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Prevalence of Celiac disease in Turkish children with type 1 Diabetes Mellitus and their non-diabetic first-degree relatives

Tip 1 Diyabetli Türk çocuklarında ve onların birinci derecede yakınlarında Çölyak hastalığı sıklığı

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Background/aims: *The objective of this study was to determine the prevalence of Celiac disease in Turkish children with type 1 Diabetes Mellitus and their non-diabetic first-degree relatives.* ***Methods:*** *Forty-eight children with type 1 Diabetes Mellitus (18 males, 30 females; age range: 3.5 to 23 years; mean age: 12.09 ± 4.78 years), 29 non-diabetic siblings, 40 non-diabetic parents, and 103 healthy children were screened for celiac disease using the IgA and IgG anti-tissue transglutaminase antibody and total serum IgA. Small intestinal biopsy was offered to all antibody-positive patients.* ***Results:*** *Eight of 48 diabetic patients had positive anti-tissue transglutaminase IgA. Selective IgA deficiency was detected in 2 diabetic children and both were positive to anti-tissue transglutaminase IgG. Intestinal biopsy was accepted by 8 of 10 (80%) diabetic children with positive celiac serology. Pathologic examination showed total villous atrophy in 3 (6.3%) diabetic children. Positive anti-tissue transglutaminase IgA was found in 1/29 siblings and 2/40 parents. Celiac disease was confirmed by biopsy in the sibling. Two parents refused the biopsy. The frequency of biopsy-proven celiac disease was found as 1.4 in relatives of diabetic children. None of the serum samples of healthy children comprising the control group showed selective IgA deficiency or positivity for anti-tissue transglutaminase IgA antibody.* ***Conclusions:*** *These findings indicate that the prevalence of celiac disease in Turkish children with type 1 diabetes mellitus is higher than in healthy controls. The 1.4% frequency of Celiac disease in relatives of diabetic children is close to that of controls.*

Key words: Type I diabetes, Celiac disease, children, relatives

Amaç: *Bu çalışmada tip 1 diyabetli Türk çocuklarında ve onların diyabetik olmayan birinci derece yakınlarında Çölyak hastalığı sıklığının araştırılması amaçlanmıştır.* ***Yöntem:*** *Tip I diabetes mellitus tanılı 48 çocuk (K/E=30/18, yaş aralığı 3,5-23 yıl, yaş ortalaması 12.09 ± 4.78 yıl), diyabetik olmayan 29 kardeş, 40 ebeveyn ve 103 sağlıklı çocuk anti-doku transglutaminazı, IgA, IgG ve serum total IgA düzeyleri bakılarak Çölyak hastalığı için tarandı. Antikor pozitifliği saptanan olgulara ince barsak biyopsisi yapılması teklif edildi.* ***Bulgular:*** *48 diyabetli çocuğun 8'inde anti-doku transglutaminazı IgA pozitifliği saptandı. İki diyabetli çocukta selektif IgA eksikliği saptandı ve her ikisinde de anti-doku transglutaminazı IgG pozitifti. İntestinal biyopsi, Çölyak serolojisi pozitif 10 hastanın 8'i (%80) tarafından kabul edildi. Üç diyabetik çocukta (%6,3) total villöz atrofi tespit edildi. Bir kardeş ve ebeveynlerin ikisinde anti-doku transglutaminazı-IgA pozitif bulundu. Kardeşte biyopsi ile Çölyak hastalığı doğrulandı. Ebeveynler intestinal biyopsiyi kabul etmedi. Diyabetik çocukların akrabalarında biyopsi ile kanıtlanmış Çölyak hastalığı sıklığı %1,4 olarak bulundu. Kontrol grubunda hiçbir çocukta anti-doku transglutaminazı pozitifliği tespit edilmedi.* ***Sonuç:*** *Diyabetli çocuklarda Çölyak hastalığı sıklığının sağlıklı çocuklara göre yüksek oranda olduğu görüldü. Diyabetik çocukların akrabalarında biyopsi ile kanıtlanmış Çölyak hastalığı sıklığında kontrol grubuna göre fark bulunmadı.*

Anahtar kelimeler: Tip I diyabet, Çölyak hastalığı, çocuk, akrabalar

INTRODUCTION

Type 1 Diabetes Mellitus (T1DM) is a common autoimmune disease in children. The risk for other autoimmune disorders is increased in children with T1DM and their relatives (1). Recent data have supported that Celiac disease (CD) is an autoimmune disease triggered by the ingestion of gluten in genetically susceptible individuals (2). Strong evidence for the association between T1DM and CD has been shown in children. Up to 8% of patients with T1DM have the characteristic featu-

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res of CD on small intestinal biopsy (3-5). Patients with associated T1DM and CD are usually asymptomatic (2). Clinically silent patients are at risk for complications that could be prevented by a gluten-free diet, so routine screening with measurement of quantitative serum IgA and antibody to human recombinant tissue transglutaminase (tTG) for CD is recommended in patients with T1DM (2). Family members of T1DM children may also be at high risk for developing CD. This can be explained by the common genetic background and sharing of similar environmental risk factors. A few reports have focused on the prevalence of CD in non-diabetic relatives of children with T1DM (6-14). In this study, we analyzed the prevalence of CD in Turkish children with T1DM and their non-diabetic first-degree relatives.

MATERIALS AND METHODS

Patients and Control Subjects

A total of 48 children with T1DM (18 boys, 30 girls; age range: 3.5 to 23 years; mean age: 12.09 ± 4.78 years), 29 non-diabetic siblings (12 boys, 17 girls; age range: 2 to 28 years; mean age: 13.5 ± 7.84 years), 40 non-diabetic parents (19 males, 21 females; age range: 25 to 53 years; mean age: 40.7 ± 6.95 years), and 103 healthy children (46 boys, 57 girls; age range: 3.5 to 17 years; mean age: 12.18 ± 3.11 years) were studied over a period of one year (2006-2007). None of the subjects had complaints related to the gastrointestinal tract or a suspicion of CD. The control group included 103 children admitted to Gazi University Hospital, Department of Pediatrics, for various reasons, such as trauma or minor respiratory infections. All the subjects were tested for total IgA levels to exclude IgA deficiency and screened for IgA-tTG antibody. In addition, IgG-tTG was analyzed in patients with selective IgA deficiency. Subjects with confirmed positive tTG antibody were offered an endoscopic small intestinal biopsy. Biopsy specimens were assessed according to a modified Marsh classification (15). Informed consent was obtained from all parents. The study was approved by the Ethics Committee at Gazi University Faculty of Medicine.

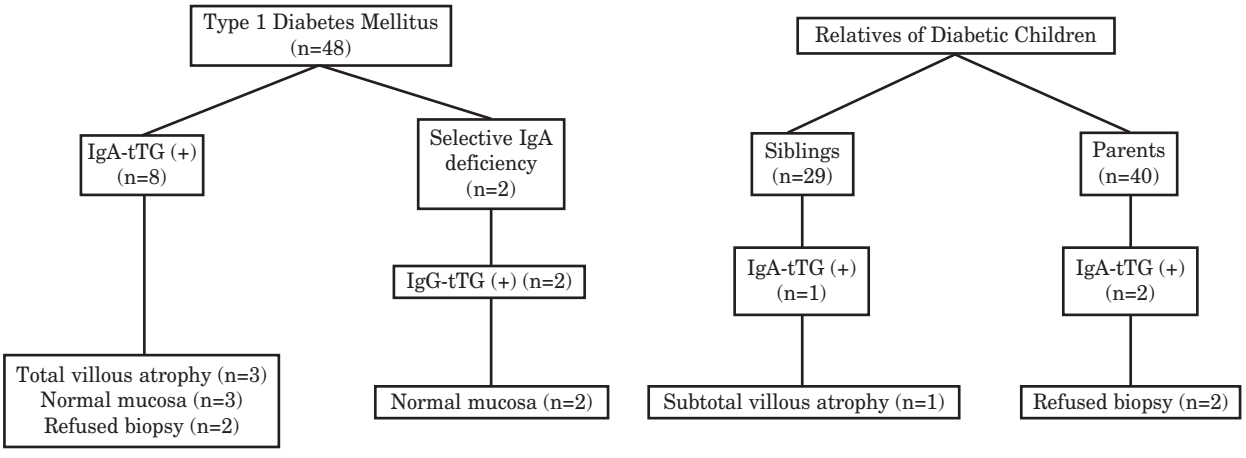
Laboratory Methods

A commercially available microplate enzyme-linked immunosorbent assay (Euroimmune, GmbH, Lübeck, Germany) was used to test for IgA and IgG-tTG. The cutoff level defining a positive result was set at 20 RU/ml. Total serum IgA level was analyzed using a routine nephelometric assay, and if levels were below 0.05 mg/dl, IgG-tTG was analyzed. To confirm the diagnosis of CD, mucosal biopsy was performed endoscopically from the second part of the duodenum (Olympus GIF P230 videogastroscope, Olympus Optical Corporation, Tokyo, Japan).

Statistical Analyses

Statistical analyses were performed with SPSS for Windows, version 10.0 (SPSS Inc, Chicago, IL), using a Pentium II–based personal computer. The statistical significance of the difference between children with T1DM, non-diabetic relatives and controls was estimated by using the Fisher exact probability test. A p value of <0.05 was considered statistically significant.

Table 1. Laboratory results of children with type 1 diabetes mellitus and their relatives



RESULTS

Positive IgA-tTG was found in 8/48 (16.7%) and selective IgA deficiency together with positive IgG-tTG in 2/48 (4.1%) of diabetic children. Seropositivity for CD in diabetic children was 20.8% (10/48). Eight patients with T1DM approved duodenal biopsy, and 3 of them (6.3%) showed total villous atrophy (Marsh type 3). The remaining 5 patients showed normal mucosa. One sibling and two parents of diabetic children were positive for IgA-tTG. Serum total IgA levels were within normal limits in these subjects. Intestinal histopathology showed sub-total villous atrophy in the sibling (Marsh type 3c). Both parents refused endoscopic biopsy. The frequency of biopsy-proven CD was found as 1.4 (1/69) in relatives of diabetic children. None of the healthy children was positive for IgA-tTG, and serum total IgA level was normal in all of them (Table 1). The prevalence of seropositivity for CD was higher in patients with T1DM than their relatives (siblings and parents of diabetic children) and healthy controls (p=0.007 and 0.00005, respectively). The prevalence of biopsy-proven CD was also higher in diabetics than controls (p=0.031) but similar to relatives (p=0.30). The prevalence of seropositivity and biopsy-proven CD in non-diabetic relatives was not different from healthy controls (p=0.06 and 0.40, respectively).

DISCUSSION

Celiac disease is a quite prevalent autoimmune disorder in Turkey. In a local study, prevalence of CD was found as 1/158 (16). Our study showed

Table 2. Literature review: the association between CD and non-diabetic relatives of T1DM

Authors	Method	Sample of Study (n)	CD frequency % (n) Serologic	Biopsy-proven	p
Boudraa et al. 1996 Algeria (13)	AEA, IgA&IgG-AGA Biopsy	Diabetic children (116) Relatives (381)	20 (24) 6.8 (26)	16.4 (19) 3.4 (13)	
Hummel et al. 2000 Germany (6)	AEA, IgA&IgG-AGA HLA typing Biopsy	Diabetic parents (99) Offspring (913) Control (71)	10.1 3.5 (32) 1.3	(11)	<0.05
Jaeger et al. 2001 Germany (7)	IgA-tTG, IgA &IgG-AGA	Diabetic children (197) Parent, sibling and offspring (882) Control (150)	16.8 7.3 4.6		>0.05
Matteucci et al. 2001 Italy (14)	AEA, IgA&IgG-AGA	Diabetic adults (74) Parent (69) Offspring (58) Control (50)	34 (25) 14 (10) 8 (5) 6 (3)		*<0.001
Not et al. 2001 Italy (8)	AEA; Biopsy	Diabetic children and adult (491) Parent, sibling and offspring (824) Control (4000)	5.7 (28) 1.9 (16) 0.25 (10)	5.7 (28) 1.9 (16) 0.25 (10)	<0.001
Williams et al. 2001 UK (10)	IgA-AEA; IgA-tTG	Diabetic children (433) Parent (871) and sibling (571) Control (347)	13.4 (58) 7 (100) 2.5 (10)		<0.05
Saukkonen et al. 2001 Finland (9)	IgA-AEA; HLA typing; Biopsy	Sibling (550)	1.6 (9)	1.1 (6)	**
Hanukoglu et al. 2003 Israel (11)	AEA; IgA&IgG-AGA Biopsy	Diabetic children (109) Relatives (100)		8.3 (9) 6 (6)	<0.0001
Sumnik et al. 2005 Czech Rep. (12)	AEA; IgA-AGA; Total IgA level; HLA typing; Biopsy	Siblings (240)	3.8 (9)	(6)	***
Our Study	IgA-tTG; Total IgA; Biopsy	Diabetic children (48) Relatives (69) Control (103)	20.8 (10) 4.3 (3) (0)	6.3 (3) 1.4 (1)	>0.05

*Only two of patients with positive-AGA have AEA positivity.
**The ratio was similar to prevalence of CD in Finnish healthy population.
*** The ratio was similar to prevalence of CD in diabetic Czech population (4.3%) and higher than in healthy population (0.69%).

that seropositivity for CD in diabetic children was significantly higher than in their relatives and the control group. The frequency of serologic test positivity in the relatives of diabetics was close to that of the control group and healthy Turkish children. In children with T1DM, increased prevalence of CD is well documented (2). The association of CD and T1DM can be explained by common HLA and non-HLA genes, the MHC I-related gene A polymorphism, antigenic mimicry, damage-induced neoantigen exposure, altered intestinal permeability, idiotype network dysregulation, and epitope spreading (1, 17). Because siblings or parents of diabetic children share the same factors, the authors assumed that prevalence of CD is higher than in healthy controls. The current recommendations for screening subjects with T1DM are to obtain autoantibodies for CD at diagnosis of diabetes and every two years thereafter or if symptomatic. The subjects with positive tTG should undergo small bowel biopsy to confirm the diagnosis (2). However, few studies have investigated the prevalence of CD in non-diabetic relatives, and there is no recommendation for routine screening of these subjects. The first study conducted by Hummel et al. (6) showed the frequent occurrence of CD- associated antibodies in relatives. Consecutive studies have yielded similar results in that increased prevalence of biopsy-proven or serology-positive CD was found in relatives of diabetics (6, 8, 10-12). Conversely, Saukkonen et al. (9) reported similar prevalence of biopsy- proven CD and Jaeger et al. (7) reported similar rates of seropositivity of IgA-tTG positivity between first-degree relatives of T1DM and control groups, similar to our results. The different results in the reported series (Table 2) can be explained by study design (i.e. different serologic tests, biopsy-proven or not), ethnic-genetic heterogeneities and sample size (18-20).

Early diagnosis of CD in asymptomatic patients and risk groups may reduce morbidity and mortality. A gluten-free diet is currently the only treatment option in CD. However, effect of gluten-free diet on control of diabetes, hemoglobin A 1c level and bone mineral density has not been shown in asymptomatic diabetics in the short term (21, 23). Adherence to a strict gluten-free diet may prevent complications such as osteoporosis, infertility, malignancy or other autoimmune disorders. Based on our study and a literature review, we think that routine screening should be carried out in diabetic children, and long-term studies should be planned to compare the natural history of treated or untreated silent CD in these children. However, routine screening for CD among all non-diabetic first-degree relatives is still questionable.

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