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Research Article

Determination of the Frequency of Celiac and Autoimmune Thyroid Diseases in Children and Adolescents Diagnosed with Type 1 Diabetes Mellitus

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Abstract

Aim: Celiac disease (CD) and autoimmune thyroid disease (AITD) are more common in individuals with Type 1 diabetes mellitus (T1DM). Hypothyroidism; has been associated with increased risk of hypoglycemia, reduced growth, and untreated CD with reduced bone mineral density has been associated with skeletal problems. It was aimed to screen the frequency of children and adolescents with T1DM in terms of CD and AITD.

Material and Method: The patients diagnosed with T1DM in July 2015-March 2022 were retrospectively analyzed. The patients' age, gender, age at diagnosis, anti-TPO, anti-TG, Islet Cytoplasmic Antibodies (ICA), Insulin Autoantibodies (IAA), Glutamic Acid Decarboxylase (GADA) antibodies and accompanying autoimmune disease were investigated.

Results: Chronological age was 12.5±4.4 (2.5-21.3), diagnosis of T1DM age 8.5±4.3 (1.0-17.5), duration of diabetes 4.0±3, 199 patients with T1DM aged 5 (0.0-18.1) years were included. 52.3% (n=104) of the cases were female. While the frequency of CD is 23.2% (n=10), the presence of anti-TPO and anti-TG antibodies is 6.9% (n=3) in patients whose diabetes diagnosis age is less than 5 years. Both CD and the presence of thyroid autoantibodies were more common in girls (73.3%, 68%).

Conclusion: We found that the frequency of CD and AITD in our patients with T1DM was higher than in the general population, the frequency of CD increased in patients with a younger age at diagnosis of T1DM, anti-TPO antibodies was observed with advancing age at diagnosis, and both conditions were more common in females.

Keywords: Adolescent, autoimmune thyroiditis, celiac disease, child, type 1 diabetes

INTRODUCTION

Type 1 diabetes mellitus (T1DM) is an autoimmune disease that specifically results in insulin deficiency as a result of an exaggerated immune response to β-cell autoantigens. The most common autoimmune diseases in patients with T1DM; autoimmune thyroid disease (AITD) is followed by Celiac disease (CD) (1-6).

Graves disease and Hashimoto's thyroiditis (HT) are the most common autoimmune thyroid diseases (7). Hyperthyroidism is more common in Graves disease and hypothyroidism is more common in HT. Genetic predisposition and environmental factors play a role in the etiology of autoimmune thyroid disease (8,9). While the prevalence of AITD in children and adolescents is 0.3-1.1%, it has been determined that it is seen at a higher rate in children with T1DM and this rate is approximately 3-8% (10). The prevalence of AITD increases up to 20% with age, and hypothyroidism is observed in most of the patients (11).

Celiac disease is an autoimmune small bowel disease caused by persistent sensitivity to gluten found in wheat, rye and barley in genetically susceptible individuals (12). CD is more common in individuals with T1DM than in the general population, and its prevalence is reported to be

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1-10% in children and adolescents with T1DM (13). The risk of celiac disease increases as the age at diagnosis of diabetes decreases, and this risk is more pronounced especially in children with T1DM under the age of 5 (14).

Hypothyroidism has been associated with an increased risk of hypoglycemia and decreased growth, while untreated CD has been associated with skeletal problems with reduced bone mineral density. In this study, determining the frequency of CD and AITD in children and adolescents followed up with the diagnosis of T1DM; it was aimed to evaluate the relationship between growth, glycemic control, age, gender and puberty. It is necessary for the patient to screen for comorbidities and to diagnose and treat them at an early stage.

MATERIAL AND METHOD

The patients diagnosed with T1DM in July 2015-March 2022 were retrospectively examined. Age, gender, age at diagnosis, duration of T1DM, presence of antithyroid peroxidase (TPO Ab), antithyroglobulin (TG Ab) antibodies, and the concomitant autoimmune disease were investigated.

Ethics committee approval for the study was obtained from the Hitit University Faculty of Medicine Clinical Research Ethics Committee decision no: 2022-27 and taken on:31/03/2022.

Statistical Analysis

Statistical analysis IBM SPSS Statistics It was carried out with the software for Windows 22.0. Pearson's chi-square test or Fisher's exact test was used to compare qualitative variables when the expected frequency was less than 5 cells. The Shapiro-Wilk test was used to determine whether the numerical variables were normally distributed, and the t-test in independent groups was used to compare the normally distributed variables in 2 groups used. Mann Whitney U test was used to compare the non-normally distributed variables in 2 groups. A p value of <0.05 was considered statistically significant.

RESULTS

199 patients with T1DM were included. Mean chronological age was 12.5±4.4 (2.5-21.3) years, mean diabetes duration was 4.0±3.5 (0.0-18.1), and 52.3% (n=104) of the study were female. While 84.9% (n=169) of the patients had no accompanying disease, 7.5% (n=15) had CD, 12.8% (n=25) had TPO Ab, 6.5% (n=13) had TG Ab, CD and AITH were present in 0.5% (n=1). The ages at diagnosis of the cases are shown in Table 1.

While the frequency of CD is 23.2% (n=10), the presence of TPO Ab and TG Ab were 6.9% (n=3) in those with diabetes diagnosis younger than 5 years. The frequency of CD was 3.3% (n=5), the presence of TPO Ab was 14.1% (n=22), and the presence of TG Ab was 6.4% (n=10) in those who were 5 years or older (Table 2). When the gender distribution is examined; the female sex ratio was 73.3% (n=11) in CD, 68% (n=17) in patients with TPO Ab, and 61.5% (n=8) in patients with TG Ab.

Table 1. T1DM, CD diagnosis and thyroid autoantibody detection ages of the cases

Diagnosis ages	n (%)	mean±SD	min-max
T1DM diagnosis age (years)	199 (100)	8.5±4.3	1.0-17.5
Celiac disease diagnosis age (years)	15 (7.5)	6.6±3.8	2.0-14.7
Age at detection of anti-TPO (years)	25 (12.8)	10.9±3.2	4.9-14.0
Anti-TG detection age (years)	13 (6.5)	10.1±3.3	4.9-13.9

Table 2. Frequency of CD and thyroid autoantibodies detection according to T1DM diagnosis age group

		T1DM diagnosis age		
		≤5 years (n=43) (n) (%)	>5 years (n=156) (n) (%)	Total (n=199) (n) (%)
Celiac disease	Yes	10 (23.2)	5 (3.3)	15 (7.5)
	No	33 (76.8)	151(96.7)	184 (92.5)
TPO Ab	Yes	3 (6.9)	22 (14.1)	25 (12.8)
	No	40 (93.1)	134 (85.9)	174 (87.2)
TG Ab	Yes	3 (6.9)	10 (6.4)	13 (6.5)
	No	40 (93.1)	146 (93.6)	186 (93.5)

DISCUSSION

We found that 7.5% of our patients with T1DM had CD, 12.8% had TPO Ab, 6.5% had TG Ab, and 0.5% had CD and AITH. In addition, while the frequency of CD is 23.2% and the presence of TPO and TG antibodies is 6.9% in patients with T1DM diagnosis age younger than 5 years; the frequency of CD is 3.3%, the presence of TPO Ab is 14.1%, and the presence of TG Ab antibody is 6.4% in diabetes diagnosis age were 5 years or older.

Patients diagnosed with T1DM, an autoimmune disease that results in insulin deficiency as a result of an exaggerated immune response to β-cell autoantigens, are more likely to develop other autoimmune diseases than the general population (15). While it is recommended to

screen for common conditions such as AITD and CD at regular intervals in T1DM patients, it is recommended to screen for other less common autoimmune diseases in the presence of symptoms (16).

Current guidelines of the American Diabetes Association (ADA) recommend testing for antithyroid peroxidase, antithyroglobulin antibody and thyroid function tests in children and adolescents immediately after diagnosis of T1DM. If thyroid function tests are normal, it is recommended to be checked every 1-2 years. if the patient develops symptoms such as thyroid dysfunction, thyromegaly, abnormal growth rate or an unexplained glycemic variation should be checked earlier (17). The International Pediatric and Adolescent Diabetes Association (ISPAD) recommends screening for thyroid stimulating hormone (TSH) and anti-TPO Ab in the diagnosis of diabetes, and then every two years in asymptomatic individuals and in the absence of goiter or in the absence of thyroid autoantibodies, otherwise more frequent evaluations should be made (18).

Celiac disease develops against gluten found in wheat, rye and barley; It is an autoimmune enteropathy that occurs in genetically predisposed individuals and is characterized by inflammation of the small intestine, villous atrophy and malabsorption (19). The clinical picture of CD may be silent in the absence of gastrointestinal signs or symptoms, so it is important to be screened (20). If there are no symptoms in children with T1DM, the ADA recommends measuring Tissue Transglutaminase Immunoglobulin A level at the time of diagnosis and then repeating it 2 and 5 years later (17). It is recommended by ISPAD that screening should be performed during the diagnosis of T1DM and every 1-2 years there after (18).

The incidence of T1DM does not differ significantly between females and males. In a study conducted in our country, it was determined that 51.4% of the cases were male and 48.6% were female (21). In our study, the gender distribution of the cases was found to be 52.3% female and 47.7% male, consistent with the literature. Studies have reported that the frequency of autoimmune thyroiditis in children and adolescents with T1DM varies between 7.3% and 21.6% (22-25). In our country, the frequency of AITD in children and adolescents with T1DM was found to be 6.2% (26), 11.9% (27), 12% (28) and 12.8% (29). We found the presence of TPO Ab in 12.8% of our cases, and the presence of TG Ab in 6.5% of our cases, consistent with the data of our country. In studies involving children with T1DM, the frequency of thyroid autoantibodies was found to be high in females (11,22,23,27), and Hashimoto's thyroiditis occurs mostly after puberty begins (22,23). Consistent with this finding; in our study, the female sex ratio was found to be 68% in patients with TPO Ab and 61.5% in patients with TG Ab. The mean age of TPO Ab detection was 10.9 years, and the mean age of TG Ab detection was 10.1 years in our cases. It was observed that the presence of autoantibodies increased with age (The presence of TPO and TG antibodies was 6.9% in those with diabetes diagnosis age 5 years and younger, while the presence of TPO Ab in those with diagnosis age over 5 years was 14.1%, TG Ab presence was found to be 6.4%). Similar to our study, many studies have found that the frequency of thyroid autoantibodies increases as age and duration of diabetes increase (30). The presence of thyroid autoimmunity significantly increases the risk of deterioration in thyroid functions in individuals with T1DM, and this risk is higher in children than in adults (10). However, the low number of patients in need of treatment in children with T1DM and Hashimoto's thyroiditis suggests that screening should be evaluated in terms of cost-benefit (27).

CD and T1DM are autoimmune diseases that share common genetic variants and are both chronic, and similar to other autoimmune diseases, the combination of genetic susceptibility and environmental factors play a role in the formation of both diseases (31). Compared to the general population, the children with T1DM have 15 times more celiac serology positivity and up to 10 times more biopsy-proven CD. Prevalence of biopsy-proven CD varies between 1.6% and 16.4% (32). In our study, the frequency of biopsy-proven CD was found to be 7.5%, which is similar to the rate of 6.7% found in the study conducted by Esen et al. in our country (29). The substantial genetic overlap between celiac disease and T1DM explains the increased prevalence of CD in T1DM patients compared with healthy individuals. Polymorphisms related to the HLA-II-DQ and DR alleles are responsible for the risk of co-development of T1DM and CD. Almost 90% of celiac patients have HLA-DQ2 or HLADQ8 with the DR3 haplotype, which is also shared 60-70% by T1DM (33). The genetic overlap between T1DM and CD (including HLA and non-HLA) highlights common pathogenic mechanisms and explains the increasing prevalence of comorbid diseases. Recent genome-wide association studies (GWAS) have identified single-nucleotide polymorphisms associated with autoimmune diseases, including T1DM and CD. CD and T1DM-associated genes discovered in GWAS show variable effect sizes and effects directions. There are also gene-environment interactions that likely increase risk, though not yet identified (34). Genetic and environmental factors that play a common role in the pathogenesis of both diseases may be the reason for the intercommunal differences in the frequency of CD in individuals with T1DM.

As the age at diagnosis of diabetes decreases, the risk of CD increases, and children diagnosed with T1DM have a higher risk of developing CD, especially around the age of five. (31). In our study, the mean age at diagnosis of CD was 6.6 years, and the frequency of CD was 23.2% in patients with diabetes diagnosis of 5 years and younger, and 3.3% in patients with a diagnosis of more than 5 years. This shows that there is a direct correlation between insulin deficiency and the duration of gluten sensitivity. In various studies conducted on children and adolescents with T1DM and CD association, gender distribution was found to be different. While it was reported that it was

seen more frequently in girls and in boys in some studies, no gender difference was found in some studies (32). In our study, it was observed that most of our cases with T1DM and CD coexistence were female (73.3%).

In addition to publications in the literature reporting that there is a weak or no relationship between CD and thyroid autoimmunity and studies that found a significant relationship between the two diseases (35). Tissue transglutaminase antibody positivity was reported at a rate of 6.4-7.8% in patients with Hashimoto's thyroiditis (35-37) and TPO Ab positivity of 10.5-14.6% in patients with CD (36, 37). In addition, the risk of developing thyroid autoimmunity is 3 times higher in children diagnosed with CD (38). Ventura et al. showed that the frequency of thyroid autoantibodies is high in patients with CD and that these antibodies disappear with a gluten-free diet (39,40). It is thought that this relationship results from the common genetic background of CD and autoimmune thyroiditis or environmental factors that affect tolerance to their own tissues (40). We detected the presence of thyroid autoantibodies and CD in only 0.5% of the cases. The fact that the mean chronological age of our cases was 12.5 years and the mean diabetes duration was 4.0 years may cause our sample not to reflect the true frequency of this association.

The limitations of our study are its retrospective design and single center experience. Multicenter and long-term follow-up cohort studies will more accurately reflect national data.

CONCLUSION

In conclusion; we detected in our patients with T1DM, the frequency of CD and AITD is more frequent than in the general population, the frequency of CD increases in patients with a younger age at diagnosis of T1DM, but the presence of thyroid antibodies occurs with advancing age at diagnosis, and both conditions are more common in females. Longer-term studies with larger patient groups will guide the development of new screening strategies.

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REFERENCES

1. Roldan MB, Alonso M, Barrio R. Thyroid autoimmunity in children and adolescents with Type 1 diabetes mellitus. Diabetes Nutr Metab. 1999;12:27-31.
2. Park YS, Kim TW, Kim WB, Cho BY. Increased prevalence of autoimmune thyroid disease in patients with type 1 diabetes. Korean J Intern Med. 2000;15:202-10.
3. Kordonouri O, Klinghammer A, Lang EB, et al. Thyroid autoimmunity in children and adolescents with type 1 diabetes: a multicenter survey. Diabetes Care. 2002;25:1346-50.
4. Piatkowska E, Szalecki M. Autoimmune thyroiditis in children and adolescents with type 1 diabetes. Pediatr Endocrinol Diabetes Metab. 2011;17:173-7.
5. Triolo TM, Armstrong TK, McFann K, et al. Additional autoimmune disease found in 33% of patients at type 1 diabetes onset. Diabetes Care. 2011;34:1211-3.
6. Riquetto ADC, de Noronha RM, Matsuo EM, et al. Thyroid function and autoimmunity in children and adolescents with type 1 diabetes mellitus. Diabetes Res Clin Pract. 2015;110:e9-11.
7. Brown RS. Autoimmune thyroiditis in childhood. J Clin Res Pediatr Endocrinol. 2013;5:45-9.
8. Villanueva R, Greenberg DA, Davies TF, Tomer Y. Sibling recurrence risk in autoimmune thyroid disease. Thyroid. 2003;13:761-4.
9. Lee HJ, Li CW, Hammerstad SS, et al. Immunogenetics of autoimmune thyroid diseases: a comprehensive review. J Autoimmun. 2015;64:82-90.
10. Shun CB, Donaghue KC, Phelan H, et al. Thyroid autoimmunity in type 1 diabetes: systematic review and meta-analysis. Diabet Med. 2014;31:126-35.
11. Hughes JW, Riddlesworth TD, DiMeglio LA, et al. Autoimmune diseases children and adults with type 1 diabetes from the T1D exchange clinic registry. J Clin Endocrinol Metab. 2016;101:4931-7.
12. Ediger TR, Hill ID. Celiac disease. Pediatr Rev. 2014;35:409-15.
13. Kliegman RM, ST Geme III JW, Blum NJ, Shah SS, Tasker RC, Wilson KM, Behrman RE. Celiac Disease. Nelson Textbook of Pediatrics. 21st Edition, Elsevier, California 2020;7909-24.
14. Mahmud FH, Elbarbary NS, Fröhlich-Reiterer E, et al. ISPAD Clinical Practice Consensus Guidelines 2018: Other complications and associated conditions in children and adolescents with type 1 diabetes. Pediatr Diabetes. 2018;19:275-86.
15. Kakleas K, Kossyva L, Korona A, et al. Predictors of associated and multiple autoimmunity in children and adolescents with type 1 diabetes mellitus. Ann Pediatr Endocrinol Metab. 2022;27:192-200.
16. Chiang JL, Maahs DM, Garvey KC, et al. Type 1 diabetes in children and adolescents: a position statement by the American Diabetes Association. Diabetes Care. 2018;41:2026-44
17. American Diabetes Association. 12. Children and adolescents. Diabetes Care. 2017;40:S105-13.
18. Besser REJ, Bell KJ, Couper JJ, et al. ISPAD Clinical Practice Consensus Guidelines 2022: Stages of type 1 diabetes in children and adolescents. Pediatr Diabetes. 2022;23:1175-87.
19. Alaedini A, Green PH. Narrative review: celiac disease: understanding a complex autoimmune disorder. Ann Intern Med. 2005;142:289-98.

20. Hoffenberg EJ, Bao F, Eisenbarth GS, et al.Transglutaminase antibodies in children with a genetic risk for celiac disease. J Pediatr. 2000;137:356-60.

21. Taşkın E, Yılmaz M, Kılıç S, Ertuğrul S. The epidemiological features of the type I diabetes mellitus. F.Ü. Sağ. Bil. Derg. 2007:21:75-9.

22. Muhame RM, Mworozi EA, McAssey K, Lubega I. Thyroid autoimmunity and function among Ugandan children and adolescents with type-1 diabetes mellitus. Pan Afr Med J. 2014;19:137.

23. Kordonouri O, Hartmann R, Deiss D, et al. Natural course of autoimmune thyroiditis in type 1 diabetes: association with gender, age, diabetes duration, and puberty. Arch Dis Child. 2005;90:411-4.

24. Kochummen E, Marwa A, Umpaichitra V, et al. Screening for autoimmune thyroiditis and celiac disease in minority children with type 1 diabetes. J Pediatr Endocrinol Metab. 2018;28;31:879-85.

25. Karavanaki K, Kakleas K, Paschali E, et al. Screening for associated autoimmunity in children and adolescents with type 1 diabetes mellitus (T1DM). Horm Res. 2009;71:201-6.

26. Hatun Ş, Demirbilek H, Darcan Ş, et al.; Turkish Pediatric Diabetes Research Group. Evaluation of therapeutics management patterns and glycemic control of pediatric type 1 diabetes mellitus patients in Turkey: a nationwide cross-sectional study. Diabetes Res Clin Pract. 2016;119:32-40.

27. Unal E, Demiral M, Öcal M, et al. Incidence of Autoimmune Thyroid Disease in Patients with Type 1 Diabetes. JCP. 2020;18:251-62.

28. Simsek DG, Aycan Z, Özen S, et al. Diabetes care, glycemic control, complications, and concomitant autoimmune diseases in children with type 1 diabetes in Turkey: a multicenter study. J Clin Res Pediatr Endocrinol. 2013;5:20-6.

29. Esen İ, Deveci U, Ökdemir D. The frequency of autoimmune polyendocrinopathy type 3b in children with type 1 diabetes mellitus. Turk J Diab Obes. 2020;2:79-83.

30. Lipman TH, Rezvani I, DiGeorge AM. The natural history of thyroid autoimmunity and thyroid function in children with type 1 diabetes. J Pediatr. 2007;151:e10-2.

31. Sange I, Mohamed MWF, Aung S, et al. Celiac disease and the autoimmune web of endocrinopathies. Cureus. 2020;12:e12383.

32. Unal E, Demiral M, Baysal B, et al. 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. 2021;13:72-9.

33. Siddiqui K, Uqaili AA, Rafiq M, Bhutto MA. Human leukocyte antigen (HLA)-DQ2 and -DQ8 haplotypes in celiac, celiac with type 1 diabetic, and celiac suspected pediatric cases. Medicine (Baltimore). 2021;100:e24954.

34. Cohn A, Sofia AM, Kupfer SS. Type 1 diabetes and celiac disease: clinical overlap and new insights into disease pathogenesis. Curr Diab Rep. 2014;14:517.

35. Valenzise M, Aversa T, Saccomanno A, et al. Epidemiological and clinical peculiarities of polyglandular syndrome type 3 in pediatric age. Ital J Pediatr. 2017;43:69.

36. Larizza D, Calcaterra V, De Giacomo C, et al. Celiac disease in children with autoimmune thyroid disease. J Pediatr. 2001;139:738-40.

37. Sari S, Yesilkaya E, Egritas O, et al. Prevalence of celiac disease in Turkish children with autoimmune thyroiditis. Dig Dis Sci. 2009;54:830-2.

38. Marwaha RK, Garg MK, Tandon N, et al. Glutamic acid decarboxylase (anti-GAD) & tissue transglutaminase (anti-TTG) antibodies in patients with thyroid autoimmunity. Indian J Med Res. 2013;137:82-6.

39. Ventura A, Neri E, Ughi C, et al. Glutendependent diabetes-related and thyroid-related autoantibodies in patients with celiac disease. J Pediatr. 2000;137:263-5.

40. Von Herrath MG, Fujinami RS, Whitton JL. Microorganisms and autoimmunity: making the barren field fertile?. Nat Rev Microbiol. 2003;1:151-7.