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Organ-specific autoimmunity in type 1 diabetes mellitus: Screening with respect to glycemic control

Mohamed Ghada A. [1] and Elsayed Amira M [2].

[1] Department of Internal Medicine, Assiut Faculty of Medicine, Assiut University, Egypt
[2]Department of Internal Medicine, Benha Faculty of Medicine, Benha University, Egypt
**Corresponding author email: amiramohamady@gmail.com*

ABSTRACT

Type 1 diabetes (T1D) is a tissue-specific autoimmune disease and often associated with other autoimmune diseases; so our study aimed to define the occurrence of thyroid peroxidase antibody (TPOAb) and thyroglobulin antibody (TGAb) in autoimmune thyroid disease (AIT), tissue transglutaminase antibody (TTGAb) in celiac disease, And to evaluate the relationship between the presence of these antibodies and glycemic control. Our retrospective study included 60 Kuwaiti patients with T1D who attended and follow in Diabetes outpatient clinics of Kuwait primary health care centers during the period of 2014-2015. For them, recorded data for age, sex, duration of diabetes, Body Mass Index (BMI), HbA1c was reviewed. Patients were screened for the presence of Specific antibodies to islet antigens (ICAb), glutamic acid decarboxylase autoantibodies (GADAb), insulin autoantibodies (IAA), TPOAb, TGAb, TTGAb and also thyroid stimulating hormone (TSH) were measured by ELISA. Of the total 60 patients (20 men, 40women, mean age was17.95 ± (5.44) y; the mean duration of diabetes was 6.63 ± (4.27) y; mean HbA1c was 10.41± (1.96) %. Only 58 (96.7%) were positive for GADAb, 32 (53.3%) were positive for ICAb, and 48 (80%) were positive for IAA, 14 (23.3%) patients were positive for TPOAb, 11 (18.3%) were positive for TGAb, 10 (16.7 %) were positive for both TPOAb and TGAb; furthermore 8 (13.3%) patients were positive for TTGAb. Neither organ-specific autoimmune disease (AIT and celiac disease) nor pancreatic β cells autoantibodies had a significant association with the glycemic control. In our study, we confirmed the high prevalence of a second organ-specific autoimmune disease in individuals with type 1 diabetes. Also Subclinical forms of these disorders have no influence on diabetes control. Further research will be necessary to test these relationships in a prospective follow-up study.

Keyword: Type 1 diabetes mellitus- HbAlc - pancreatic autoantibodies – Organ-specific autoantibodies.

INTRODUCTION

T1D is a tissue-specific autoimmune disease initiated by antibodies against pancreatic β cells. Numerous autoantibodies, such as a GAD65 antibody (GADA), islet cell antibody (ICA), protein tyrosine phosphatase antibody (IA-2 antibodies [IA-2A]), and zinc transporter antibody (ZnT8A), were recognized and used for diagnosis and expectation of T1DM (1). T1D is often associated with other autoimmune diseases, such as autoimmune thyroid disease, and its frequency is estimated at more than 90% among patients with T1D and autoimmune diseases (2). Additionally, the occurrence of anti-thyroid antibodies at the onset of T1D predicts the development of future thyroid disease (3). It was noted that Patients with antithyroid antibodies are 18 times more likely to develop thyroid disease than patients without anti-thyroid antibodies (4). The association between celiac disease (CD) and type 1 diabetes mellitus (T1DM) is well described because both of them shared the same genetic background (5). Human leukocyte antigen (HLA) DQ2 and/or DQ8 are present in over 95% of patients with celiac disease and in 55% of those with T1DM compared to nearly 40% in the overall population (6). These diseases are associated with organ-specific autoantibodies: thyroid peroxidase (TPO) and thyroglobulin (TG) with autoimmune thyroid disease (AIT), endomysial (EMA) autoantibodies and transglutaminase (TTG) autoantibodies with CD, and 21-hydroxylase (21-

OH) autoantibodies with Addison's disease (AD). Detection of these autoantibodies before the development of the clinical disease has the potential to prevent significant morbidity related to unrecognized disease (7).

Aim of the study:
The aim of the present study was directed to evaluate the prevalence of serum anti-TPO autoantibodies, anti-TG autoantibodies, and TTG autoantibodies in adolescent and young adult type 1 DM. And to evaluate the relationship between these antibodies and glycemic control.

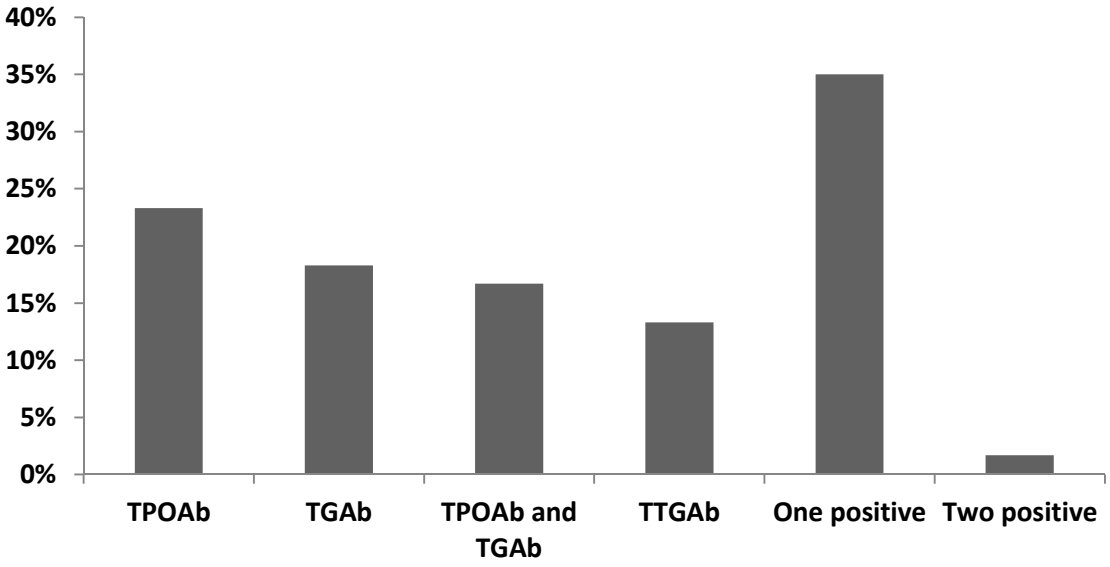
Research design and methods:
Our retrospective cross-sectional study conducted on patients with T1DM who were followed up at Diabetes outpatient clinics of Kuwait primary health care center during the period of MAY 2014 to May 2015. The study population consisted of 60 adolescents and young adult patients with T1DM aged 13 to 35 years. The recorded data were obtained, including; all laboratory findings, clinical, demographic information, data regarding "status of the patients, metabolic control, and the existence of other autoimmune diseases". Patients with a major shortage of data and those with secondary or monogenic diabetes, and/or polyendocrinopathies were excluded from the study. Glycated hemoglobin (HbA1c) is the most frequently used test to measure the glycemic control. All patients were divided into 3 groups according to the glycemic control as follows: good glycemic control (HbA1c <7%), moderate glycemic control (HbA1c 7-9%), and poor glycemic control (HbA1c >9%). Serological markers of the autoimmune process that indicate and can predict T1DM, such as glutamic acid decarboxylase antibodies (anti-GAD), islet cell autoantibodies (ICAb) and insulin autoantibodies (IAA) and Data on glycemic control were recorded from the patients' medical histories. Detection of AIT was based on physical examination and laboratory findings, including the serum levels of free thyroxine (FT4), thyroid-stimulating hormone (TSH), anti-thyroid peroxidase, and anti-thyroglobulin. The presence of at least one positive antibody in addition to low serum FT4 (normal range, 12-22 pmol/L) and high TSH levels (normal range, 0.27-5 mIU/L) was mandatory to establish the diagnosis (8). The diagnosis of CD was based on the presence of tissue transglutaminase antibody (TTGAb.). Serum levels of free T4 (fT4), thyroid-stimulating hormone (TSH), anti-thyroid peroxidase, and anti-thyroglobulin, TTGAb were determined by commercial kits and the results were expressed as positive and negative according to the reference ranges provided by the laboratory.

Statistical analyses
Collected data were reviewed and analyzed using the Statistic Package for Social Science (SPSS) version 16. Values were expressed as percentages, means ± SD. Normally distributed continuous variables compared with 2-independent samples t-test, Mann-Whitney test was used for non-normally distributed continuous variables. The chi-Square test was used to compare qualitative data. The level of significance was taken as the P-value of ≤ 0.05.

RESULTS

Of the 60 individuals recruited in the study, 40 (66.7%) were females and males were 20 (33.3%), with the mean age was17. 95 ± (5.44) y; the mean duration of diabetes was 6.63 ± (4.27) y and the mean BMI was 22.93 ± (4.74) Kg/m^2. Our result showed that mean HbA1c was 10.41± (1.96) % with 23.3% showed moderate glycemic control (HbA1c 7-9) and 75% showed poor glycemic control (HbA1c > 9), neither organ-specific autoimmune disease (AI thyroid and celiac disease) nor pancreatic β cells autoantibodies had significant association with the glycemic control. All subjects had autoantibodies measured once. Of the study group, 58 (96.7%) were positive for GAD autoantibodies, 32 (53.3%) were positive for islet autoantibodies, and a 48 (80%) were positive for insulin autoantibodies (table 1). Our study revealed, 14 (23.3%) patients were positive for TPOAb, 11 (18.3%) were positive for TGAb, 10 (16.7 %) were positive for both TPOAb and TGAb. Furthermore, 8 (13.3%) patients were positive for TTGAb. As regards to the prevalence of organ-specific autoantibodies in type 1 diabetic patients, we found 21 subjects (35%) were Positive for either one of those organ-specific autoantibodies (thyroid or celiac autoantibodies), and only one individual was positive for two organs-specific autoantibodies (thyroid and celiac). The prevalence of positive autoantibodies is shown in (Fig. 1). In our study, thyroid function test results showed 14 patients (23.3%) had subclinical hypothyroidism and 2 patients had hypothyroidism. There was a significant association between subclinical hypothyroidism and thyroid autoimmunity (p= < 0.001). The thyroid autoantibody positive subjects were more likely to be female than male (20 vs. 5%), but with no significant difference, also there was no significant association with age and the positive subject of TTGAb. There was a significant association between detected thyroid autoimmunity and longer duration of diabetes ($U = 179.5$, $p = 0.007$). Individual's positive for TTGAb had no significant association with Sex, age, duration of diabetes and thyroid autoantibodies. In our study, there was a statistically significant difference (P= 0.017) in the association of thyroid autoimmunity to ICA with more prevalence of thyroid autoimmunity in patients who were negative for ICA than Patients who were positive for ICA (18.3 vs. 6.7 %,) respectively. But there was no significant association between GAD autoantibodies, insulin autoantibodies and thyroid autoimmunity. When gender was taken in consideration, females

showed more positive results in all detected autoantibodies except GAD autoantibodies which more positive in males than females (100% vs. 95%) respectively; this comparison between male and females as regard to autoantibodies distribution statistically not significant (P> 0.05) (Table 2). Our result described significant association between duration of diabetes prevalence of pancreatic B cell autoantibodies (GADAb and ICA) and TPOA; it showed that patients who were negative for (GADAb and ICA) had long duration in comparison to patients who were positive, in contrast, patients who were positive for TPOA had a longer duration than those who were negative for TPOA. (Table 3).



TPOAb= thyroid peroxidase antibody; TGAb= thyroglobulin antibody; TTGAb= tissue transglutaminase antibody.

Figure 1: Prevalence of positive autoantibodies in 60 individuals with type 1 diabetes.

Table 1: Initial Characteristics of Patients with Type 1 Diabetes

Age, years	17.95 ± 5.44
Gender Female Male	 40 (66.7%) 20 (33.3%)
T1D duration of DM (year)	6.63 ± 4.27
BMI (Kg/m^2)	22.93 ± 4.74
HbA1c, %	10.41± 1.96%
GAD autoantibodies	58 (96.7%)
ICA	32 (53.3%)
IAA	48(80%)

BMI=Body Mass Index; HbA1c= Glycated hemoglobin; GAD= Glutamic Acid Decarboxylase; ICA= islet cell antibodies; IAA: Insulin autoantibodies.

Table (2): Distribution of positive autoantibodies in 60 individuals with type 1 diabetes according to the gender.

Parameters	Type 1DM		P value
	Females (n=40)	Males (n=20)	
GAD	38/40 (95%)	20/20 (100%)	>0.05
ICA	23/40 (57.5%)	9/20 (45%)	>0.05
IAA	34/40 (85%)	14/20 (70%)	>0.05
TPOAb	11/40 (27.5%)	3/20 (15%)	>0.05
TGAb	8/40 (20%)	3/20 (15%)	>0.05
TTGAb	7/40 (17.5%)	1/20 (5%)	>0.05

GAD= Glutamic Acid Decarboxylase; ICA= islet cell antibodies; IAA: Insulin autoantibodies; TPOAb= thyroid peroxidase antibody; TGAb= thyroglobulin antibody; TTGAb= tissue transglutaminase antibody.

Table (3): Relation between duration of diabetes and detected autoantibodies

Duration of DM	P values					
	GAD	ICA	IAA	TPOAb	TGAb	TTGAb
	0.018	< 0.001	0.052	0.005	0.061	0.844

GAD= Glutamic Acid Decarboxylase; ICA= islet cell antibodies; IAA: Insulin autoantibodies; TPOAb= thyroid peroxidase antibody; TGAb= thyroglobulin antibody; TTGAb= tissue transglutaminase antibody.

DISCUSSION

T1D is associated with the presence of additional autoimmune diseases such as AIT, CD, and AD, which are accompanied with the production of organ-specific autoantibodies. These autoantibodies can be used to screen individuals with T1D for autoimmunity associated with clinical disease. The current American Diabetes Association (ADA, 2015) recommendations are to screen for celiac antibodies shortly after diagnosis of DM, unexplained hypoglycemia, in symptomatic patients, or deteriorations in glycemic control. In addition to the screening of autoimmune thyroid disease soon after diagnosis of DM1, then at 1-2 years intervals or sooner if the patient becomes symptomatic, abnormal growth rate, or unusual glycemic variations (9). Our study revealed high prevalence of a second organ-specific autoimmune disease in individuals with type 1 diabetes; this came in accordance with Jennifer et al (10) who stated that the appearance of Organ-specific autoantibodies in type 1 diabetes was very high. IAA only has clinical value for diabetes classification if measured before starting treatment with exogenous insulin. ICA, IA-2A commonly decline after the diagnosis of T1D. Therefore, ICA, IA-2A and IAA have a narrow role in the investigation of patients with long-standing disease. However, GADA appears to remain positive for long periods of time (11). Our study showed a significant long duration of diabetes in those patients who were negative for GADA (P=0.018) and ICA (p=< 0.001); This came in contrast to study done by Rodacki et al (12) who reported that duration of disease has no impact on the prevalence of GADA or its titers in patients with T1D after one year of diagnosis. Also, Borg et al (13) stated a high rate of persistence of GADA positivity (81%) in a 12-year follow-up study. IAA was present in 80% of cases because these patients were on insulin therapy. In our study, females showed non-significant more positive results for most of the detecting autoantibodies. The explanation of this finding is the fact that autoimmune disease is more common in females than males and the reasonable causes for this difference would be the sex hormone, females might respond more to conventional antigen due to sex hormone (14)**.** In the present study, we reported different types of thyroid dysfunction; 3.3 % of serum anti-TPO positive cases with clinical hypothyroidism (defined as a raised serum TSH and a low free serum T4 level) and 13.3% of anti-TPO and anti-TG positive cases with subclinical hypothyroidism (defined as elevated serum TSH concentrations with serum free thyroxine (T4) levels within the reference range). Magdy et al reported that despite serum TSH screening is more sensitive for identifying thyroid abnormalities in type1 diabetics, the presence of positive serum anti-TPO antibodies may be an earlier marker for thyroid disease. So, patients with positive antibodies should be checked for serum TSH elevation at yearly intervals. (15)**.** The present study showed that there was no relationship between the level of control of diabetes (HbA1c level) and anti-TPO antibody positivity (P = 0.299). The same finding was reported by Prazny et al, Kakleas et al, and Hansen et al (16-18). CD and T1DM are associated with genetic loci on the short arm of chromosome six. The HLA loci give the main genetic predilection, but both diseases also depend on the involvement of many non-HLA genes with a small effect. Consequently, a high prevalence of CD is reported in patients with T1DM worldwide with a large percentage of individuals being asymptomatic (19). In accordance with our result Sanjay et al reported that Celiac disease is highly prevalent in patients with type 1 diabetes mellitus (11.1%) and most of them (90.5%) were diagnosed with screening. (20) In our study there was no significant relationship between the control of diabetes evaluated by HbA1c and organ-specific antibody positivity; this came in accordance to study done by Prazny et al(16) . This may be explained by of the subclinical form of the disease, so autoantibody positivity alone might have no influence on the control of diabetes and small numbers of the patients in the study.

CONCLUSION

Screening of autoimmune diseases has important significances for the clinical care of individuals with type 1 diabetes, as it adds encumbrance of more than one disease in the patients (e.g; T1DM and celiac disease) and more complications. In our study, we confirmed the high prevalence of a second organ-specific autoimmune disease in individuals with type 1 diabetes. Also Subclinical forms of these disorders have no effect on diabetes control.

Recommendation: We recommend screening for thyroid disease on a yearly with a serum TSH and TPO autoantibody and for celiac with autoantibody testing every 2 years and at any time of manifestations. Also, as a subset of the subjects with organ-specific autoantibodies will develop a clinical disease, so follow-up of patients with positive autoantibodies is necessary because further deterioration of the corresponding organs may occur.

Limitation of the study:
This study is limited because small sample size and confirmatory small-intestinal biopsies for the CD were not performed on all TTGAb positive subjects. Further research will be necessary to test these relationships in a prospective follow-up study.

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