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Is There a Predictive Factor for an Association with Autoimmune Glandular Disease in Children Diagnosed with Celiac Disease?

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What is already known on this topic?

Celiac disease (CD) can coexist with autoimmune glandular diseases (AGD) such as type 1 diabetes mellitus, Hashimoto's thyroiditis, Graves disease, and other autoimmune diseases. In the literature, there is little information about the clinical or laboratory characteristics of patients with CD and an accompanying AGD.

What this study adds?

In patients with CD there was no predictive value between gender, celiac symptoms, anti-tissue transglutaminase IgA antibody level, human leucocyte antigen type, and histopathological stage and the coexistence of AGD.

Abstract

Objective: A close relationship has been suggested between Celiac disease (CD) and glandular autoimmunity. The aim of this study was to determine the predictive factors for autoimmune glandular disease (AGD) in children with CD.

Methods: The study included 228 pediatric patients, diagnosed with CD between 2010 and 2019. The cases with AGD (Group 1) and those without AGD (Group 2) and the patients with type 1 diabetes mellitus (T1DM) (Group A) and those without T1DM (Group B) were retrospectively reviewed and compared in terms of clinical and laboratory features.

Results: AGD was detected in 8.8% (n = 20) of the patients: T1DM in 13 (65%), T1DM and Hashimoto's thyroiditis (HT) in 3 (15%), HT only in 2 (10%), T1DM and Graves disease (GD) in 1 (5%), and GD only in 1(5%). The mean age at the diagnosis of CD was significantly higher in Group 1 (10.93 ± 4.15 years) compared to Group 2 (8.10 ± 4.19 years) ($p < 0.05$) and also was significantly higher in Group A compared to Group B ($p < 0.05$). Most of the diagnoses of AGD were made before the diagnosis of CD and age was an effective factor. There was no difference between Group 1 and Group 2 and Group A and Group B in terms of gender, typical/atypical CD ratio, tissue transglutaminase IgA (TTGA) level, human leucocyte antigen (HLA)-DQ2 and/or HLA-DQ8 positivity rate, and histopathological stage.

Conclusion: Although patients with a diagnosis of co-existent CD and AGD were significantly older than patients with isolated CD, gender, celiac symptoms, TTGA level, HLA type, and histopathological stage had no predictive value for the coexistence of AGD in patients with CD.

Keywords: Autoimmune glandular disease, Celiac disease, child, diabetes mellitus type 1, Graves disease, Hashimoto's thyroiditis

Introduction

Celiac disease (CD) is a chronic inflammatory enteropathy, characterized by inflammation of the proximal intestine, which is triggered by exposure to gluten, a protein present in dietary wheat, barley, and rye, in genetically susceptible individuals (1).

CD is reported to coexist with autoimmune glandular diseases (AGD) including type 1 diabetes mellitus (T1DM), Hashimoto's thyroiditis (HT), Graves disease (GD), as well as with other autoimmune diseases (2). In various studies, the frequency of T1DM in children with CD has been reported to be 3.2-11.0% (3,4,5,6,7). The human leucocyte antigen

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(HLA) allotypes that are risk factors for CD and T1DM are similar. HLA-DQ2 and HLA-DQ8 genotypes are found to be positive in 40% of the general population, while these are present in approximately 90% of individuals with a diagnosis of T1DM and 100% of individuals with a diagnosis of CD (8).

The prevalence of HT, which is the most common autoimmune thyroid disease (AITD), was found to be 1.2-3% and the prevalence of GD was reported to be 0.02%, in the pediatric age group (9,10). The frequency of AITD is higher in children with CD, and it has been reported to have a frequency of 2.4-41.4% in different populations (11). The coexistence of CD and an AITD is explained by a common genetic predisposition (12). In many studies it has been suggested that this relationship is due to similar HLA haplotypes or the defects of genes encoding the autoimmune-predisposing cytotoxic T-lymphocyte-associated antigen-4 (13,14,15).

The aim of this study was to determine the predictive factors for AGD in children with a pre-existing diagnosis of CD.

Methods

In this retrospective study, the files of 228 patients aged between 0-18 years who were diagnosed with CD between 2010 and 2019 in the Pediatric Gastroenterology Clinic of İnönü University Medical Faculty, were reviewed. Age at diagnosis, gender, symptoms at the time of diagnosis (typical/atypical), anthropometric findings [body weight, height, body mass index (BMI) and their respective standard deviation (SD) scores (SDS)], tissue transglutaminase IgA antibody (TTGA) levels, the presence of HLA DQ2 and HLA DQ8 genotypes, histopathological stage by endoscopic biopsy, and accompanying AGD's were recorded.

The diagnosis of CD was made according to the revised criteria of the European Committee of Pediatric Gastroenterology, Hepatology and Nutrition. The patients were considered positive if titration of TTGA increased 3 times the upper limit of normal values (18 Ru/mL). Histopathological staging was performed using the Modified Marsh-Oberhuber Classification, and patients with stage 2 and above were considered to have CD. The patients were divided as typical and atypical, according to the complaints at the time of diagnosis (16). The diagnosis of T1DM was made with a fasting blood sugar of 126 mg/dL and above, a postprandial blood sugar of 200 mg/dL and above, and a HbA1c value above 6.5% (17). The diagnosis of HT was made with the positivity of thyroid autoantibodies (anti-thyroglobulin Ab and/or anti-thyroid peroxidase antibody) in the patient (18). The diagnosis of GD was made with high free T3 and free T4 levels, low TSH level and positive anti-TSH receptor antibody (19).

Clinical and laboratory findings of the patients with AGD (Group 1) and those without AGD (Group 2) and the patients with T1DM (Group A) and those without T1DM (Group B) were compared.

Ethical approval (no: 2020/1351, date: 01.06.2021) for the study was obtained from the Scientific Research Ethics Committee of İnönü University and the study was carried out in accordance with the principles of the Helsinki Declaration.

Statistical Analysis

Statistical analyses of the data were performed using Statistical Package for the Social Sciences, version 20.0 (IBM Inc., Armonk, NY, USA). Normality of distribution of the data were examined using visual (histogram and probability charts) and analytical methods (Kolmogorov-Smirnov/Shapiro-Wilk tests). Descriptive analyzes were expressed as percentage, mean ± SD (for normally distributed data), and median (minimum-maximum) (for non-normally distributed data). Normally distributed numerical data were compared by using independent samples t-test and non-normally distributed numerical data were compared using the Mann-Whitney U test. Pearson's chi-square and Fisher's Exact tests were used to compare the frequency rates of categorical variables. A value of $p < 0.05$ was considered statistically significant.

Results

The mean age at diagnosis of CD of the 228 patients included in the study was 8.35 ± 4.25 years and 69.3% (n = 158) of the patients were female. Most of the patients (n = 174, 76.3%) presented with atypical findings (short stature and anemia). AGD was detected in 8.8% (n = 20) of the patients, including T1DM in 13 (65%), T1DM and HT in 3 (15%), HT only in 2 (10%), T1DM and GD in 1 (5%), and GD only in 1 (5%). The mean age of the CD patients at the time of diagnosis of T1DM was 9.24 ± 4.53 years, and similarly the mean age of diagnosis of HT was 10.71 ± 2.57 years. GD was diagnosed when both patients were over the age of 15 years. T1DM was diagnosed before CD in ten patients, concurrently with CD in six patients, and after CD in only one patient. The diagnosis of HT was made before the diagnosis of CD in three patients, and after the diagnosis of CD in two patients. The diagnoses of GD were made simultaneously with CD.

The average age of diagnosis of CD was 10.93 ± 4.15 years

in cases with AGD (Group 1) but was significantly younger in patients without AGD (Group 2) at 8.10 ± 4.19 years ($p < 0.05$). There was no difference between Group 1 and Group 2 in terms of gender, typical/atypical CD ratio, serum TTGA level, HLA-DQ2 or HLA-DQ8 positivity rate, and histopathological stage. The mean weight SDS, height SDS, and BMI SDS were significantly higher in Group 1 compared to Group 2 ($p < 0.001$, $p = 0.003$ and $p = 0.01$, respectively) (Table 1).

The mean age at diagnosis of CD was 10.62 ± 4.09 years in patients with T1DM (Group A), and 8.17 ± 4.22 years in those without T1DM (Group B). The mean age at diagnosis of CD was significantly higher in Group A ($p < 0.05$). There was no difference between Group A and Group B in terms of gender, frequency of the presece of typical or atypical CD, serum TTGA level, HLA-DQ2 or HLA-DQ8 positivity rate, and histopathological stage. However, the mean weight SDS, height SDS, and BMI SDS were significantly higher in Group A compared to Group B ($p < 0.001$, $p = 0.006$ and $p = 0.001$, respectively) (Table 2).

The positivity of both HLA-DQ2 and HLA-DQ8 genotypes was approximately twice as frequent in Group 1 (22.2%) compared to Group 2 (11.2%), butthis was not statistically significant. Similarly, the positivity of both HLA-DQ2 and HLA-DQ8 genotypes was 26.7% in Group A, and was more than twice as frequent as in Group B (11%), but again the difference was not statistically significant (Tables 1, 2).

Discussion

There are studies reporting that the prevalence of autoimmune diseases are higher in children with CD compared to the normal population. Ventura et al. (20), found the prevalence of autoimmune disease was 14% in 909 Italian patients between the ages of 10 and 25 with a diagnosis of CD and 2.8% in controls ($p < 0.001$). In the same study, the frequency of AGD was 6.3%, and the most common autoimmune disease was T1DM (3.9%) (17). In a study conducted in Iran, it was reported that 15.4% of 130 pediatric patients diagnosed with CD had T1DM and 7.7% had hypothyroidism (5). In a study conducted in India, on 363 patients with CD aged between 2 and 50 years (mean 19 years), it was found that T1DM was present in 3.5%, hypothyroidism in 3%, and GD in 0.2% (21). In a study conducted in Turkey, it was reported that AGD was present in 8.7% of 148 pediatric CD patients (4% T1DM, 4.7% HT) (4). Another study conducted in Turkey reported that anti-thyroid antibodies were negative in all of the pediatric patients with CD, but after 2-3 years, 16.4% (11/67) of the patients became positive. It has been reported that only 3/11 (27.2%) CD patients with positive anti-thyroid antibodies have clinical hypothyroidism (22). In our study, the prevalence of AGD in pediatric patients with CD was 8.8%, and, as previously reported, the most common accompanying diseases were T1DM (7.5%) and HT (2.2%). In our study, the prevalence of T1DM detected in children with CD was relatively high compared to the prevalence in the general pediatric population in Turkey (0.075%) (23). Again in our study, the prevalence of GD in children with CD was 0.9% and this rate was found to be significantly higher compared to the general pediatric population (0.02%), while the prevalence of HT was similar to the general pediatric population. Although the rates vary according to

Table 1. Comparison of CD patients with (Group 1) or without (Group 2) an accompanying autoimmune disease

	Group 1 (n = 20)	Group 2 (n = 208)	p
Age	10.93 ± 4.15	8.10 ± 4.19	0.004
Gender	80% female 20% male	68.3% female 31.7% male	0.277
Clinical findings	90% atypical 10% typical	75.4% atypical 24.6% typical	0.174
Weight SD	-0.77 (-2.11-1.74)	-1.6 (-5.15-7.8)	0.001
Height SD	-0.77 (-3.2-1.08)	-1.73 (-2.5-1.06)	0.003
BMI SD	-0.19 (-3-1.4)	-0.82 (-8.17-2.26)	0.01
TTGA level	100 (54.9-300)	100 (54-300)	0.831
Positive HLA DQ2	88.9%	86.7%	1.000
Positive HLA DQ8	27.8%	23.0%	0.771
Positive HLA DQ2&DQ8	22.2% (4/18)	11.2% (21/188)	0.245
Hystopathological examination (Marsh-Oberhuber staging distribution)	10.0% type 2 30.0% type 3A 40.0% type 3B 20.0% type 3C	5.3% type 2 31.7% type 3A 43.3% type 3B 19.7% type 3C	0.856

SD: standard deviation, BMI: body mass index, HLA: human leucocyte antigen, CD: Celiac disease, TTGA: tissue transglutaminase IgA

populations, it has been reported that the prevalence of AGD is higher in children with CD, and T1DM or AITD are the most common AGDs. Moreover, the prevalence of CD in children with T1DM was higher (0.6-16.4%) than the general population (3). In these patients, CD is often asymptomatic or presents with atypical symptoms. As delayed diagnosis increases morbidity, it is recommended to screen for CD in children with T1DM (16).

In the literature, it was not specified which disease was diagnosed first in cases with concomitant CD and AGD. In our study, all of the cases of accompanying CD were diagnosed simultaneously with T1DM or as a result of screening performed following the diagnosis of T1DM. It was thought that, this situation caused the frequency of T1DM to be found misleadingly high in CD. In contrast, Nijhawan et al. (21) reported that in 10 of 13 (76.9%) patients with accompanying T1DM and CD, CD was diagnosed before T1DM and T1DM was detected later during screening. In order to clarify this issue, there is a need for prospective studies examining the frequency of AGD in patients diagnosed with CD.

More than one autoimmune disease can be present in CD patients. Ventura et al. (20), found that multiple autoimmune diseases (coexistence of AGD and other autoimmune diseases like dermatitis herpetiformis, alopecia areata, psoriasis etc.) were present in 1.7% (16/909) of the patients with CD, and multiple AGD were present in only three patients. In our study, T1DM and HT were found to accompany CD in three patients and T1DM and GD were found concurrently in one patient with CD.

In the literature, although the frequency of AGD in patients with CD has been reported in various studies, there is little information about the clinical or laboratory characteristics of patients with an accompanying AGD. Ventura at al. (20), reported that, the frequency of accompanying autoimmune diseases (T1DM and AITD) increased as the age of diagnosis increased in patients with CD. They reported that, this rate was four times higher in children diagnosed with CD after 10 years of age compared to those who were diagnosed at the age of two years. They reported that the age at the time of diagnosis is the only significant predictor of the development of an autoimmune disease ($r = 0.3$; $p < 0.001$) (17). In a study conducted by Rasheed et al. (24), it was reported that the mean age of the children with an accompanying AITD at the time of the diagnosis of CD was higher compared to those without AITD. However, the timing of diagnosis was not specified in either of the studies, so whether CD preceeded AGD was not clear. In our study, consistent with the above mentioned studies, the mean age at the time of diagnosis of CD was found to be higher in cases with an AGD. However, as most of the patients in our cohort were diagnosed with CD simultaneously with AGD or after the diagnosis of in asymptomatic cases, there may be some bias in the age of diagnosis which may be misleadingly high. In a prospective study conducted by Kalyoncu and Urganci (22), it was reported that CD patients with positive antithyroid antibodies were significantly younger compared to patients with negative antithyroid antibodies.

In our study, no difference was found between the CD patients with an AGD or T1DM and those without in terms of gender, symptoms on admission, serum TTGA levels, HLA allotypes, and histopathological CD stage. In two studies conducted previously, it was found that gender had no effect on the frequency of an accompanying autoimmune

Table 2. Comparison of CD patients with (Group A) or without (Group B) an accompanying T1DM

	Group A (n = 17)	Group B (n = 211)	p
Age	10.62 ± 4.09	8.17 ± 4.22	0.022
Gender	76.5% female 23.5% male	68.7% female 31.3% male	0.505
Clinical findings	88.2% atypical 11.8% typical	75.7% atypical 24.3% typical	0.372
Weight SD	-0.56 (-2 to 1.74)	-1.6 (-5.15 to 7.8)	< 0.001
Height SD	-0.77 (-3.2 to 1.08)	-1.73 (-2.5 to 1.06)	0.006
BMI SD	-.08 (-1.22 to 1.4)	-0.84 (-8.17 to 2.26)	0.001
TTGA level	100 (54.9-300)	100 (54-300)	0.799
Positive HLA DQ2	93.3%	86.4%	0.698
Positive HLA DQ8	33.3%	22.6%	0.350
Positive HLA DQ2&DQ8	26.7% (4/15)	11.0% (21/191)	0.091
Hystopathological examination (Marsh-Oberhuber staging distribution)	11.8% type 2 29.4% type 3A 35.3% type 3B 23.5% type 3C	5.2% type 2 31.8% type 3A 43.6% type 3B 19.4% type 3C	0.66

T1DM: type 1 diabetes mellitus, SD: standard deviation, BMI: body mass index, HLA: human leucocyte antigen, CD: Celiac disease, TTGA: tissue transglutaminase IgA

disease (20,22,24). To the best of our knowledge, there are no studies evaluating other parameters. In our study, anthropometric measurements of the patients were also evaluated. The higher mean values of weight, height and BMI in CD patients with an accompanying AGD or T1DM can be explained by the fact that the mean age at the time of diagnosis was higher in these groups. The higher mean weight SDS, height SDS, and BMI SDS in groups with accompanying AGD or T1DM compared to those without may be due to the higher but non-significant rate of patients presenting with atypical clinical presentation in these groups. Especially in patients with T1DM, the diagnosis of CD was mostly made by screening during or after the diagnosis of T1DM. Therefore, we hypothesize that anthropometric findings were less affected in these groups.

It is known that autoimmune diseases are associated with alleles in genes in the major histocompatibility complex, especially DQ2 (DQA1*05/ DQB1*02) and DQ8 (DQA1*0301/ DQB*302) (25). It has been reported that the HLA DQ2 and/or DQ8 locus is the most important predictor of susceptibility to T1DM (8). In the literature, the presence of HLA-DQ2/ HLA-DQ8 alleles or HLA-DR3/HLA-DR4 alleles has been reported as a risk factor for accompanying T1DM in CD patients (26). In our study, DQ2 was found to be positive in 93.3% of the patients with T1DM. HLA-DQ2 and HLA-DQ8 genotypes were found to be present together, twice as often in the group with T1DM compared to the group without T1DM and in the group with AGD compared to the group without AGD, but the frequency difference was not statistically significant. The lack of a significant difference is likely due to the small number of patients.

Understanding of the likelihood of AGDs that may accompany CD and screening for CD in these patients will facilitate early diagnosis and treatment. It has been reported that a gluten-free diet improves the metabolic control of diabetes, has a protective effect on the development of vascular complications, and prevents growth retardation in patients with T1DM and CD (27). In addition, increasing awareness of other autoimmune diseases that may accompany CD in children is important for their early diagnosis and treatment.

Study Limitations

The retrospective nature of our study and small sample size are limitations, and prospective studies with a larger number of patients are needed.

Conclusion

In our study, although patients with a diagnosis of co-existent CD and AGD were significantly older than patients with isolated CD, gender, celiac symptoms, TTGA level, HLA type, and histopathological stage were not found to have a predictive role in predicting the presence of AGD in CD patients. There is a need for prospective studies in larger pediatric patient populations.

Ethics

Ethics Committee Approval: Ethical approval (no: 2020/1351, date: 01.06.2021) for the study was obtained from the Scientific Research Ethics Committee of İnönü University and the study was carried out in accordance with the principles of the Helsinki Declaration.

Informed Consent: Retrospective study.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: Fatma İlknur Varol, Mukadder Ayşe Selimoğlu, Şükrü Güngör, Concept: Fatma İlknur Varol, Emine Çamtosun, Design: Fatma İlknur Varol, Emine Çamtosun, Data Collection or Processing: Fatma İlknur Varol, Emine Çamtosun, Analysis or Interpretation: Fatma İlknur Varol, Mukadder Ayşe Selimoğlu, Şükrü Güngör, Literature Search: Fatma İlknur Varol, Emine Çamtosun, Writing: Fatma İlknur Varol, Emine Çamtosun, Mukadder Ayşe Selimoğlu, Şükrü Güngör.

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References

1. Fasano A. Clinical presentation of celiac disease in the pediatric population. Gastroenterology 2005;128(4 Suppl 1):68-73.
2. Villano MJ, Huber AK, Greenberg DA, Golden BK, Concepcion E, Tomer Y. Autoimmune thyroiditis and diabetes: dissecting the joint genetic susceptibility in a large cohort of multiplex families. J Clin Endocrinol Metab 2009;94:1458-1466. Epub 2009 Jan 13
3. Ventura A, Neri E, Ughi C, Leopaldi A, Città A, Not T. Gluten-dependent diabetes-related and thyroid-related autoantibodies in patients with celiac disease. J Pediatr 2000;137:263-265.
4. Güven B, Sağ E, Çakır M. Is Clinical Spectrum of Celiac Disease Changing in Children? Turkiye Klinikleri J Pediatr 2020;29:133-138.
5. Dehbozorgi M, Honar N, Ekramzadeh M, Saki F. Clinical manifestations and associated disorders in children with celiac disease in southern Iran. BMC Pediatr 2020;20:256.
6. Balamtekin N, Uslu N, Baysoy G, Usta Y, Demir H, Saltik-Temizel IN, Ozen H, Gürakan F, Yüce A. The presentation of celiac disease in 220 Turkish children. Turk J Pediatr 2010;52:239-244.
7. Dinler G, Atalay E, Kalayci AG. Celiac disease in 87 children with typical and atypical symptoms in Black Sea region of Turkey. World J Pediatr 2009;5:282-286. Epub 2009 Nov 13
8. Camarca ME, Mozzillo E, Nugnes R, Zito E, Falco M, Fattorusso V, Mobilia S, Buono P, Valerio G, Troncone R, Franzese A. Celiac disease in type 1 diabetes mellitus. Ital J Pediatr 2012;38:10.

9. Binay Ç, Şimşek E. Hashimoto Thyroiditis In Children And Adolescents. Osmangazi Journal of Medicine 2016;38:1-8.
10. Huang SA, LaFranchi SH. Graves' disease. In: Kliegman RM, Stanton BF, St. Geme III JW, Schor NF, Behrman RE (eds). Nelson textbook of pediatrics. 20th ed. Philadelphia, Elsevier, Inc, 2016;2681-2684.
11. Minelli R, Gaiani F, Kayali S, Di Mario F, Fornaroli F, Leandro G, Nouvenne A, Vincenzi F, De' Angelis GL. Thyroid and celiac disease in pediatric age: a literature review. Acta Biomed 2018;89:11-16.
12. Ch'ng CL, Jones MK, Kingham JGC, "Celiac disease and autoimmune thyroid disease. Clin Med Res 2007;5:184-192.
13. King AL, Moodie SJ, Fraser JS, Curtis D, Reid E, Dearlove AM, Ciclitira PJ. Coeliac disease: investigation of proposed causal variants in the CTLA4 gene region. Eur J Immunogenet 2003;30:427-432.
14. Chistiakov DA, Turakulov RI. CTLA-4 and its role in autoimmune thyroid disease. J Mol Endocrinol 2003;31:21-36.
15. Hunt KA, McGovern DP, Kumar PJ, Ghosh S, Travis SP, Walters JR, Jewell DP, Playford RJ, van Heel DA. A common CTLA4 haplotype associated with coeliac disease. Eur J Hum Genet 2005;13:440-444.
16. Husby S, Koletzko S, Korponay-Szabó IR, Mearin ML, Phillips A, Shamir R, Troncone R, Giersiepen K, Branski D, Catassi C, Lelgeman M, Mäki M, Ribes-Koninckx C, Ventura A, Zimmer KP; 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;54:136-160.
17. Vurallı D, Kandemir N. Diyabetin Tanımı ve Sınıflandırılması. Darenderliler F, Aycan Z, Kara C, Özen S, Eren E (eds). Çocuk Endokrinoloji ve Diyabet. İstanbul. İstanbul Tıp Kitabevleri, 2021;1308-1321.
18. Kara C. Troid Gelişimi Fizyolojisi ve İşlevlerinin Değerlendirilmesi. Darenderliler F, Aycan Z, Kara C, Özen S, Eren E (eds). Çocuk Endokrinoloji ve Diyabet. İstanbul. İstanbul Tıp Kitabevleri, 2021;1058-1098.
19. Esen İ. Tirotoksikoz. Darenderliler F, Aycan Z, Kara C, Özen S, Eren E (eds). Çocuk Endokrinoloji ve Diyabet. İstanbul. İstanbul Tıp Kitabevleri, 2021;1170-1181.
20. Ventura A, Magazzu G, Greco L. Duration of exposure to gluten and risk for autoimmune disorders in patients with celiac disease. SIGEP Study Group for Autoimmune Disorders in Celiac Disease. Gastroenterology 1999;177:297-303.
21. Nijhawan S, Katiyar P, Nagaich N, Saradava V, Nijhawan M, Gupta G, Mathur A, Sharma R, Nepalia S. Prevalence of associated disorders in Indian patients with celiac disease. Indian J Gastroenterol 2013;32:330-334. Epub 2013 Jul 30
22. Kalyoncu D, Urganci N. Antithyroid antibodies and thyroid function in pediatric patients with celiac disease. Int J Endocrinol 2015;2015:276575. Epub 2015 Feb 19
23. Yeşilkaya E, Cinaz P, Andıran N, Bideci A, Hatun Ş, Sarı E, Türker T, Akgül Ö, Saldır M, Kılıçaslan H, Açıkel C, Craig ME. First report on the nationwide incidence and prevalence of Type 1 diabetes among children in Turkey. Diabet Med 2017;34:405-410. Epub 2016 Feb 12
24. Rasheed J, Hassan R, Khalid M, Zafar F. Frequency of autoimmune thyroiditis in children with Celiac disease and effect of gluten free diet. Pak J Med Sci 2020;36:1280-1284.
25. Neuhausen SL, Steele L, Ryan S, Mousavi M, Pinto M, Osann KE, Flodman P, Zone JJ. Co-occurrence of celiac disease and other autoimmune diseases in celiacs and their first-degree relatives. J Autoimmun 2008;31:160-165. Epub 2008 Aug 8
26. Hagopian W, Lee HS, Liu E, Rewers M, She JX, Ziegler AG, Lernmark Å, Toppari J, Rich SS, Krischer JP, Erlich H, Akolkar B, Agardh D; TEDDY Study Group. Co-occurrence of Type 1 Diabetes and Celiac Disease Autoimmunity. Pediatrics 2017;140:e20171305. Epub 2017 Oct 10
27. Bakker SF, Tushuizen ME, von Blomberg ME, Mulder CJ, Simsek S. Type 1 diabetes and celiac disease in adults: glycemic control and diabetic complications. Acta Diabetol 2013;50:319-324. Epub 2012 Apr 27