DOI: 10.4274/jcrpe.galenos.2021.2021.0139

Review

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

Hatun Ş et al. Celiac Disease in Children with Type 1 Diabetes

Şükrü Hatun[1], Buket Dalgıç[2], Damla Gökşen[3], Sema Aydoğdu[4], Şenay Savaş Erdeve[5], Zarife Kuloğu[6], Yaşar Doğan[7], Zehra Aycan[8], Gül Yeşiltepe Mutlu[1], Nuray Uslu Kızılkan[9], Alev Keser[10], Ömer Faruk Beşer[11], Mehmet Nuri Özbek[12], Aysun Bideci[13], Deniz Ertem[14], Olcay Evliyaoğlu[15], Beyza Eliuz Tipici[16], Tuğba Gökçe[1], Serra Muradoğlu[1], Orhun Çığ Taşkın[17], Tuğba Koca[18], Filiz Tütüncüler[19], Firdevs Baş[20], Feyza Darendeliler[20], Mukadder Ayşe Selimoğlu[21]
[1]Division of Pediatric Endocrinology and Diabetes, Koç University School of Medicine, İstanbul, Turkey
[2]Division of Pediatric Gastroenterology, Department of Pediatrics, Gazi University Faculty of Medicine, Ankara, Turkey
[3]Division of Pediatric Endocrinology, Ege University School of Medicine, İzmir, Turkey
[4]Division of Pediatric Gastroenterology, Ege University Faculty of Medicine, Izmir, Turkey
[5]Pediatric Endocrinology Clinic, Dr. Sami Ulus Obstetrics and Gynecology and Pediatrics Training and Research Hospital, Ankara, Turkey
[6]Division of Pediatric Gastroenterology, Department of Pediatrics, Ankara University School of Medicine, Ankara, Turkey
[7]Division of Pediatric Gastroenterology, Faculty of Medicine, Firat University, Elazig, Turkey
[8]Division of Pediatric Endocrinology, Ankara University School of Medicine, Ankara, Turkey
[9]Division of Pediatric Gastroenterology, Koç University Hospital, İstanbul, Turkey
[10]Department of Nutrition and Dietetics, Faculty of Health Sciences, Ankara University, Ankara, Turkey
[11]Division of Pediatric Gastroenterology, Hepatology, and Nutrition, Istanbul University Cerrahpasa Medical Faculty, Istanbul, Turkey
[12]Department of Pediatric Endocrinology, Gazi Yasargil Education and Training Hospital, University of Health Sciences, Diyarbakir, Turkey
[13]Division of Pediatric Endocrinology and Diabetes, Gazi University Faculty of Medicine, Ankara, Turkey
[14]Department of Pediatric Gastroenterology, Hepatology and Nutrition, Marmara University Faculty of Medicine, İstanbul, Turkey
[15]Division of Pediatric Endocrinology, Department of Pediatrics, İstanbul University-Cerrahpaşa, Cerrahpaşa Faculty of Medicine, İstanbul, Turkey
[16]İstanbul University İstanbul Faculty of Medicine, Department of Nutrition and Dietetics, İstanbul, Turkey
[17]Department of Pathology, Koç University School of Medicine, Istanbul, Turkey
[18]Department of Pediatric Gastroenterology, Hepatology and Nutrition, Faculty of Medicine, Suleyman Demirel University, Isparta, Turkey
[19]Department of Pediatrics, Division of Pediatric Endocrinology, Trakya University School of Medicine, Edirne, Turkey
[20]Department of Pediatric Endocrinology, Istanbul Faculty of Medicine, Istanbul University, Istanbul, Turkey
[21]Pediatric Gastroenterology, Hepatology and Nutrition, Memorial Ataşehir/Bahçelievler Hospitals, İstanbul, Turkey.

Abstract
It is well-known that in children with type 1 diabetes (T1D), the frequency of celiac disease (CD) is increased due to unclear mechanisms including autoimmune injury as well as shared genetic predisposition. Although histopathologic examination is gold standard, avoiding unnecessary endoscopy is crucial. Therefore, from the perspective of the clinicians and patients' families, the diagnosis of celiac disease remains challenging. With these in mind, a joint working group (Type 1 Diabetes and Celiac Disease Joint Working Group) was gathered, with the aim of reporting institutional data, as well as the current recommendations of international organizations, 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 tTG-IgA (tissue transglutaminase-Immunoglobulin A) and/or endomysial (EMA-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 most of the cases who have biopsy-proven CD had tTG-IgA levels 7-10 times above the upper limit. The decision of endoscopy based solely on tTG-IgA levels should be avoided, except in cases where tTG-IgA levels are 7 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

Şükrü Hatun MD, Division of Pediatric Endocrinology and Diabetes, Koç University School of Medicine, İstanbul, Turkey
+0905323468006
sukruhatun@gmail.com
18.05.2021
10.08.2021
0000-0003-1633-9570

Published: 18 August 2021

Introduction

Among children with type 1 diabetes (T1D), the prevalence of celiac disease (CD) is higher than the general population (1.6-16.4% vs 0.7%) since they are susceptible to autoimmune damage of 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 our country, recent developments in the literature, and recommendations of international societies in relation to CD in children with T1D. It has been prepared by professionals assigned by the administrative boards of **"Pediatric Endocrinology and Diabetes Association" and "Turkish Society of Pediatric Gastroenterology, Hepatology and Nutrition"** based on data of respective centers and discussions that took place at three different meetings have also been used in the preparation of this report.

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

Main questions that have been 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 can tTG-IgA antibody levels would 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 for 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 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% 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 (6-10).

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 and within the first 5 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 have been presented to seek answers to the previously posed questions: Koç University, Gazi University, Ege University, Ankara University, Dr. Sami Ulus Children's Hospital, Cerrahpasa Medical Faculty and Elazig Firat University:

- In the last 5 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 cases in the first year, 37% between 1st and 5th years, and after 5th years of T1D diagnosis in 2%. The prevalence of biopsy-proven CD was found 3.7% in this cohort.
- In the last 10 years, 559 children have been diagnosed with T1D at Gazi University. The prevalence of biopsy-proven CD was found 3.4% in this cohort. Of these patients, 82.4% were asymptomatic. 50% were diagnosed within the first 2 years of receiving the diagnosis of T1D, 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 2 years after 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 first 5 years of diagnosis of T1D.
- Data from Dr. Sami Ulus Children's Hospital included a 9-year period, during which 550 children were diagnosed with T1D. In this cohort, 5.2% had biopsy-proven celiac disease. In the first year, 72.4% of the patients were diagnosed with CD.
- Data from Cerrahpasa Medical Faculty included 100 children, among whom 4% were diagnosed with CD based on histopathology.
- Data from Firat 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 years 2 and 5 (or every year), but the recommendations regarding the frequency of screening after 5 years are less clear. While the risk of developing CD decreases significantly after the 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 3 years old, IgG based tests (Deaminated gliadin peptide (DGP), 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 folds of the upper limit (e.g., 3-folds, 10-folds). 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 (IF).

2. International studies have reported that celiac-related antibody levels show a fluctuating trend in 10.7-41% of the patients and resolve in 30-40% despite continued gluten intake (5,13-15). Data from Gazi University indicate that 12.7% had a fluctuating course (in this group antibody levels were < 3x Upper limit of normal (ULN) and the rate of spontaneous resolution of antibodies was 97%). Diyarbakir Gazi Yasargil Hospital and Koc University Hospital have reported an antibody resolution rate of 23.3% and 22% within 5 years, respectively (15).

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

4. When the above findings are taken into account, tTG-IgA levels (with the exception of levels 7x ULN or above, family history of CD or presence of symptoms) should not be the sole criterion for performing endoscopy. 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, it would be clinically beneficial if the aforementioned societies prepared joint consensus guidelines for the diagnosis and management of CD in children with T1D.

Decision to perform endoscopy and the management

In the light of the data presented in the literature and the meetings, as well as the current consensus opinions, the following recommendations regarding the indications of endoscopy and 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 not one standard testing procedure to measure antibody levels. Hence, endoscopy should not be undertaken based on tTG-IgA levels measured at another center and, instead a repeat measurement should be conducted.
3. Apart from the cases with tTG-IgA levels x7 the ULN or above, tTG-IgA levels measured at the time of diagnosis of T1D should not guide the decision to perform endoscopy.
4. Prior to measuring tTG-IgA levels, it should be ensured that patients have been consuming gluten for the past 2 weeks.
5. If the tTG-IgA levels are 3x the ULN or less there is no indication to perform endoscopy in patients without the aforementioned risk factors. Such patients can be followed up by the pediatric endocrinology department through serial antibody testing.
6. All patients with a tTG-IgA level above the 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 or above, the families should be informed that a diagnosis of CD can be made without further endoscopic evaluation (if a second antibody test reveals EMA positivity). 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 less than 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 positive or immediate endoscopy depending on the center's preference.
10. There is seldom needed to perform testing for HLA DQ2 and HLADQ8 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.
12. **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 (history, endoscopic findings, laboratory findings, serology, medications, and diet) must be available to the pathologist (16,17).
2. In terms of localization and the number of biopsied tissues, international guidelines should be followed. As per current recommendations of the American College of Gastroenterology and the American Gastroenterological Association, at least 2 samples from the duodenal bulb and 4 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 the patients with Marsh 0 grading (i.e., Marsh I-III), all patients should be followed by both the pediatric endocrinology and gastroenterology departments (16,19).
4. The diagnosis of CD may require be a consensus of pathological, clinical and laboratory findings. Findings of the histopathologic examination should be clinically correlated.

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 be used individually by the patient alone. 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, teff, amaranth, buckwheat, quinoa, sorghum as a source of carbohydrate since these do not contain gluten (25).
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 (26,27-30). 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. On the other hand, 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 (28-32).
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. Children and adolescents with T1D should carry gluten-free carbohydrates with themselves to avoid the intake of products containing gluten to counteract episodes of hypoglycemia occurring outside the house (28-31).
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 beneficence 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. Furthermore, gluten consumption is necessary to avoid false negative results and appropriately diagnose CD (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 in children presenting with predominantly psychological and behavioral manifestations as well.
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 in terms of both physical and mental health into adulthood.
3. Dealing with multiple chronic conditions can lead to unsatisfactory 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 can be some of the daily struggles in health management. Gluten-free products are highly 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 have heterogenous practices 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 including pathologists, dieticians and psychologists.
2. Standards for screening of CD within the first 5 years following the diagnosis of T1D should be set and implemented in the 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.

Acknowledgement

The authors would like to thank Elif Özdoğan for her contributions on English translation of the manuscript.

References

1. Pham-Short A, Donaghue KC, Ambler G, Phelan H, Twigg S, Craig ME. Screening for Celiac Disease in Type 1 Diabetes: A Systematic Review. Pediatrics. 2015 Jul;136(1):e170-6. doi: 10.1542/peds.2014-2883. Epub 2015 Jun 15. PMID: 26077482.
2. Al-Toma A, Volta U, Auricchio R, Castillejo G, Sanders DS, Cellier C, Mulder CJ, Lundin KEA. European Society for the Study of Coeliac Disease (ESsCD) guideline for coeliac disease and other gluten-related disorders. United European Gastroenterol J. 2019 Jun;7(5):583-613.
3. Mahmud FH, Elbarbary NS, Fröhlich-Reiterer E, Holl RW, Kordonouri O, Knip M, Simmons K, Craig ME. ISPAD Clinical Practice Consensus Guidelines 2018: Other complications and associated conditions in children and adolescents with type 1 diabetes. Pediatr Diabetes. 2018 Oct;19 Suppl 27(Suppl 27):275-286.
4. Craig ME, Prinz N, Boyle CT, Campbell FM, Jones TW, Hofer SE, Simmons JH, Holman N, Tham E, Fröhlich-Reiterer E, DuBose S, Thornton H, King B, Maahs DM, Holl RW, Warner JT; Australasian Diabetes Data Network (ADDN); T1D Exchange Clinic Network (T1DX); National Paediatric Diabetes Audit (NPDA) and the Royal College of Paediatrics and Child Health; Prospective Diabetes Follow-up Registry (DPV) initiative. Prevalence of Celiac Disease in

52,721 Youth with Type 1 Diabetes: International Comparison Across Three Continents. Diabetes Care. 2017 Aug;40(8):1034-1040.
5. Castellaneta S, Piccinno E, Oliva M, Cristofori F, Vendemiale M, Ortolani F, Papadia F, Catassi C, Cavallo L, Francavilla R. High rate of spontaneous normalization of celiac serology in a cohort of 446 children with type 1 diabetes: a prospective study. Diabetes Care. 2015 May;38(5):760-6.
6. Poulain C, Johanet C, Delcroix C, Levy-Marchal C, Tubiana-Rufi N. Prevalence and clinical features of celiac disease in 950 children with type 1 diabetes in France. Diabetes Metab. 2007;33(6):453–8.
7. Al-Hussaini A, Sulaiman N, Al-Zahrani M, Alenizi A, El Haj I. High prevalence of celiac disease among Saudi children with type 1 diabetes: A prospective cross-sectional study. BMC Gastroenterol. 2012;12:180.
8. Baptista ML, Koda YK, Mitsunori R, Ioshii SO; Nisihara. Prevalence of celiac disease in Brazilian children and adolescents with type 1 diabetes mellitus. J Pediatr Gastroenterol Nutr. 2005;41(5):621–4.
9. Djuric Z, Stamenkovic H, Stankovic T, Milicevic R, Brankovic L, Ciric V, et al. Celiac disease prevalence in children and adolescents with type 1 diabetes from Serbia. Pediatr Int. 2010;52(4):579–83.
10. Boudraa G, Hachelaf W, Benbouabdellah M, Belkadi M, Benmansour FZ, Touhami M. Prevalence of coeliac disease in diabetic children and their first- degree relatives in west Algeria: Screening with serological markers. Acta Paediatr Suppl. 1996;412:58–60.
11. Sari S, Yeşilkaya E, Eğritaş O, Bideci A, Cinaz P, Dalgiç B. Prevalence of Celiac disease in Turkish children with type 1 diabetes mellitus and their non-diabetic first-degree relatives. Turk J Gastroenterol. 2010 Mar;21(1):34-8.
12. Ertekin V, Selimoglu MA, Doneray H, Orbak Z, Ozkan B. Prevalence of celiac disease in a sample of Turkish children and adolescents with type 1 diabetes mellitus. J Clin Gastroenterol. 2006 Aug;40(7):655-7.
13. Puñales M, Bastos MD, Ramos ARL, Pinto RB, Ott EA, Provenzi V, Geremia C, Soledade MA, Schonardie AP, da Silveira TR, Tschiedel B. Prevalence of celiac disease in a large cohort of young patients with type 1 diabetes. Pediatr Diabetes. 2019 Jun;20(4):414-420.
14. Wessels M, Velthuis A, van Lochem E, Duijndam E, Hoorweg-Nijman G, de Kruijff I, Wolters V, Berghout E, Meijer J, Bokma JA, Mul D, van der Velden J, Roovers L, Mearin ML, van Setten P. Raising the Cut-Off Level of Anti-Tissue Transglutaminase Antibodies to Detect Celiac Disease Reduces the Number of Small Bowel Biopsies in Children with Type 1 Diabetes: A Retrospective Study. J Pediatr. 2020 Aug; 223:87-92.
15. Unal E, Demiral M, Baysal B, Agın M, Devecioğlu EG, Demirbilek H, Özbek MN. Frequency of Celiac Disease and Spontaneous Normalization Rate of Celiac Serology in Children and Adolescent Patients with Type 1 Diabetes. J Clin Res Pediatr Endocrinol. 2020 Aug 21.
16. Robert ME, Crowe SE, Burgart L, Yantiss RK, Lebwohl B, Greenson JK, Guandalini S, Murray JA. Statement on Best Practices in the Use of Pathology as a Diagnostic Tool for Celiac Disease: A Guide for Clinicians and Pathologists. Am J Surg Pathol. 2018 Sep;42(9):e44-e58.
17. Ensari A. Gluten-sensitive enteropathy (celiac disease): controversies in diagnosis and classification. Arch Pathol Lab Med. 2010 Jun;134(6):826-36.
18. Rubio-Tapia A, Hill ID, Kelly CP, Calderwood AH, Murray JA; American College of Gastroenterology. ACG clinical guidelines: diagnosis and management of celiac disease. Am J Gastroenterol. 2013 May;108(5):656-76; quiz 677.
19. Walker MM, Ludvigsson JF, Sanders DS. Coeliac disease: review of diagnosis and management. Med J Aust. 2017 Aug 21;207(4):173-178. doi: 10.5694/mja16.00788. PMID: 28814219.
20. Koehler P, Wieser H, Konitzer K. Celiac disease and gluten: multidisciplinary challenges and opportunities. United States of America, Academic Press, 2014; 149-156.
21. Schwarzenberg SJ, Brunzell C. Type 1 diabetes and celiac disease: Overview and medical nutrition therapy. *Diabetes Spectrum* 2002;15(3):197-201.
22. Johnson AN, Skaff AN, Senesac L. Medication and supplement use in celiac disease. US Pharmacist 2014; 39(12): 44-48.
23. Kupper C, Higgins LA. Combining diabetes and gluten-free dietary management guidelines. Practical Gastroenterology, The Celiac Diet, 2007; 68-83.
24. Bascuñán KA, Vespa MC, Araya M. Celiac disease: understanding the gluten-free diet. *Eur J Nutr.* 2017;56(2):449-459.
25. Talwinder S. Kahlon, Mei-Chen M. Chiu. Teff, Buckwheat, Quinoa and Amaranth: Ancient Whole Grain Gluten-Free Egg-Free Pasta. Food and Nutrition Sciences, 2015, 6, 1460-1467.
26. Pham-Short A, Donaghue KC, Ambler G, Garnett S, Craig ME. Greater postprandial glucose excursions and inadequate nutrient intake in youth with type 1 diabetes and celiac disease. *Sci Rep* 2017; 7(1):1-7.
27. Foster-Powell K, Holt SH, Brand-Miller JC. International table of glycemic index and glycemic load values: 2002. *Am J Clin Nutr* 2002;76(1):5-56.
28. Camarca ME, Mozzillo E, Nugnes R, et al. Celiac disease in type 1 diabetes mellitus. *Ital J Pediatr* 2012; 38(1):1-7.
29. Kaur N, Bhadada SK, Minz RW, Dayal D, Kochhar R. Interplay between Type 1 Diabetes Mellitus and Celiac Disease: Implications in Treatment. Digestive Diseases 2018;36(6):399-408.
30. Rodbard D. Optimizing the Estimation of Carbohydrate-to-Insulin Ratio and Correction Factor. *Diabetes Technol Ther* 2018;20(2):94-97.
31. Bell KJ, Smart CE, Steil GM, Brand-Miller JC, King B, Wolpert HA. Impact of fat, protein, and glycemic index on postprandial glucose control in type 1 diabetes: implications for intensive diabetes management in the continuous glucose monitoring era. Diabetes Care 2015; 38(6):1008-1015.
32. Scaramuzza AE, Mantegazza C, Bosetti A, Zuccotti GV. Type 1 diabetes and celiac disease: The effects of gluten free diet on metabolic control. World J Diabetes 2013;4(4):130-134.

33. Paterson MA, Smart CEM, Lopez PE, Howley P, McElduff P, Attia J, Morbey C, King BR. Increasing the protein quantity in a meal results in dose-dependent effects on postprandial glucose levels in individuals with Type 1 diabetes mellitus. Diabet Med. 2017 Jun;34(6):851-854.
34. Jones AL. The gluten-free diet: fad or necessity? Diabetes Spectrum 2017;30(2):118-123.
35. Serena G, Camhi S, Sturgeon C, Yan S, Fasano A. The role of gluten in celiac disease and type 1 diabetes. Nutrients 2015; 7(9):7143-7162.
36. Smith LB, Kurppa K, & Agardh D. Further Support for Psychological Symptoms in Pediatric Celiac Disease. Pediatrics, 2019,144(4).
37. Butwicka A, Lichtenstein P, Frisén L, Almqvist C, Larsson H, & Ludvigsson JF. Celiac disease is associated with childhood psychiatric disorders: a population-based study. The Journal of Pediatrics,2017, 184, 87-93.
38. Erickson K., Freeborn D, Roper SO, Mandleco B, Anderson A, & Dyches T. Parent experiences raising young people with type 1 diabetes and celiac disease. Journal of pediatric nursing. 2015, 30(2), 353-363.

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

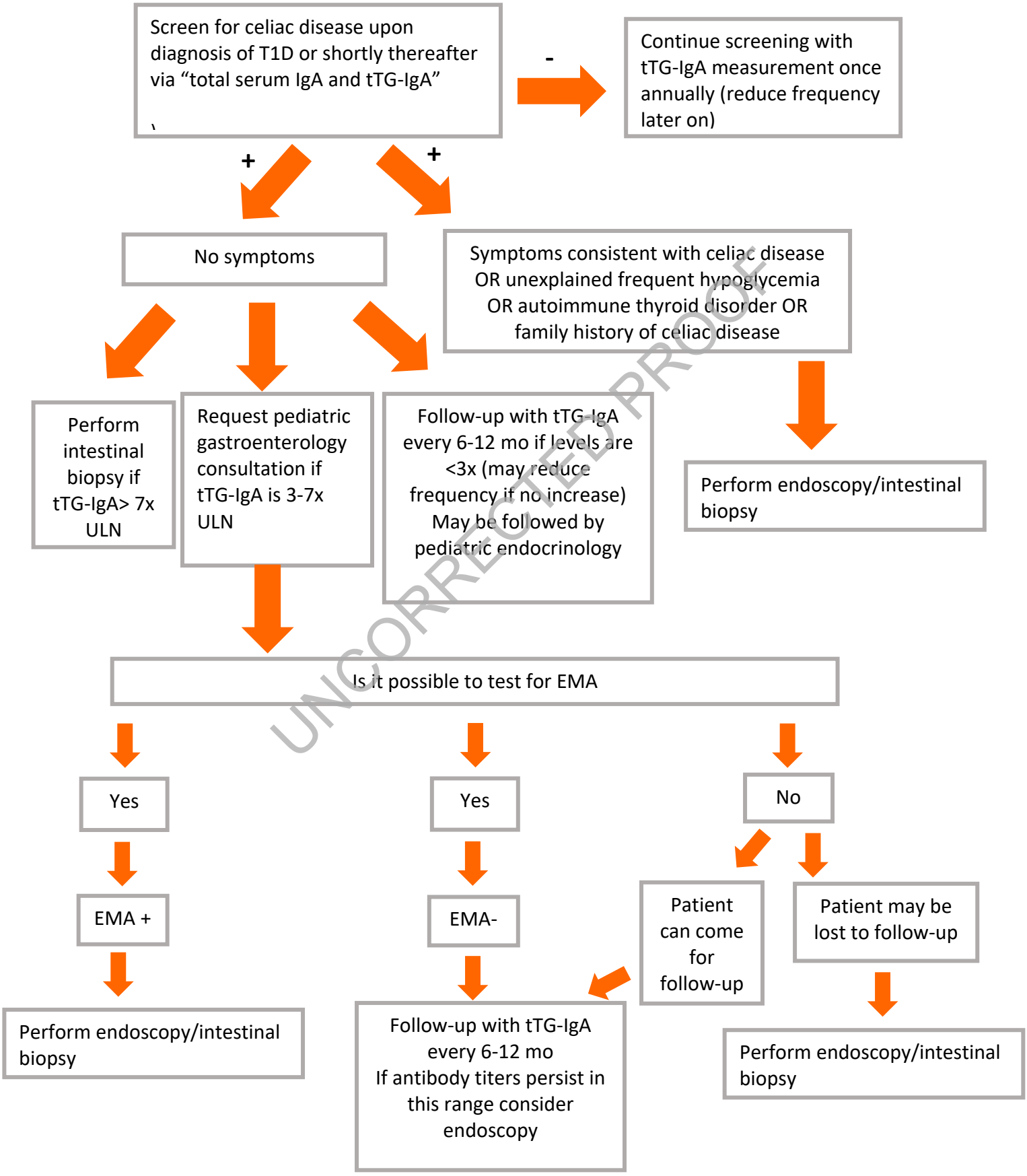

Table 1. Foods that should be avoided vs are allowed in a gluten-free diet

Types of 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, corn, 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.