REVIEW

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Recommendations for Clinical Decision-making in Children with Type 1 Diabetes and Celiac Disease: Type 1 Diabetes and Celiac Disease Joint Working Group Report

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Abstract

It is well-known that in children with type 1 diabetes (T1D), the frequency of Celiac disease (CD) is increased due to mechanisms which are not fully elucidated but include autoimmune injury as well as shared genetic predisposition. Although histopathologic examination is the gold standard for diagnosis, avoiding unnecessary endoscopy is crucial. Therefore, for both clinicians and patients' families, the diagnosis of CD remains challenging. In light of this, a joint working group, the Type 1 Diabetes and Celiac Disease Joint Working Group, was convened, with the aim of reporting institutional data and reviewing current international guidelines, in order to provide a framework for clinicians. Several controversial issues were discussed: For CD screening in children with T1D, regardless of age, it is recommended to measure tissue transglutaminase-immunoglobulin A (tTG-IgA) and/or endomysial-IgA antibody due to their high sensitivity and specificity. However, the decision-making process based on tTG-IgA titer in children with T1D is still debated, since tTG-IgA titers may fluctuate in children with T1D. Moreover, seronegativity may occur spontaneously. The authors' own data showed that

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most of the cases who have biopsy-proven CD had tTG-IgA levels 7-10 times above the upper limit. The decision for endoscopy based solely on tTG-IgA levels should be avoided, except in cases where tTG-IgA levels are seven times and above the upper limit. A closer collaboration should be built between divisions of pediatric endocrinology and gastroenterology in terms of screening, diagnosis and follow-up of children with T1D and suspicious CD.

Keywords: Children, type 1 diabetes, Celiac disease, anti-tissue transglutaminase-IgA

Introduction

Among children with type 1 diabetes (T1D), the prevalence of Celiac disease (CD) is higher than in the general population (1.6-16.4% vs 0.7%) since they are susceptible to autoimmune damage to several organ systems (1). Therefore, the screening of children with T1D for CD is critical, and the current screening protocol includes the measurement of tissue transglutaminase-IgA (tTG-IgA) levels regardless of symptom status, followed by endoscopic biopsy in those with positive tTG-IgA titers (2,3). The treatment then involves the institution of a gluten-free diet. Overall, the timing of tTG-IgA measurements has an important role in the decision-making process and the management of the patients.

From the perspective of pediatric endocrinologists, pediatric gastroenterologists and families, avoiding clinically unjustified endoscopies is just as critical as the timely diagnosis of CD. Furthermore, variations exist in the indications for endoscopy and treatment among different countries and centers (4).

This report is intended to convey the most up-to-date information regarding the current diagnostic algorithms, the role of a gluten-free diet, the epidemiologic data in Turkey, recent developments in the literature, and recommendations of international societies in relation to CD in children with T1D. This report was prepared by professionals assigned by the administrative boards of "Pediatric Endocrinology and Diabetes Association" and "Turkish Society of Pediatric Gastroenterology, Hepatology and Nutrition" and was based on data from several centers and discussions that took place at three different meetings.

The goal of this report was to further detail the current recommendations by international societies and to provide a basic framework to be used by practicing physicians.

Main Questions That were Discussed in the Joint Meetings

- What is the prevalence of CD in children with T1D in Turkey? What are the main issues regarding the screening and diagnosis?

- In general, how long after the diagnosis of T1D would tTG-IgA antibody levels be reliable?

- What is the rate of transient tTG-IgA positivity and how does this affect diagnosis?

- Would making the decision to perform endoscopy according to tTG-IgA titers measured just after a diagnosis of T1D in children with no symptoms and family history of CD lead to unnecessary invasive procedures?

- Does tTG-IgA positivity and incidence of CD in children with T1D vary depending on age and time after the initial diagnosis T1D? Is autoimmune thyroiditis an additional risk factor?

- Would it be beneficial to conduct multidisciplinary meetings for clinical decision-making in caring for children with T1D and a diagnosis of/suspicion of CD? Alternatively, should this process be under the responsibility of pediatric gastroenterologists alone?

- From the perspective of pathologists, what are the basic issues encountered in the diagnosis of CD?

- Why has gluten-free diet become so popular among the public? What do the scientific data suggest?

- What are the issues associated with gluten consumption apart from in the context of CD?

- What do the families experience in terms of the possibility of having a diagnosis of CD, the diagnostic process and the period after the diagnosis? What are their concerns? Does a gluten-free diet have any role in preventing T1D?

- In children who are already diagnosed with T1D, would a gluten-free diet reduce the risk of acquiring CD? Would this diet have any impact on the autoimmune destruction of beta-cells?

- How should we follow children with high tTG-IgA titers but normal endoscopic findings? Should a gluten-free diet be recommended?

- How should the dietary management of a child with T1D and CD be?

Results and Suggestions

The Relationship Between Diabetes and Celiac Disease

1. The prevalence of positive CD autoimmunity and overt CD was 14.3% [95% confidence interval (CI): 11-17] and

8.5% (95% CI: 5-10), 15- and 8-times higher than the general pediatric population, respectively (5). According to international studies, the prevalence of biopsy-proven CD ranges between 1.6-16.4% among people with T1D (6,7,8,9,10).

2. In a recently published study including 52751 children with T1D from the US, Germany, Austria, England and Australia the prevalence of CD was found to be 3.5% (4). In general, the risk of receiving a diagnosis of biopsy-proven CD is higher before the age of 5 years and within the first five years after the diagnosis of T1D. Concomitant autoimmune thyroid disease further increases this risk (3).

3. CD is asymptomatic in 85% of children with T1D who have biopsy-proven diagnosis. As a result, it is necessary to screen for CD in this population.

4. According to studies from Turkey, the prevalence of biopsy-proven CD in children with T1D is 3.5-12.2% (11,12).

5. During the meetings for the preparation of this report, data gathered by the following institutions were presented to seek answers to the previously posed questions: Koç University, Gazi University, Ege University, Ankara University, Dr. Sami Ulus Children's Hospital, Cerrahpaşa Medical Faculty and Elazığ Fırat University:

- In the last five years, 1061 children with T1D were followed-up at Koç University. A total of 401 whose CD screening was conducted in Koç University Hospital were evaluated. tTG-IgA positivity was detected in 61% of CD cases in the first year, 37% between the first and fifth years, and in 2% after the fifth year of T1D diagnosis. The prevalence of biopsy-proven CD was 3.7% in this cohort.

- In the last 10 years, 559 children were diagnosed with T1D at Gazi University. The prevalence of biopsy-proven CD was 3.4% in this cohort. Of these patients, 82.4% were asymptomatic. CD diagnosis was made within the first two years of T1D diagnosis in 50%, and 94% were diagnosed within the first 5 years.

- Data from Ege University encompassed 1300 children with T1D and the prevalence of biopsy-proven CD was 1.9% in this cohort. 72% of the cohort was asymptomatic and 59% were diagnosed within two years following the diagnosis of T1D.

- Data from Ankara University included 158 children with T1D and the prevalence of biopsy-proven CD was 4.4%. 85% of the cases received a diagnosis within the first 5 years following the diagnosis of T1D.

- Data from Dr. Sami Ulus Children's Hospital included a nine-year period, during which 550 children were diagnosed with T1D. In this cohort, 5.2% had biopsy-proven CD. In the first year, 72.4% of the children with CD were diagnosed with CD.

- Data from Cerrahpaşa Medical Faculty included 100 children, among whom 4% were diagnosed with CD based on histopathology.

- Data from Fırat University included a 14-year period, during which 453 children were diagnosed with T1D. Among these, the prevalence of biopsy-proven CD was 5.5%. 76% of the patients were asymptomatic and 64% were diagnosed within the first year following the diagnosis of T1D.

6. In the follow-up of children with T1D, the current recommendations for the timing of Celiac serology screening include within first two years and five years after diagnosis of T1D or every year, but the recommendations regarding the frequency of screening after five years following T1D diagnosis are less clear. While the risk of developing CD decreases significantly after this 5-year mark, the possibility of CD should still be kept in mind. In addition to the above recommendations, screening should be conducted in case of any of the below:

- Symptom and laboratory findings suggestive of CD,

- First degree relative with a diagnosis of CD,

- Unexplained frequent hypoglycemia.

Screening Tests and Their Interpretation

1. After checking that the child is consuming normal quantities of gluten, in children with normal serum IgA values for age, tTG-IgA measurements should be used as an initial test regardless of age (2). If serum IgA levels are found to be low for age or <0.2 g/L in children older than three years old, IgG based tests (deaminated gliadin peptide, EMA or tTG) should be use. tTG-IgA titers are reported as international unit (IU) or relative unit (RU). The upper limits for IU and RU are 20 and 1, respectively. Threshold tTG-IgA levels that justify performing endoscopy are generally reported as multiples of the upper limit (e.g. 3-fold, 10-fold). In addition, recommendations outlined by the specific testing kits should be considered. On the other hand, EMA-IgA testing should be conducted with techniques involving immunofluorescence.

2. International studies have reported that tTG-IgA levels show a fluctuating trend in 10.7-41% of the patients and resolve in 30-40%, despite continued gluten intake (5,13,14,15). Data from Gazi University indicate that 12.7% had a fluctuating course; in this group tTG-IgA levels

were <3x upper limit of normal (ULN) and the rate of spontaneous resolution of antibodies was 97%. Diyarbakır Gazi Yaşargil Hospital and Koç University Hospital have reported spontaneous antibody resolution rates of 23.3% and 22% within five years, respectively (15).

3. In recent years, there has been an increasing debate regarding the threshold tTG-IgA level for offering endoscopy. Data presented by Gazi University have been assessed, and the best cut-off was judged to be ≥7-times the ULN in terms of sensitivity, specificity, negative predictive value and positive predictive value. Data from centers that submitted their data to this committee were also congruent in that the majority of the patients with biopsy-proven CD had tTG-IgA levels 7-10x the ULN.

4. We therefore recommend that tTG-IgA levels should not be the sole criterion for performing endoscopy, except when tTG-IgA levels ≥7x ULN, there is a family history of CD or the patient has symptoms suggestive of CD. Physicians should keep in mind that during the early stages of T1D, there can be a transient "antibody storm" against not only the pancreatic beta-cells but also other tissues, which may eventually resolve. In children with antibody levels within 3-7 times the ULN and without any of the exceptions highlighted above, antibody test can be repeated at 3-6 months prior to seeking endoscopic evaluation.

5. Despite the increasing data on transient and fluctuating antibody positivity, the European Society of Pediatric Gastroenterology Hepatology and Nutrition (ESPGHAN) and the International Society of Pediatric and Adolescent Diabetes (ISPAD) currently do not detail any recommendations on this issue in their respective guidelines. Therefore, we believe that it would be clinically beneficial if these societies prepared a joint consensus guideline for the diagnosis and management of CD in children with T1D.

Decision to Perform Endoscopy and Clinical Management

In the light of the data presented at the meetings and available in the literature, and after taking into consideration the current consensus opinions, the following recommendations regarding the indications for endoscopy and clinical management are set forth below:

1. With the exception of frequent attacks of hypoglycemia and symptoms suggestive of CD, invasive procedures, such as endoscopy, should be planned for the most appropriate date given that the diagnosis of CD is not considered urgent, and families require time to get accustomed to the diagnosis of T1D.

2. There is no single standard test for measuring antibody levels. Hence, endoscopy should not be undertaken based on tTG-IgA levels measured at another center. Instead a repeat measurement should be conducted prior to deciding on the need for endoscopy.

3. Apart from the cases with tTG-IgA levels ≥7x the ULN, tTG-IgA levels measured at the time of diagnosis of T1D should not be used to guide the decision to perform endoscopy.

4. Prior to measuring tTG-IgA levels, it should be confirmed that patients have been consuming gluten for at least two weeks.

5. If the tTG-IgA levels are ≤3x the ULN there is no indication to perform endoscopy in patients without a family history of CD or symptoms suggestive of CD. Such patients can be followed up by the pediatric endocrinology department through serial antibody testing.

6. All patients with a tTG-IgA level >3x the ULN should be referred to the pediatric gastroenterology department as soon as possible.

7. For patients with tTG-IgA levels ≥10x the ULN and a second antibody test reveals EMA positivity, the family should be informed that a diagnosis of CD can be made without further endoscopic evaluation. However, making a definitive diagnosis through endoscopic biopsy may improve compliance to dietary management, especially in the setting of our country.

8. Patients with fluctuating antibody titers and antibody levels <3x the ULN can be followed up without endoscopy.

9. In patients with tTG-IgA levels between 3-7x the ULN, further diagnostic steps may include EMA-IgA testing followed by endoscopy if EMA positive or immediate endoscopy depending on the center's preference.

10. There is seldom need to perform testing for HLA DQ2 and HLA DQ8 subgroups for the diagnosis of CD. This testing can be useful in ruling out CD in challenging cases with equivocal biopsy findings.

11. All children with biopsy-proven CD should be managed with a gluten-free diet regardless of the presence of symptoms.

The algorithm prepared through these analyses and committee recommendations are presented in the Figure 1.

Pathology

1. All patients scheduled for endoscopic evaluation should be on a gluten-containing diet prior to the endoscopy. The relevant clinical data of the patient, including medical

history, endoscopic findings, laboratory findings, serology, medications, and diet, must be available to the pathologist (16,17).

2. In terms of location and the number of biopsy sites and samples, international guidelines should be followed. As per current recommendations of the American College of Gastroenterology and the American Gastroenterological Association, at least two samples from the duodenal bulb and four samples from the distal duodenum should be obtained (18).

3. To avoid processing artifacts that can interfere with the histopathological interpretation, endoscopy units and the pathology laboratory should be arranged as required. Biopsies should be reported according to the most recent Marsh-Oberhuber classification. Apart from patients with Marsh 0 grading all patients should be followed by both the pediatric endocrinology and gastroenterology departments (16,19).

4. The diagnosis of CD may require a consensus of pathological, clinical and laboratory findings. Findings of the histopathologic examination should be clinically correlated.

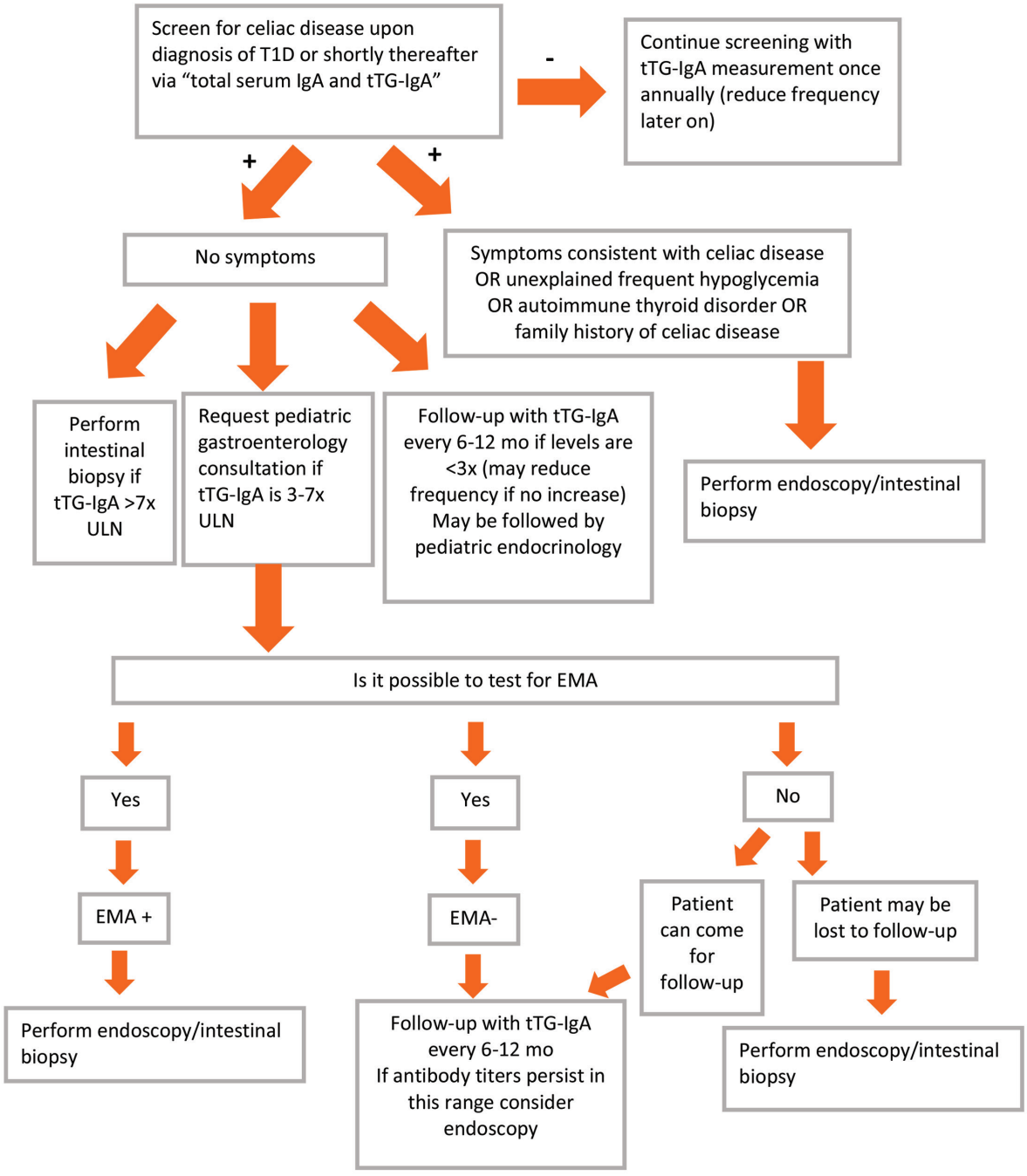

Figure 1. An algorithm for the screening and diagnosis of Celiac disease in children with type 1 diabetes

Dietary Recommendations

1. Patients with a diagnosis of CD must follow a strict life-long gluten-free diet (20). Hence, when CD accompanies T1D, patients need closer follow-up along with more intensive counseling and dietary management (21).

2. A gluten-free diet involves the complete removal of wheat, barley, rye, and their hybrids/products from the diet (Table 1) (21). Nevertheless, conserved foods, premade salad/pasta sauces, some ice creams, charcuterie products such as sausage and pepperoni, premade jams, sugar cubes, premade meat-chicken broth, fruit jelly, malt drinks and beverage powder may include gluten. Other less conspicuous sources of gluten include toothpaste, mouthwash, the glue on stamps and envelopes (21).

3. Patients with CD must inspect whether any orally administered medication, supplement or vitamin includes gluten. Wheat flour and wheat starch are among the products used in drug manufacture. In general, if a medical product does not include wheat flour or wheat starch it is considered to be free of gluten. The amount of gluten contained in a drug is directly related to the amount of wheat flour used in its production. Therefore, if a drug description does not include information about gluten content but mentions wheat flour, that drug should be avoided by patients with CD. Medications may also include other compounds obtained through the processing of wheat flour and starch. Generally, the amount of gluten in a single unit dose of these medications are lower than the gluten amount found in foods labeled as "gluten-free". Oral intake of such medications does not interfere with a gluten-free diet (22).

4. Some topical products that are applied to the lips and/or the skin may contain wheat germ oil. The gluten content in highly refined wheat germ oil is infinitesimal and its topical application does not interfere with a gluten-free diet (22).

5. Foods with a label that reads "Does not contain gluten" or "Gluten-free" should contain ≤20 ppm of gluten, which can be safely consumed (2).

6. When preparing foods at home, communal use of kitchen equipment without adequate cleaning, especially of the oven and bread maker can lead to contamination with gluten. To prevent contamination, ovens and bread makers should be appropriately cleaned after each use to remove any gluten. Kitchen equipment, such as toasters, that cannot be washed should only be used by the patient. In addition, the use of cooking bags in the oven may reduce the risk of contamination. All gluten-free food products that belong to the patient with CD must be labeled and stored separately in their own drawer/cupboard, on higher racks than the products containing gluten (21,23).

7. It is safer to use stainless steel pots and pans or glass containers when cooking meals for patients with CD. Equipment such as pots, pans and serving spoons should not be made of materials that may have pores (e.g., wood). Prior to use, all equipment should be thoroughly cleaned and separately provided for the patient (24).

8. Children and adolescents with T1D and CD can consume rice, potato, corn (maize), teff, amaranth, buckwheat, quinoa, and sorghum as a source of carbohydrate, since these do not contain gluten (25).

Table 1. Foods that should be avoided vs are allowed in a gluten-free diet

Foods to be avoided	
Milk and milk products	Milk products containing malt
Meats and meat products	Breaded meats, processed meats (salami, sausage, pepperoni, bacon, etc.), premade meatballs
Grains	Barley, rye, wheat and products prepared from them: semolina, bulgur, couscous, noodles, pasta, bread, cereal, baked goods and soup made with these grains
Other	Soupmixes, malt products, mustard, mayonnaise, ketchup, soy sauce, tomato paste, sugar cube, powdered sugar, ice cream cone, chocolate, wafer
Foods that are allowed	
Milk and milk products	Milk and milk products that do not contain malt
Meat and meat products	Plain meat, chicken, fish and eggs without flour and sauce
Grains	Rice, rice flour, maize, corn flour, corn bread (without wheat flour), any flour without gluten, quinoa, buckwheat, soy, teff, amaranth, sorghum, soup made with these grains
Vegetables	All fresh, unpackaged, uncanned vegetables
Fruits	All fresh, unpackaged, uncanned fruits
Legumes	All legumes
Fats	All fats and fatty seeds

The table was adapted from reference 21

9. The macronutrient composition of gluten-free products is different from that of their counterparts containing gluten. Most gluten-free foods are poor in protein and fiber, but rich in carbohydrates and fats with a high glycemic index (26,27,28,29,30). Consequently, the glucose peaks in children with T1D and CD may be earlier and higher than those without CD (26). Accordingly, the dose and timing of insulin administration must be determined based on the nutrient content of the gluten-free products. Consumption of soup with meat/vegetables or salad prior to the main source of carbohydrate may improve postprandial glycemic control and dampen potential fluctuations (30,31).

10. Increasing the variety of gluten-free foods may help improve the dietary compliance of children and adolescents with T1D and CD and help them achieve a better quality of life and control of their diabetes (26).

11. Commonly consumed gluten-free products, such as rice and potatoes, and packaged gluten-free items sold in the supermarkets have a high glycemic index. Instead, including products with a low glycemic index and high fiber content in the diet such as teff, amaranth, buckwheat, quinoa, sorghum, soy, vegetables, fruits with edible skin and legumes helps control the postprandial blood glucose levels (26,27).

12. However, some gluten-free products may be poor in carbohydrates and the administration of standard doses of insulin may result in severe hypoglycemia. Labels on food packages must be read and evaluated carefully (28,29,30,31,32).

13. To reduce the occurrence of postprandial glucose peaks, meals should include sources of protein such as ayran, kefir, eggs, meat, chicken and fish (33).

14. When leaving the home children and adolescents with T1D should carry gluten-free carbohydrates to avoid the intake of products containing gluten to counteract episodes of hypoglycemia occurring outside the house (28,29,30,31).

15. In addition to protein and fiber, micronutrients such as iron, calcium and B vitamins should be included in the diet to improve the overall benefit of the gluten-free diet (23,32).

16. It may be challenging for children and adolescents with T1D and CD to follow a gluten-free diet. To improve dietary adherence, nutrition-centered education and regular counseling with a dietician specialized in pediatric diabetes management are essential (21).

17. In children with T1D, some parents may opt for a prophylactic gluten-free diet in the absence of a diagnosis of CD because of their awareness of this association. Nevertheless, there is no evidence to support that a gluten-free diet can prevent the development of CD in patients with T1D. Such an approach further complicates the management of diabetes in these patients. Moreover, gluten consumption is necessary to avoid false negative results and appropriately diagnose CD should it occur (34,35).

18. There is no evidence to support the benefits of a gluten-free diet in individuals without CD or gluten intolerance. Therefore, the gluten-free diet cannot be a medical recommendation for such individuals (34,35).

Recommendations for Psychological Support

1. Parents of children with CD may report higher levels of anxiety, depression, aggression and sleep difficulties in their children, even before the definitive diagnosis is made or positive serology is detected (36). Therefore, pediatric endocrinology and gastroenterology specialists should be aware of the emotional and behavioral signs of CD and consider investigating for CD in children presenting with predominantly psychological and behavioral manifestations.

2. Studies show that childhood CD is a risk factor for mood disorders, anxiety disorders, eating disorders, behavioral disorders, attention deficit hyperactivity disorder, autism spectrum disorder and intellectual disability disorder (37). It is recommended for children with CD to be monitored into adulthood in terms of both physical and mental health.

3. Dealing with multiple chronic conditions can lead to poorer health outcomes, increasing financial costs and difficulties in the daily management of health. Although studies investigating the experiences of parents of children with T1D and CD are limited, families usually focus on health issues, financial concerns, psychological wellbeing of the child and social situations outside the house (38). Families worry more about the short and long-term complications of diabetes than those of CD. Routinely measuring blood glucose levels, counting carbohydrates and adhering to a strict gluten-free diet are likely to be some of the daily struggles for health management. Gluten-free products are very expensive and both preparing appropriate foods and doctor visits can take significant amounts of time. Children may feel different from their peers and suffer misunderstandings or bullying. False or incomplete information can lead to lack of physical and/or emotional support by society, especially in social settings such as schools.

General Recommendations

1. According to the results of a “questionnaire” conducted prior to the meeting, pediatric endocrinology and

pediatric gastroenterology departments in Turkey exhibit heterogenous practice regarding the screening, diagnosis and management of CD in children with T1D, and 20% do not follow consensus guidelines. As such, greater cooperation between pediatric endocrinology and pediatric gastroenterology departments is necessary, which should be further supported by regular multidisciplinary team meetings that should include pathologists, dieticians and psychologists.

2. Standards for screening of CD within the first five years following the diagnosis of T1D should be set and implemented in clinics.

3. The main recommendations set forth by this script should be shared with ESPGHAN and ISPAD societies in order to request a joint consensus guideline for the diagnosis and management of children with T1D and CD.

4. Efforts should be made to improve the management of children with CD in schools and to garner greater governmental support.

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Ethics

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Authorship Contributions

Concept – Design - Data Collection or Processing - Analysis or Interpretation - Literature Search - Writing: All authors.

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