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ORIGINAL ARTICLE

Autoimmune Diseases in Turkish Patients with Type 1 and Type 2 Diabetes: A Single-center Experience

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Abstract

Introduction: Diabetes guidelines recommend routine screening for autoimmune thyroid disease (ATD) and celiac disease, especially in cases of childhood-onset type 1 diabetes (T1D). However, the level of evidence is weak (expert opinion), and for adult-onset T1D even less clear. The aim of this study is to evaluate the prevalence of comorbid autoimmune diseases (ADs) in childhood-onset and adult-onset T1D patients, and to compare the distribution of individual ADs with those with type 2 diabetes mellitus (T2D).

Methods: Among a total of 1594 adult diabetes patients who were consecutively followed by a single Diabetes Center, 22% (n=351) had T1D. Patients with T1D were screened for ATD, pernicious anemia, vitiligo, celiac, and when clinically relevant for Addison's, and other organ-specific/systemic autoimmune/autoinflammatory diseases. To compare the distribution of ADs, we included a group of 50 T2D patients with at least one known autoimmunity. In addition, the relationship between ADs, and the level of glycemic control and the presence of micro- and macrovascular complications were investigated.

Results: The prevalence of AD was 26.2% in T1D with females being more affected than males. ATD was the most prevalent, followed by pernicious anemia, vitiligo, celiac, and premature gonadal failure. Over 60% had single (mostly ATD; T1D 83.6%, T2D 68.6%), and over 20% had double AD with no significant difference between T1D and T2D. Of T1D patients, 8.2% had triple AD. The majority of ATDs was Hashimoto's thyroiditis and/or hypothyroidism, only 12% had Graves' disease (T1D 10.9% and T2D 14%). In T1D women, pernicious anemia (22.8%), vitiligo (9.8%), and celiac (8.7%) were the most common comorbidities of ATD. There was no significant relationship between the frequency of ADs and individual ADs and glycemic control, age-at-onset of diabetes, and micro- and macrovascular complications.

Discussion and Conclusion: Screening for ATD should be included in the routine management protocol of adult-onset T1D as recommended in those with childhood-onset. Furthermore, we suggest investigation for pernicious anemia, vitiligo, and celiac disease in women with T1D.

Keywords: Addison's disease; autoimmune disease; autoimmune thyroid disease; celiac disease; type 1 diabetes mellitus; type 2 diabetes mellitus; vitiligo.

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Diabetes mellitus is an important cause of mortality and morbidity in worldwide with increasing frequency over the years. According to the population-based survey in 2010, diabetes prevalence has reached 13.7% in Turkish adults[1]. Not only type 2 diabetes mellitus (T2D) but also type 1 diabetes (T1D) prevalence increased worldwide. Cell-mediated autoimmune destruction of insulin-producing beta cells leads to T1D. Overlapping of common genetic factors and immunological pathways may also affect other organs as well and linked to polyautoimmunity[2]. Autoimmune thyroid disease (ATD), gastric autoimmunity, celiac disease, vitiligo, rheumatoid arthritis (RA), systemic lupus erythematosus, and Addison's disease are the most common autoimmune diseases (ADs) seen concomitant to T1D. Older age, female sex, and longer duration of diabetes increase the risk of additional AD[3]. The importance of additional AD is that they can complicate diabetes management causing hypo or hyperglycemia, complications, and increase morbidity. Optimal screening and clinical evaluation of ADs are important for T1D patients as some of the ADs may lead to life-threatening conditions like Addison's disease.

Autoimmune pathways in the pathogenesis of T2D are less clear[4]. In recent studies, low-grade inflammation, self-reactive T-cells, and inflammatory pathways shared by ADs had shown to play role in the development and the progression to T2D[5,6]. Thus, ADs can be seen with T2D also.

Diabetes guidelines recommend routine screening for ATD and celiac disease, especially in cases of childhood-onset T1D[7]. However, the level of evidence is weak (expert opinion), and for adult-onset T1D is even less clear. Moreover, the studies on adult-onset T1D are scarce.

The aim of this study is to examine the prevalence of ADs, especially endocrine glandular ADs in T1D cases diagnosed before and after the age of 18, and to examine the relationships between ADs and glycemic control, and micro- and macrovascular complications. Individual distributions of ADs were compared with a group of patients with T2D known to have at least one AD.

Materials and Methods

The study included diabetes patients who were consecutively seen in a Diabetes Outpatient Clinic between March 1, 2016, and March 1, 2018. The medical records of a total of 1594 adult diabetes patients were reviewed retrospectively, 22% had T1D (n=351). According to our management protocol, all patients with T1D are screened for ATD, pernicious anemia, vitiligo, and when clinically relevant for celiac, Addison's, and other organ-specific/systemic autoimmune/autoinflammatory diseases. Diabetes diagnosed according to universally accepted criteria[8]. Patients with a diagnosis of maturity-onset diabetes of the young, and drug- or chemical-induced diabetes were excluded from the study. Fifty T2D patients with known at least one AD were also included in the study to compare the distribution of ADs. Other AD diseases were investigated in this T2D group. In addition, we also evaluated the level of glycemic control and the distribution of complications in both groups. Patient data on demographic and clinical characteristics, metabolic parameters (fasting blood glucose, [FBG] glycosylated hemoglobin A1c, HbA1c; and C-peptide levels, and diabetes complications were obtained from medical records.

The presence of ATD (Hashimoto's thyroiditis and Graves' disease) was evaluated on a yearly basis. Graves' disease was defined based on clinical presentation, low serum thyrotropin (TSH) with elevated serum levels of triiodothyronine (T3) and/or free thyroxine (free T4), thyrotropin receptor antibodies, and radioactive iodine uptake if needed, as stated in the literature[9]. TSH above the upper limit of normal and free T4 under the lower limit of the normal, presence of anti-thyroid autoantibodies anti-thyroglobulin and anti-thyroid peroxidase was defined as Hashimoto's disease according to American Association of Clinical Endocrinologists guidelines[10]. Macrocytic anemia with subnormal Vitamin B12 levels and positive gastric parietal cell antibody was defined as pernicious anemia. Celiac disease was screened by anti-tissue transglutaminase antibodies. All seropositive patients were referred to gastroenterology for confirmation of celiac disease (i.e., evaluation and/or small bowel biopsy). Autoimmune hypoparathyroidism was defined as low calcium, elevated phosphate levels with low serum parathyroid hormone levels. Although we could not check the 21-hydroxylase antibodies, Addison's disease was diagnosed through low serum cortisol levels, elevated ACTH levels, and lack of response to a Synacthene test. All patients were screened for cutaneous manifestations, and vitiligo was diagnosed according to clinical presentation. Non-endocrinological ADs were checked from medical records and patient interviews.

Statistical Analysis

Statistical analyses were performed using SPSS version 22.0. Normal distribution was evaluated with the appropriate test (Kolmogorov–Smirnov or Shapiro–Wilk). Descriptive statistical methods (mean, standard deviation, frequency, and ratio) were used. In two independent group comparisons, the t-test or Mann–Whitney U test was used as appropriate. Chi-square test and Fisher's Exact test were used

for comparison of qualitative data. Pearson or Spearman correlation analysis is used to test relationships between quantitative variables or categorical variables. "P"<0.05 was accepted as statistically significant.

Results

The prevalence of AD was 26.2% (n=92) in T1D with females being more affected than males. The prevalence of ATD, pernicious anemia, vitiligo, celiac disease, premature gonadal failure, and Addison's disease among T1D was 22.8%, 6%, 2.5%, 2.28%, 1.4%, and 1.14%, respectively. Clinical hypothyroidism was detected in 11.1%, and hyperthyroidism in 2.8% of T1D. General features of the whole group (n=142) with AD by diabetes type are presented in Table 1. FBG and HbA1c levels were higher in patients with T1D than T2D (p<0.05).

The number of maximum ADs was five in T1D, and three in T2D. Over 65% had single, and more than 20% had double ADs with no significant difference between T1D and T2D. The percentage of patients with three or more concomitant ADs was higher in T1D than T2D (Table 2).

ATD was the most prevalent, followed by pernicious anemia, vitiligo, celiac, and premature gonadal failure in both groups (Table 3). The majority of ATDs were thyroiditis and/or hypothyroidism (81.7%), only 12% had Graves' disease (T1D 10.9% and T2D 14%).

In T1D women, pernicious anemia (18%) and vitiligo (10%) were the most common comorbidities to ATD, whereas pernicious anemia (11%) and celiac disease (11%) were the most common comorbidities to ATD in T2D. However, Addison's disease and vitiligo were the most prevalent diseases clustered with hyperthyroidism. All patients with Addison's disease had ATDs. Similarly, 70% of the T1D patients with pernicious anemia had hypothyroidism also. Rheumatologic diseases were more commonly seen in T2D than T1D (p=0.004).

Of T1D patients, 37.7% were childhood-onset and 62.3% adult-onset. Among childhood-onset T1D patients, 62.1% had one AD, 31% had two, and 6.9% had three or more ADs. Whereas in adult-onset T1D cases, the distribution was 72.9%, 18.8%, and 8.3%, respectively. There was no statistical difference between the two groups. The percentage of cases with one and two ADs by gender was similar. Three or more ADs were seen only in women in both groups (Table 4).

FBG, HbA1c, and C-peptide levels and duration of diabetes were found to be similar in childhood and adult-onset T1D groups (data not shown).

Microvascular complications were detected in 36.4% of T1D (retinopathy in 24.7%, nephropathy in 20.8%, and neuropathy in 20.8%). In 9% of the T1D group, macrovascular complications were detected. The prevalence of microvascular complications was 31.9% in T2D (retinopathy in 14.9%, nephropathy in 19.1%, and neuropathy in 12.8%). Macrovascular complications were 12.8% in T2D.

Age, duration of diabetes, presence of diabetic micro-and macrovascular complications, and HbA1c levels did not differ between any specific or additional ADs.

Discussion

The current study showed that every fourth patient with T1D had concomitant AD. This result highlights the importance of screening for ADs among patients with T1D not only in childhood-onset but also in adult-onset cases.

Table 1. General features of the patients with type 1 and type 2 diabetes

	T1D (n=92)	T2D (n=50)
Gender-W, %	75	82
Current age, yr*	36.8 (12.32)**	55.3 (13.4)
Age-at-onset of DM, yr*	21.3 (12.5)**	43.5 (12.2)
DM duration, yr*	16.4 (10.4)***	11.6 (9.2)
FBG, mg/dL*	208.3 (93.3)***	166.1 (72)
HbA1c, %*	8.5 (1.7)***	7.7 (1.5)
C-peptide, ng/mL*	0.16 (0.32)**	3.13 (1.29)

T1D: type 1 diabetes; T2D: type 2 diabetes; W: Women; DM: Diabetes mellitus; FBG: Fasting blood glucose; HbA1c: Glycosylated hemoglobin A1c; SD: Standard deviation; yr: years. *: mean (SD); **: p<0.001; ***: p<0.05. T1D versus T2D.

Table 2. The number of autoimmune diseases in type 1 and type 2 diabetes groups

Number of additional ADs	T1D (n=92)	T2D (n=50)
Single AD, %	65.2 (W: 62.3, M: 73.9)	74 (W: 72, M: 85.7)
Double ADs, %	25 (W: 24.6, M: 26)	24 (W: 25.5, M: 14.2)
Triple ADs, %	8.7 (W: 8.7)	2 (W: 2.3)
Multiple ADs, %	1.0 (W: 1)	-

T1D: type 1 diabetes; T2D: type 2 diabetes; W: Women; M: Men; ADs: Autoimmune diseases.

Table 3. The distribution of individual autoimmune diseases

Autoimmune diseases	T1D (n=92)	T2D (n=50)	p[1]
ATD, %	87 (W: 88.4, M: 82.6)	72 (W: 74.4, M: 57.1)	0.048*
Pernicious anemia, %	22.8 (W: 23.1, M: 21.7)	12 (W: 11.6)	0.087
Vitiligo, %	9.8 (W: 11.6, M: 4.3)	10 (W: 9.3, M: 14.2)	0.591
Celiac disease, %	8.7 (W: 8.6, M: 8.7)	8 (W: 7.0, M: 14.2)	0.579
Prem gonad failure, %	5.4 (W: 4.3, M: 8.7)	4 (W: 4.6)	0.527
Addison's disease, %	4.3 (W: 5.8)	2 (W: 2.3)	0.422
Autoimmune hepatitis, %	1.1 (W: 1.4)	-	-
Hypoparathyroidism, %	1.1 (W: 1.4)	-	-
Alopecia, %	1.1 (W: 1.4)	-	-
Mc candidias, %	1.1 (W:1.4)	2 (W: 2.3)	-
Rheumatological diseases, %	3.2	18	0.004*
RA, %	2.1 (W: 2.9)	8 (W: 7)	
SLE, %	1.1 (W: 1.4)	8 (W: 7, M: 14.5)	
PSS, %	-	2 (W: 2.3)	

[1]: Fisher's Exact Test; *: p<0.05. T1D: type 1 diabetes; T2D: type 2 diabetes; W: Women; M: Men; ATD: Autoimmune thyroid disease; Prem. gonad fail: Premature gonadal failure; Mc candidias: Mucocutaneous candidiasis; RA: Rheumatoid arthritis; SLE: Systemic lupus erythematosus; PSS: Progressive systemic sclerosis.

Table 4. The number of autoimmune diseases in patients with type 1 diabetes according to the age-at-onset

Number of additional ADs	Childhood-onset T1D (n=35)	Adult-onset T1D (n=57)
Single AD, %	62.1 (W: 63.6, M: 57.1)	72.9 (W: 69.4, M: 83.37)
Double ADs, %	31 (W: 27.3, M: 42.9)	18.8 (W: 19.4, M: 16.7)
Triple or more ADs, %	6.9 (W: 9.1)	8.3 (W: 11.1)
Total ADs, %	37.7 (W: 37.9, M: 36.8)	62.3 (W: 62.1, M: 63.2)

T1D: type 1 diabetes; T2D: type 2 diabetes; W: Women; M: Men; ADs: Autoimmune diseases.

The prevalence of ADs concomitant to T1D was 26.2% which was higher than stated in the literature (18-23%) [11,12]. The first reason for that may be the inclusion of both glandular and non-glandular ADs in our study, whereas the other studies included only glandular AD[11]. The second reason may be the use of data from national health registries in the literature[11,12], whereas the results of the university hospital were evaluated in our study. Third, it may be due to the routine screening program for glandular ADs in our group. In comparison to a recent multinational meta-analysis in patients with T1D, prevalence rates of hypothyroidism, hyperthyroidism, and pernicious anemia were higher in our cohort. Moreover, the rate of adrenal insufficiency was approximately more than 5 times higher[13]. However, the prevalence of celiac disease was lower in our study compared to that in the meta-analysis. These differences may be related to diagnostic criteria used, geographical origin, genetic, and environmental differences between the studies. The prevalence of celiac disease was found at 2.28% in our study which was comparable with another study from Turkey (2.45%)[14], but lower than other studies (6-7.6%)[15,16].

Disease duration and age may affect the prevalence of ADs seen in T1D[11]. Frommer and Kahaly[17] reported a higher prevalence of Graves' disease (43%), hypogonadism (10%), type A gastritis (42%), vitiligo (18%), and celiac disease (15%) in their study compared to ours. This may be related to the differences in the mean age of the patients were older (56±16 vs. 36±12 years,), and the duration of T1D was longer (27±16 vs. 16±10 years) in that study than the present study.

Polyautoimmunity can accompany diabetes. In a recent study, it was reported that 19.7% of T1D patients had at only one, 3% had two, and 0.13% had three additional ADs which were lower than our results (17.1%, 6.5%, and 2.2%, respectively)[11]. The higher rate of additional ADs in our cohort may be due to the inclusion of patients from a tertiary center, and also our routine screening protocol, whereas

patients included in Mäkimattila et al.[11] were from a nationwide multicenter study cohort. All the patients with Addison's disease and diabetes mellitus had ATDs also in our study. Similarly, 89% of the cases in the previously published study reported at least one additional AD to Addison's disease and T1D[11]. All the patients with Addison's disease were female patients in our study. In comparison, 41% of the cases were female in Chantzichristos et al.[18], and 66% in another study[11].

Similar to the results in the literature, HbA1c levels were not different in any of the specific AD types[11,18]. In our study, FBG, HbA1c, and C-peptide levels and duration of diabetes were found to be similar in childhood and adult-onset T1D groups. Complication rates in T1D were similar to the literature[19,20]. Contrary to the literature, there was no association between retinopathy and celiac disease[21].

ADs were detected in 4% of T2D patients and the prevalence's of AD were less than stated in the literature. This may be due to not screening T2D patients for ADs routinely. We found a higher prevalence of rheumatological diseases among T2D with AD compared to T1D. Similarly, Hemminki et al.[22] reported increased T2D in patients with chorea minor, lupoid hepatitis, Addison's disease, psoriasis, and RA. Moreover, increased risks of AD after T2D were reported. In a study from Spain, an increased odds ratio was reported for newly diagnosed hypothyroidism in T2D[23]. In the current study, we did not analyze the first disease identified, whether T2D or AD and confounding lifestyle factors. We showed no significant difference between type and number of ADs and metabolic control.

The main strengths of this study are well-characterized patients and the use of certain criteria for ADs. We evaluated both glandular and non-glandular ADs in a large cohort of patients. However, there are also limitations to our study. The main limitation is the retrospective design of the study. Especially in the childhood-onset T1D group, our case number was limited. We were unable to check factors such as obesity, physical inactivity, smoking, alcohol consumption, and age at the onset of ADs.

Conclusion

Screening for ATD should be routinely considered in adult-onset T1D as in childhood-onset patients; in women we recommend further investigation for pernicious anemia, vitiligo, and celiac disease.

Ethics Committee Approval: This is a retrospective study therefore it is not needed to obtain ethics commitee approval.

Peer-review: Externally peer-reviewed.

Authorship Contributions: Concept: S.T., G.Y.Y., İ.S., A.K.Ü.; Design: S.T., İ.S., N.D., G.Y.Y.; Supervision: S.T., N.G., Ö.S.S.; Funding; SA.T., R.Ç., H.H., K.K.; Materials: Y.T., R.Ç., H.H.; Data Collection or Processing: S.T., SA.T., G.Y.Y., R.Ç., H.H.; Analysis or Interpretation: S.T., SA.T., İ.S.; Literature Search: N.G., A.K.Ü., Ö.S.S.; Writing: S.T., İ.S., G.Y.Y.; Critical Review: İ.S., N.D., K.K., M.T.Y.

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