, country (year)	Study type/description	Age (years)	Sample size	Objectives	Main findings
Auricchio, Italy (2014)	Prospective cohort	Median 6.4	210 Potential CD children	Natural history potential CD.	Control every 6 months. Biopsy repeated after 1-2-years. Antibodies: 20% negative, 37% fluctuating, 43% persistently positive. Still potential: 86% at 3 years, 73% at 6 years, 67% at 9 years.
Auricchio, Italy (2019)	Prospective cohort	Range 2-18	280 Potential CD children	Natural history of potential CD.	Controls every 6 months, biopsies every 2 years. At 12 years follow-up: 89 antibodies negative. Age>3 years, density of gamma delta intestinal IELs, presence of intestinal anti-tTG antibodies predictive VA.
Fernandez, Spain (2019)	Prospective cohort	2-3 First screening, 10-12 second screening	262 children first screening, 185 children second screening	Evolution of a cohort genetically at-risk for CD.	First screening by 3 years of age: 5 potential CD + 6 antibody positive. After 10 years follow-up: 2 still potential and 1 CD.
Kondola, India (2016)	Prospective cohorts	Mean 28.7	57	Natural history of potential CD.	Controls every 6 month. 22 History of diarrhoea, 9 anaemia.

			adults/children with potential CD		57 Followed-up:12 antibody: negative, 41 persistently positive, 4 become CD.
Kurppa, Finland (2010)	Dietary intervention	Median 6	76 Children with potential CD	Effect of dietary intervention GFD in potential CD.	Follow-up available in 13 patients with potential CD disease. Disease exacerbated in those who continued gluten consumption (n=8): developed VA: 5 after 1 year and 2 after 2 years. In those on GFD (n=5): disappearance of symptoms and antibodies.
Lionetti, Italy (2012)	Prospective cohort	Mean 29 ± 12 months	96 children with potential CD	Natural history of potential CD in a cohort of first-degree relatives followed since birth.	Controls every 6 months. Biopsy repeated after 1-2 years. 21 Followed-up: 18 antibodies negative, 12 fluctuating antibodies, 1 become CD.
Lionetti, Italy (2019)	Prospective cohort	Median 24 months	96 children with potential CD	Natural history of potential CD in a cohort of first-degree relatives followed since birth.	26 potential CD, 23 followed up on gluten containing diet: after 10 years follow up 19 antibodies negative (83%), 1 fluctuating antibodies (4%), 3 become CD (13%).
Mandile, Italy (2018)	Prospective cohort	Median 7.27	65 children with potential CD	Effect of GFD.	Controls every 6 months. 47 Followed up, response evaluated in 35: 19 positive response to GFD, 2 partial response, 14 no response. After GFD no changes of immunohistochemical parameters in biopsies.
Tosco, Italy, (2011)	Prospective cohort	Median 6 years and 8 months	106 children with potential CD	To determine the natural history of potential CD in children.	Most children with potential CD remain healthy. After 3 years, approximately 33% of patients develop VA. Intestinal deposits of anti-TGA-IgA identify children at risk for VA.

Q9. How to improve the communication: To parents? To patients?

A search was conducted in Medline using the search terms celiac, coeliac, children, follow-up, gluten-free diet, communication, patient satisfaction, caregivers/education, education, consultants/education, consultants/organization and administration. The search identified a total of 46 records. Further publications were identified from other searches. In total, of which 14 publications were included for this question:12 primary observational studies (638 children), 2 literature reviews (34 studies). Since there weren't enough studies in children, we included 4 studies in adults (Halmos 2018, Paganizza 2019, Ukkola 2011 and Ukkola 2012) and 1 in both adults and children (Sainsbury 2018). We included two articles published before 2010 (Gardiner 1999 and Cahill 2007) since they were considered especially informative.

Author, country (year)	Study type/ Description	Age (years)	Sample size	Objectives	Main findings
Barnea, Israel (2014)	Telephone questionnaire	At diagnosis <18	50 LTFU 52 controls	To characterize LTFU population, and thus identify compliance barriers to GFD and follow-up	LTFU is associated with non-adherence to GFD and positive serology. Risk factors for LFTU should be identified and addressed in order to improve patient care
Cahill, UK (2007)	Systematic review	6-12	21 Studies	To ascertain the evidence available on the amount and type of involvement that children in the 6–12-year age group have in their primary care consultations when the consultation was held with a child, a general practitioner (GP), and an adult.	Children in the 6–12 age group have little meaningful involvement in their consultations.
Connan, Canada (2019)	Qualitative semi-structured interviews	Mean 13.5 ± 4.5	18 CD children with T1DM	To develop and test the usability of an E-learning module aimed at educating patients and caregivers regarding implementation of the GFD in children with concurrent CD and T1DM.	A multifaceted user-cantered usability approach demonstrated that an innovative, interactive E-learning module is effective in knowledge retention and can provide comprehensive and accessible information in the implementation of the GFD teaching in children with CD and T1D.
Gardiner, UK (1999)	Letter to editor	N/A	N/A	Pointing out that well done patient information on internet may be superior to paper-based information	Information on internet may be superior to paper-based information.
Germini, Italy (2018)	Case-control	25-54 Bartter	26 mothers of children with BS or with CD	To elucidate how the diagnosis of a rare disease, as compared	Maximization of both emotional and instrumental social support, through provision of appropriate information or establishment of disease-specific

		syndrome (BS) 25-64 CD		to a common, chronic condition, may influence maternal experiences of childhood illness.	support groups, could greatly contribute to rare disease families' efforts to cope with childhood illness and regain a sense of normality.
Halmos, Australia and New Zealand (2018)	Online survey	>36	5310 CD adults	To comprehensively assess the patient factors that influence GFD adherence in patients with CD.	Poor knowledge of a GFD and psychological wellbeing were independent modifiable risk factors for inadequate adherence to the diet in patients with CD. Involvement of a dietitian and mental health care professional, in the presence of psychological distress, is likely to be necessary to improve adherence and health outcomes.
Kinos, Finland (2012)	Prospective cohort	1-16	222 CD children	To assess health and well-being and the effect of a 1- year GFD in children with CD detected by screening in at-risk groups.	Screen-detected children with CD can attain satisfactory dietary adherence and benefit from treatment similarly to symptom-detected patients. The results support intensified screening for coeliac disease in at-risk children.
Nordyke, Sweden (2014)	Qualitative written narratives	Median 14.6	153 CD adolescents	To describe adolescents´ experience living with screening-detected CD five years after diagnosis with the aim to explore how their perceptions, practices, and beliefs evolved.	Maintenance and evolution in the perceptions, practices, and beliefs of the adolescents after 5 years. Some have adjusted to the disease and adapted new habits and coping strategies to deal with the GFD, while others still doubt they have CD or that being detected was beneficial.
Paganizza, Italy (2019)	Questionnaire	18-45 ≥45	104 CD adults	To investigate adherence to a GFD and potentially associated factors, focusing on the relationship between adherence and knowledge of the gluten content of foods and of CD in general.	The more patients know about their disease and their required diet, the better they are able to adhere to the diet. Supporting and informing patients should be an integral part of the management of CD, and our findings point to ways in which adherence to a GFD might be improved by healthcare practitioners

Rosen, Sweden (2011)	Qualitative follow-up	Median 14.6	117 CD adolescents	To explore how screening-detected CD impacts adolescents' quality of life, as perceived by themselves and their parents.	Screening-detected CD has varying impact on adolescents' quality of life, where their perceived change in health has to be balanced against the social sacrifices the diagnosis may cause.
Sainsbury, Australia and New Zealand (2018)	Online survey	Mean 50.2	5573 CD adults/children	To evaluate an expanded collection of theoretical constructs specifically relevant to the maintenance of behaviour change, in the understanding and prediction of GFD adherence.	Screening-detected CD has varying impact on adolescents' quality of life, where their perceived change in health has to be balanced against the social sacrifices that the diagnosis may cause. This needs to be taken into account in any future suggestion for CD mass screening and in the management of these patients.
Ukkola, Finland (2011)	Prospective	N/A	698 CD adults	To investigate the impact of a GFD on self-perceived health and well-being in symptomatic and asymptomatic patients with CD.	Self-perceived health and well-being were low among patients at the time they were diagnosed with CD. Most patients benefited from a GFD. Perception of health decreased among asymptomatic cases, which discourages population-based screening.
Ukkola, Finland (2012)	Prospective	N/A	698 CD adults	To investigate patients' perceptions of their disease, dietary treatment and self-rated healthcare needs.	Established doctor-patient communication is essential in minimizing the disease burden. Particularly young and screen-detected asymptomatic patients and those with extraintestinal manifestations require extensive support.
White, UK (2016)	Narrative review	Focused on adolescents	13 Studies	To review current literature on the burdens associated with following a GFD and the factors associated with adherence	Poor adherence in adolescence associated with older age, absence of immediate symptoms, poor palatability of GF foods. Emotional support and organisation skills associated with superior adherence. Associations have been reported between HRQoL measures and adherence.

Q10: How to organize the transition from paediatric care to adult health-care?

A search was conducted in PubMed using the search terms celiac, coeliac, children, follow-up, childhood celiac and transition of care. The search identified a total of 85 records, of which 7 were included for this question:4 primary observational studies (17172 children) and 3 reviews/guidelines (Crowley

2011(10 studies), Ludvigsson 2016 and Nagra 2015). Two studies on adults were included since they were considered especially informative (Kivelä 2020 and Reilly 2020).

Author, country (year)	Study type/ description	Age (years)	Sample size	Objectives	Main findings
Crowley, UK (2011)	Systematic review	11-25	10 studies	To systematically review the evidence of effectiveness of transitional care programmes in young people aged 11-25 with chronic illness (physical or mental) or disability and identify their successful components.	The most commonly used strategies in successful programmes were patient education and specific transition clinics. It is not clear how generalisable these successful studies in DM will be to other conditions.
Kivelä, Finland (2020)	Retrospective, mail questionnaire	Adults	235 CD adults	To evaluate the implementation and significance of long-term follow-up.	75% in follow-up not associated with health or dietary adherence. Non-adherent patients were without follow-up.
Ludvigsson, UK (2016)	Systematic review	N/A	N/A	To help healthcare personnel manage CD in the adolescent and young adult and provide optimal care and transition into adult healthcare.	CD adolescents should gradually assume exclusive responsibility for their care, parental support still important. Biopsy may be considered where paediatric diagnostic criteria have not been fulfilled.
McManus, USA (2013)	Survey	12-18	17114 Children (Youth) with Special Health Care Needs (YSHCN)	To examine current United States (US) performance on transition from paediatric to adult health care and discuss strategies for improvement.	Most youth with YSHCN are not receiving transition preparation. There have been no discernible improvements since this transition outcome was measured in the 2005-2006 National Survey of Children with Special Health Care Needs.
Nagra, UK (2015)	Ready Steady Go program	>11	N/A	To set out some of the obstacles that have delayed the implementation of effective transition and report on a successful transition programme	Successful generic transition programme 'Ready Steady Go' that has been implemented within a large National Health Service teaching hospital in the UK, with secondary and tertiary paediatric services, where it is now established as part of routine care

Reilly, USA and Sweden (2020)	Retrospective, anonymous online survey	18 -25	98 CD adults	To discern rates and predictors of successful transition of care for young adults with childhood diagnosed CD.	Transition of care is inconsistent, particularly among asymptomatic patients. Referral for an adult provider is significantly useful.
Zingone, Italy (2018)	Questionnaire	Mean 14.5	58 CD children	To assess adherence to GFD, CD knowledge, QoL, relationship with caregivers.	A good CD knowledge is positively related to dietary compliance and QOL. TRANSIT-CD disk is proposed.

Abbreviations

A: Adenine
AGA: American Gastroenterological Association
ALT: Alanine Aminotransferase
AP: Abdominal Pain
AP-FGDI: Abdominal Pain related Functional GI disorders
APOA4:Ki67: Apolipoprotein A4:Ki-67 protein
AST: Aspartate Aminotransferase
AtH: Adult type Hypolactasia
BL: Randomized Baseline
BMD: Bone Mineral Density
BMI: Body Mass Index
BMI-SDS: Standardised Body Mass
BP: Blood Pressure
BS: Bartter Syndrome
C: Cytosine
CBC: Complete Blood Cells
CCL2: C-C Motif Chemokine Ligand 2
CD: Coeliac Disease
CD138: Proteoglycan syndecan-1
CD3+: Cluster of differentiation 3+ cells
CD-Chart: CD Children's Activities Report
CDDUX: CD-specific Coeliac Disease DUX
CDPQOL: CD-specific quality of life
CeD PRO: Coeliac Disease Patient Reported Outcome
CLIA: Chemiluminescence Immunoassay
DEXA: Bone density measurement
DGP: Deamidated Gliadin Peptide
DH: Dermatitis Herpetiformis
IEL: Intraepithelial lymphocyte
IFNγ: Interferon gamma
IgA: Immunoglobulin A
IgG: Immunoglobulin G
IHC: Immunohistochemical
IL10: Interleukine-10
IL-15: Interleukin-15
IL-2: Interleukin-2
IL22: Interleukin-22
IL-6: Interleukin 6
LAMA: Urinary Lactulose-Mannitol ratio
LCT: Lactase
LoC: Locus of Control
LR: Likelihood Ratio
LTFU: Lost to Follow Up
MCS12: Mental Component Summary score
mRNA: Messenger RNA
N/A: Not Available
NASPGHAN: North American Society for Paediatric Gastroenterology, Hepatology and Nutrition
NK: Natural Killer
NPV: Negative Predictive Value
OR: Odds Ratio
P/SVA: Partial or Subtotal Villous Atrophy
PGWB: Psychological General Well-Being
PGWB: Psychological General Well-Being
PGWBI: Psychological General Well Being Index
PLD: Primary Lactase Deficiency

D-HSPG: short-chain HSPG
DM: Diabetes Mellitus
DXA: Dual-energy x-ray absorptiometry
ED: Eating Disorders
EDE: Eating Disorder Examination
ELISA: Standard enzyme-linked immunosorbent assay
EMA: Anti-Endomysial Antibody
EN: Enteral Nutrition
EOS: End of study
ESPGHAN: European Society of Paediatric Gastroenterology Hepatology and Nutrition
FDR: First-Degree Relatives
Foxp3: Transcription factor forkhead box P3
G: Guanosine
GAG: Glycosaminoglycan
GC: Gluten Challenge
GFD: Gluten Free Diet
GGS: Gastrointestinal Symptom Scale
GI: Gastrointestinal
GI-CON: Parent/child with mild gastrointestinal complaints
GIP: Gluten Immunogenic Peptides
GP: General Practitioner
GSRS: Gastrointestinal Symptom Rating Scale
HAV: Hepatitis A Virus
HAZ: Height for Age Z score
HbA1c: Haemoglobin A1c
HBsAb: Hepatitis B surface Antibody
HBV: Hepatitis B Virus
HC: Healthy Control
HLA: Human Leukocyte Antigen
HR: Hazard ratio
HRQOL: Health-related quality of life
HSPG: Heparan sulphate proteoglycan
Ht-SDS: Height growth velocity
Ht-SDS: Height standard deviation score
POC: Point Of Care
PPV: Positive Predictive Value
QOL: Quality Of Life
RBA-Anti-TGA: Radio Binding Assay of anti-tissue Transglutaminase Antibodies
RCDII: Type II refractory CD
RCT: Randomized Clinical Trial
SB: Small Bowel
SD: Standard Deviation
SF-12: Form Health Survey 12
SNPs: Single nucleotide polymorphisms
T: Thymine
T1D: Type 1 Diabetes
T1DM: Type 1 Diabetes Mellitus
TEACH: Text Message Educational Automated Compliance Help
TG: Transglutaminase
TG2: Transglutaminasa 2
TG3: Transglutaminase 3
TGA: Antibodies to Transglutaminase
T-IEL: T-cell receptor positive Intraepithelial Lymphocytes
TNFα: Tumor Necrosis Factor alpha
TPN: Total Parenteral Nutrition
TRC: T-Cell Receptor
Treg: Regulatory T cell
tTG: Tissue Transglutaminase
tTG-IgA: tissue transglutaminase-immunoglobulin A
TVA: Total Villous Atrophy
UEG: United European Gastroenterology
ULN: Upper Limit of Normal
US: United States
VA: Villous Atrophy
VH:CrD: Villous Height/Crypt ratio
WAZ: Weight for age Z score
Wt-SDS: Weight Standard Deviation Score
YSHCN: Youth with Special Health Care Needs

CD DUX Child version

We would like to know how you feel these days.
Therefore, could you please indicate how you feel in different situations?
You can do that by circling in each question one of the faces that fits you best.
There are no wrong answers; it's about what you feel.

Please express how you've been feeling lately.	
1.	When I think of food containing gluten, I feel … 
2.	When at school I am given food containing gluten, I find it … 
3.	Talking about my coeliac disease with others my age, I find … 
4.	Not being able to eat just everything, I find … 
5.	When someone offers me food that I can't have, I feel … 
6.	When I have to explain to others what coeliac disease is, I feel … 

Please express how you've been feeling lately.	
7.	Talking about coeliac disease I find ... 
8.	Having to follow a lifelong diet, I find ... 
9.	Having to pay attention to what I eat, I find ... 
10.	Having coeliac disease is ... 
11.	Not being able to eat anything I want like other people, I find ... 
12.	Following a diet for my coeliac disease is ... 

Thanks for filling in this questionnaire!

CD DUX Parent- Girl version

We would like to know how your daughter feels these days.
Therefore, could you please indicate how your daughter feels in different situations?
You can do that by circling in each question one of the faces that fits your daughter's feelings best. There are no wrong answers; it's about what you think your daughter feels.

Please express how your daughter has been feeling lately.	
1.	When your daughter thinks of food containing gluten, she feels … 
2.	When at school your daughter is given food containing gluten, she finds it … 
3.	Talking about celiac disease with others her age, she finds … 
4.	Not being able to eat just everything, she finds … 
5.	When someone offers her food that she can't have, she feels … 
6.	When your daughter has to explain to others what celiac disease is, she feels … 

Please express how your daughter has been feeling lately.	
7.	Talking about celiac disease your daughter finds ... 
8.	Having to follow a lifelong diet, your daughter finds ... 
9.	Having to pay attention to what she eats, she finds ... 
10.	Having celiac disease your daughter finds ... 
11.	Not being able to eat anything she wants like other people, she finds ... 
12.	Following a diet for her celiac disease your daughter finds ... 

Thanks for filling in this questionnaire!

CD DUX Parent- Boy version

We would like to know how your son feels these days.
Therefore, could you please indicate how your son feels in different situations? You can do that by circling in each question one of the faces that fits your son's feelings best. There are no wrong answers; it's about what you think your son feels.

Please express how your son has been feeling lately.	
1.	When your son thinks of food containing gluten, he feels … 
2.	When at school your son is given food containing gluten, he finds it … 
3.	Talking about celiac disease with others his age, he finds … 
4.	Not being able to eat just everything, he finds … 
5.	When someone offers him food that he can't have, he feels … 
6.	When your son has to explain to others what celiac disease is, he feels … 

Please express how your son has been feeling lately.	
7.	Talking about celiac disease your son finds ... 
8.	Having to follow a lifelong diet, your son finds ... 
9.	Having to pay attention to what he eats, he finds ... 
10.	Having celiac disease your son finds ... 
11.	Not being able to eat anything he wants like other people, he finds ... 
12.	Following a diet for his celiac disease your son finds ... 

Thanks for filling in this questionnaire!