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Seroprevalence of autoimmune thyroiditis and celiac disease in children with insulin-dependent diabetes mellitus in the Thrace region of Turkey

Türkiye'nin Trakya bölgesindeki insülin bağımlı diabetes mellituslu çocuklarda çölyak hastalığı ve otoimmün tiroidit seroprevelansı

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Background/aims: *We aimed to estimate the seroprevalence of celiac disease, a gluten-sensitive enteropathy, and autoimmune thyroiditis in children with insulin-dependent diabetes mellitus in the Thrace region of Turkey.* ***Methods:*** *The population studied consisted of 33 children with insulin-dependent diabetes mellitus and 41 healthy children with demographic features similar to the study subjects. Free triiodothyronine, free thyroxine, thyroid-stimulating hormone, anti-thyroid peroxidase antibody, anti-thyroglobulin antibody, IgA, anti-endomysium IgA, and anti-gliadin IgA were measured in all cases and controls.* ***Results:*** *The serum levels of free triiodothyronine and free thyroxine were within the normal range in all cases. However, in one patient who had anti-thyroid peroxidase and anti-thyroglobulin antibodies, the thyroid-stimulating hormone level was high despite a normal free triiodothyronine and free thyroxine value. Ultrasonographic findings confirmed thyroiditis in this patient. Anti-thyroid peroxidase antibodies, anti-thyroglobulin antibodies, anti-endomysium IgA and anti-gliadin IgA were detected in 15.4%, 6%, 9.1% and 3% of the diabetic cases, respectively. None of these antibodies was detected in the control group. In the diabetic group, the seroprevalences of the anti-thyroid peroxidase antibodies and the anti-endomysium IgA were statistically higher than in the control group ($p<0.05$).* ***Conclusions:*** *Children with insulin-dependent diabetes mellitus in our region should undergo periodic screenings for autoimmune thyroiditis and celiac disease.*

Key words: Autoimmune thyroiditis, celiac disease, insulin-dependent diabetes mellitus, autoimmune disease

Amaç: *Türkiye'nin Trakya bölgesindeki insülin bağımlı diabetes mellituslu çocuklarda otoimmün tiroidit ve çölyak hastalığı (gluten hassas enteropati) sıklığının araştırılması.* ***Yöntem:*** *Çalışma grubunu, 33 insülin bağımlı diabetes mellituslu hasta ile kontrol grubunu dermografik özellikleri benzer olan 41 çocuk oluşturdu. Tüm çalışma ve kontol grubunda serbest T_3, serbest T_4 tiroid stimulant hormon, antitiroid peroksidaz antikoru, antitiroglobülin antikoru, IgA, IgA-antiendomisyum antikoru ve IgA-antigliadin antikoru ölçüldü.* ***Bulgular:*** *Serum serbest T_3 ve serbest T_4 seviyesi tüm olgularda normal sınırlarda saptandı. Serbest T_3 ve serbest T_4 düzeyi normal olan bir hastada tioid stimule edici horman düzeyi yüksek saptandı. Aynı olguda antiroid peroksidaz ve anti-tiroglobulin antikoru da pozitifti. Bu hastada ultrasonografi bulguları tiroidit bulgularını doğruluyordu. Diyabetik olgularda; Antitiroid peroksidaz, anti-tiroglobulin antikoru, IgA-antiendomisyum antikoru ve IgA-antigliadin antikoru sırasıyla %15.4, %6, %9.1, %3 oranında pozitif saptandı. Kontrol grubunda bütün antikorlar negatifti. Çalışma grubunda antitiroid peroksidaz ve IgA-antiendomisyum antikoru pozitifliği, çalışma grubundan istatistiksel olarak daha yüksek saptandı ($p<0.05$).* ***Sonuç:*** *Bölgemizdeki insülin bağımlı diabetes mellituslu çocuklara peryodik olarak otoimmün tiroidit ve çölyak hastalığı için tarama testleri yapılmalıdır.*

Anahtar kelimeler: Otoimmun tiroidit, çölyak hastalığı, insülin bağımlı diabetes mellitus, otoimmün hastalık

INTRODUCTION

The destruction of insulin-secreting beta (β)-cells in the pancreas is responsible for insulin-dependent diabetes mellitus (IDDM). A variety of factors, including viruses, chemicals and immune reactions mediated by cells or antibodies, have been implicated as possible causes of the destruction.

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The diseases associated with autoimmunity are numerous and varied. At one end of the autoimmune spectrum are organ-specific autoimmune diseases, such as Hashimoto's thyroiditis, celiac disease (CD), pernicious anemia, and Addison's disease, in which autoantibodies and inflammatory cells target a single organ (1). The frequently targeted organs in organ-specific diseases are the pancreatic islet cells, thyroid gland, adrenal gland, gonads, anterior pituitary gland, skin, liver, and stomach, whereas in non-organ-specific diseases, the skin, blood vessels, kidneys, joints, and muscles are usually targeted. The coincidence of CD and IDDM has been described in most atypical or silent cases. CD is detected only by screening for immunoglobulin A anti-gliadin (AGA-IgA) or immunoglobulin A anti-endomysium (EMA-IgA) (2). Among the serological tests needed to diagnose CD, the measurement of AGA-IgA has been justifiably abandoned, as its sensitivity and specificity are very low (around 50%). EMA-IgA is preferred for clinical use because its sensitivity is greater than 90% and its specificity is around 95%, although small variations among the different commercially available kits have been reported (3, 4). Hidden CD may exist in patients with a positive antibody test but a negative intestinal biopsy. The diagnosis of CD based solely on serologic markers is not accepted, and the identification of the characteristic changes in the duodenal mucosa is required before a gluten-free diet is prescribed. In clinical practice, serologic tests for CD are frequently used to identify both symptomatic and asymptomatic at-risk individuals who require an intestinal biopsy to confirm the diagnosis (3). The prevalence of CD in patients with IDDM ranges from 0.6% to 17.8% and varies widely between different geographical areas (5-7). The high seroprevalence of EMA-IgA (13.5%) observed in Turkish diabetic children can be explained by the high prevalence of CD (0.87%) in the same general population (7).

Individuals with IDDM have an increased risk of developing autoimmune thyroiditis (AIT), and the most common autoimmune disease associated with IDDM is Hashimoto's thyroiditis. Its prevalence varies from 8% to 50% in IDDM patients, depending on the age, sex and ethnic origin of the subject. Thirty-nine percent of AIT diagnoses come within one year of IDDM diagnosis (8, 9).

The present study is the first to report the seroprevalence of CD and AIT in children with IDDM from the Thrace region of Turkey.

MATERIALS AND METHODS

The study was carried out by the Department of Pediatric Endocrinology of Trakya University. Trakya University is located in the Thrace region of Turkey, which is the area of Turkey in southeastern Europe. The study population consisted of 33 patients with IDDM and 41 non-diabetic children with demographic features similar to those of the study subjects. The parents/guardians of the patients were informed about the study, and their consent was obtained. The diabetic group consisted only of IDDM patients who had no additional acute or chronic diseases. None of the patients or control cases received thyroid hormone preparations. Since a low serum level of IgA could affect the EMA-IgA test results, only patients with a normal serum IgA level (>17.3 mg/dl) were included in the study. Age, sex, height, weight, and body mass index (BMI) were used as demographic features. None of the study participants had any family history of autoimmune disease.

Three milliliters of venous blood was drawn from each subject, and serum samples were stored at -70°C until analysis. The IgA level was determined using electro-immunodiffusion, while EMA-IgA and AGA-IgA were measured using indirect immunofluorescence. Serum samples were tested for free triiodothyronine (fT3), free thyroxine (fT4), thyroid-stimulating hormone (TSH), anti-thyroid peroxidase antibody (anti-TPOab), and anti-thyroglobulin antibody (Tg-ab) using a radioimmunoassay. Thyroid ultrasonograms were performed in all cases positive for anti-TPOab and/or Tg-ab. The normal reference ranges of the test kits were 1.8–4.8 pg/dl for fT3, 0.8-1.9 ng/dl for fT4, 0.4–4.0 mIU/ml for TSH, 0.0-40 IU/ml for Tg-ab, and 0.0–35 IU/ml for anti-TPOab. Any serum titer of Tg-ab and anti-TPOab greater than these values was considered positive. Patients who were positive for EMA-IgA and/or AGA-IgA underwent an intestinal biopsy to confirm the diagnosis of CD. Seropositivity for anti-TPOab and/or Tg-ab was considered indicative of AIT. The values of the two groups were statistically compared using the Student's *t*-test and χ-square test; a p value less than 0.05 was considered significant.

RESULTS

There was no difference between the diabetic and control groups in terms of demographic features ($p>0.05$). Table 1 summarizes the demographic features of all study participants. In both groups,

Table 1. The demographic features of the diabetic and control groups

	Diabetic group (n=33)	Control group (n=41)	p
Sex *			
Male	14 (42.4%)	23 (56.1%)	>0.05
Female	19 (57.6%)	18 (43.9%)	>0.05
Age (y)**	10.0±3.5	9.1±3.1	>0.05
Weight (kg)**	33.6±15.0	29.8±10.5	>0.05
Height (m)**	1.37±0.22	1.3±0.17	>0.05
BMI**	16.9±2.9	16.8±1.7	>0.05

*n (%) **mean ± standard deviation
BMI: Body mass index.

one subject seropositive for anti-thyroid antibodies had a family history of thyroid disease (3.0%). Seven diabetic subjects had a family history of IDDM (21.2%), and six subjects had a family history of non-insulin-dependent diabetes mellitus (NIDDM) (18.2%). However, no controls had a family history of IDDM, although seven had a family history of NIDDM. This difference between the two groups in terms of family history of IDDM was significant. No family history of CD was found in either group. In the diabetic subjects, the age of diagnosis of IDDM was 7.9±3.6 years (range: 3.5–13) for males and 7.4±3.0 years (range: 2.5–13) for females. In the IDDM cases, the duration of the disease was 2.01 years (range: 0.5–7). An IDDM duration of less than 3 years was reported in 19 cases (57.6%), and a duration of more than 3 years was found in 14 cases (42.3%). Based on the mean fT3, fT4 and TSH levels, there were no statistical differences between the diabetic and control groups. The mean fT3, fT4 and TSH levels are shown in Table 2. While five diabetic subjects were seropositive for anti-TPOab (15.2%), all controls were negative ($p<0.05$). In Tg-ab–positive patients, the IDDM duration was longer than 3 years. With the exception of two diabetic subjects (6.1%), all were seronegative for Tg-ab. No statistical difference was observed in the Tg-ab seroprevalence of the two groups ($p>0.05$). Since one of the diabetic subjects had a serum TSH value of 10.4 mIU/ml, L-thyroxine was given.

Although three diabetic subjects were seropositive for EMA-IgA (9.1%), none of the controls was seropositive ($p<0.05$). One of the EMA-IgA seropositive cases was also seropositive for AGA-IgA (3.0%). There was no statistically significant difference between the two groups regarding the seroprevalence of AGA-IgA. EMA-IgA, AGA-IgA and anti-TPOab were detected in one IDDM case (3.0%). The anti-TPOab, Tg-ab, EMA-IgA and AGA-IgA levels are shown in Table 3.

DISCUSSION

For many years, a relationship was thought to exist between IDDM and various autoimmune diseases. In our study, seven patients had a family history of IDDM (21.2%) and six had a family history of NIDDM (18.2%). In contrast, none of the control subjects had a family history of IDDM, while seven had a family history of NIDDM. This difference between the two groups in terms of family history of IDDM was significant ($p<0.05$). In general, IDDM is considered a complex genetic trait; that is, not only do multiple genetic loci contribute to susceptibility, but environmental factors also play a major role in determining risk. A large body of evidence indicates that inherited genetic factors influence both susceptibility and resistance to the disease. There is significant familial clustering of diabetes mellitus, with an average prevalence risk in siblings of 6% compared to 0.4% in the general population (8, 10). In our study population, we detected a family history of DM that is higher than is usually reported. However, our study examined only a small number of cases. No family history of CD was found in either group, possibly for the same reason.

The most prevalent autoimmune disease associated with IDDM is AIT. Its prevalence varies from

Table 2. Mean fT3, fT4 and TSH values

	Case group (n=33)	Control group (n=41)	p
fT3* (pg/dl)	3.04±0.84	3.03±0.74	>0.05
fT4* (ng/dl)	1.27±0.28	1.33±0.21	>0.05
TSH* (mIU/ml)	2.14±1.75	2.07±1.27	>0.05

*mean ± standard deviation fT3; Free triiodothyronine. fT4: Free thyroxine. TSH: Thyroid-stimulating hormone.

Table 3. Seroprevalence of anti-TPOabs, Tg-abs, EMA-IgA and AGA-IgA

	Case group Number (percent) (n=33)	Control group Number (n=41)	P
Anti-TPOab	5 (15.2%)	-	<0.05
Tg-ab	2 (6.1%)	-	>0.05
Anti-TPOab + Tg-ab	2 (6.1%)	-	>0.05
EMA-IgA	3 (9.1%)	-	<0.05
AGA-IgA	1 (3.0%)	-	>0.05
AGA-IgA + EMA-IgA	1 (3.0%)	-	>0.05
Anti-TPOab + EMA-IgA + AGA-IgA1	(3.0%)	-	>0.05

Anti-TPOab: Anti-thyroid peroxidase antibody. Tg-ab: Anti-thyroglobulin antibody. EMA-IgA: Anti-endomysium immunoglobulin A. AGA-IgA: Anti-gliadin immunoglobulin A.

8% to 50%, depending on the age, sex and ethnic origin of the subjects. In control populations, anti-TPOabs are present in 0–27.0% of patients (8, 9, 11). It has been reported that follow-up of AIT is important not only for the detection of hypothyroidism, but also for the early diagnosis of papillary carcinoma and thyroid lymphoma. It has been suggested that an immunologic mechanism stimulates lymphocytic infiltration into the thyroid through an autoimmune mechanism, thereby promoting the pathogenesis of papillary carcinoma (9, 11, 12). The TSH level was increased in only one subject in our study, and 15.2% of cases were seropositive for Tg-abs and TPOabs. McKenna et al. (13) reported that thyroid-specific autoantibodies are present in 19% of subjects. Souza et al. (14) found the seroprevalence of thyroid-specific antibodies to be 30.7% in Brazil. Although an increased seroprevalence of anti-TPOabs and Tg-abs was found in our diabetic group, there was no difference between the two groups in terms of serum TSH values. However, screening for thyroid-specific autoantibodies may aid in the detection of thyroid diseases in the future (9, 11). Therefore, in our study, anti-thyroid autoantibodies were established in patients who had been diagnosed with IDDM for at least 3 years.

Thyroid ultrasonography was performed in all subjects seropositive for anti-thyroid autoantibodies, and AIT was found in one case, where it was detected in the normal range. The anti-TPOab and Tg-ab seroprevalences were 15.2% ($p<0.05$) and 6.1% ($p>0.05$), respectively.

The most sensitive autoantibodies used for the diagnosis of CD are EMA-IgA, anti-reticulin and AGA-IgA. Because EMA-IgA is a very sensitive screening test for CD, the estimated prevalence of CD in the population has increased (15,16). Although three subjects were seropositive for EMA-IgA, AGA-IgA was only detected in one of them. An intestinal biopsy was performed in these three patients. Duodenal biopsies must be interpreted in detail by a pathologist experienced in the study of CD, using Marsh's criteria (modified), which stratify CD into four types or stages. In the three duodenal biopsies we performed, one patient was normal (stage 0), and two patients had increased intraepithelial lymphocytes (stage 1). Duodenal biopsy is still considered the "gold standard" in the diagnosis of CD, although its usefulness in adults is still slightly controversial. If the results of the histological study are negative, but serologic tests are positive and CD is strongly suspected, the results of the biopsy should be reviewed by an expert gastrointestinal pathologist before additional biopsies are considered. In recent years, many studies have examined the incidence of CD in subjects with IDDM. In diabetic children and adults, the prevalence of CD varies from 0.6% to 17.8% (4-7). It has been reported that the CD in patients with IDDM is mostly silent and that symptoms of malabsorption are seen rarely (4). Various studies examining the seroprevalence of CD in diabetic children and adolescents have found different results in different countries: in France, 1.6% (6); Austria, 2.9% (15); Tunisia, 8.3% (16); Algeria, 16.4%; and India, 17.8% (5). We found a prevalence of 9.1% in the IDDM cases. This value is lower than that reported by Ertekin et al. (13.5%) (7) but higher than that reported by Güvenç et al. (8.0%) (19). The diagnosis of subclinical CD associated with IDDM is important. Stable blood glucose regulation and a decreased frequency of hypoglycemic attacks have been achieved in patients with IDDM by adhering to a gluten-free diet; therefore, the progression of diabetes can be prevented. Furthermore, CD may impair the growth of diabetic children (2-4). While the diabetic subjects seropositive for EMA-IgA had no symptoms of malabsorption, one of them had recurrent hypoglycemic attacks and inadequate regulation of blood glucose. In this subject, two measurements of HbA1C values were 9.6% and 9.2%. However, after we started this patient on a gluten-free diet, the blood glucose was regulated properly.

A duration of IDDM of less than 3 years was found in 19 cases (57.6%) and of more than 3 years in 14 cases (42.3%). Three EMA-IgA-positive cases and one AGA-IgA-positive case had been diagnosed with IDDM for more than 3 years. We found anti-TPOabs in 9.1% (3 cases) and Tg-abs in 6.1% (2 cases), all of whom had been diagnosed with IDDM for longer than 3 years. We recommend all children with IDDM be routinely screened for CD and AIT. At what intervals this population should be screened for CD is currently unknown. Our data suggest that the initial screening of asymptomatic patients should begin 1-2 years after the diagnosis of IDDM. Further studies are planned to assess the appropriate interval for the serial screening of asymptomatic, CD-seronegative diabetic patients.

In conclusion, we detected AIT and CD in some children with IDDM. This detection can be important for the early diagnosis of hypo- or hyperth-

yroidism, the prevention of associated complications, the regulation of blood glucose, and the early detection of autoimmune-mediated malignancies stemming from these diseases in the future. The prevalence of other autoimmune diseases in children with IDDM varies, and there have been few studies examining this matter in children in Turkey. We conclude that children with IDDM in our region should be screened periodically for AIT and CD.

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