The Profile of Autoimmunity in Type 1 Diabetes Patients

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Abstract

Background: Type 1 diabetes mellitus (T1DM) is an autoimmune disorder caused by pancreatic β-cells destruction. Anti-pancreatic antibodies are the witness of β-cell destruction and their dosage is mainly used for etiological diagnosis. Patients with T1DM are at increased risk of developing other autoimmune reactions, which may involve other organs, resulting in organ specific autoimmune disease. The most frequently encountered are autoimmune thyroid disease, followed by celiac and gastric disease and other rare autoimmune diseases. Objectives: The purpose of this study is to investigate the prevalence of autoimmune markers in patients with T1DM. Methods: The study was conducted at the Department of Endocrinology of the Military Hospital Moulay Ismail in Meknes Morocco, from January 2016 to December 2018. All Type 1 diabetes patients consulting during the study period were included in the study. Their clinical and biochemical data were collected at their first presentation, made up of anti-pancreatic antibodies (glutamic acid decarboxylase [GAD] antibody, tyrosine phosphatase antibody, and islet cell antibody) and other organ-specific antibodies: the thyroid (antithyroid peroxidase antibody, antithyroglobulin antibody, and antithyroid-stimulating hormone receptor antibody), the intestine (IgA antitissue transglutaminase antibody), the adrenal gland (anti-21 hydroxylase antibody), and the stomach (antigastric parietal cell antibody and anti-intrinsic factor antibody). Results: Fifty-four patients were included, with an average age of 26 years. GAD, tyrosine phosphatase, and islet cell antibodies were detected in 74%, 22%, and 3.7%, respectively, of the 54 patients examined. The prevalence of extrapancreatic autoimmunity was 45% with a large preponderance among different immunities of those from thyroid and celiac diseases (CDs). Conclusion: Our results confirm that patients with Type 1 diabetes should be investigated for the presence of autoimmune diseases mainly from thyroid and CDs.

Keywords: Autoimmunity, celiac disease, thyroiditis, type 1 diabetes

Résumé

Contex: Le diabète sucré de type 1 est une maladie auto-immune causée par la destruction des cellules bêta pancréatiques. Les anticorps anti-pancréatiques sont les témoins d’une destruction des cellules β et leur dosage est principalement utilisé pour le diagnostic étiologique. Les patients atteints de diabète de type 1 courent un risque accru de développer d’autres réactions auto-immunes, qui peuvent impliquer d’autres organes, entraînant une maladie auto-immune spécifique à l’organe. Les plus souvent rencontrées sont les maladies thyroïdiennes auto-immunes, suivies des maladies cœliaques et gastriques et d’autres maladies auto-immunes rares. Objectifs: Le but de ce travail est d’étudier la prévalence des marqueurs auto-immunes des patients atteints de diabète de type 1. Méthodes: L’étude a été menée au Département d’Endocrinologie de l’Hôpital Militaire Moulay Ismail à Meknès Maroc, de janvier 2016 à décembre 2018. Tous les patients diabétiques de type 1 consultant pendant la période d’étude ont été inclus dans l’étude. Leurs données cliniques et biochimiques ont été recueillies à leur première présentation, composées d’anticorps anti-pancréatiques (anticorps anti-acide-glutamique décarboxylase, anticorps anti-tyrosine phosphatase, et les anticorps anti-cellules des îlots de langerhans) et d’autres anticorps spécifiques à certains organes: la thyroïde (anticorps anti-thyroperoxydase, anticorps anti-thyroglobuline et anticorps anti-récepteur de thyroid stimulating hormone), l’intestin (anticorps anti-transglutaminase IgA), la glande surrénale (anticorps anti-21 hydroxylase) et l’estomac (anticorps anti-cellules pariétales gastrique et anticorps anti-facteur intrinsèque). Résultats: 54 patients

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INTRODUCTION
Type 1 diabetes mellitus (T1DM), better known as “classic autoimmune type diabetes,” is the final consequence of an insulitis process, responsible for the destruction of β cells in the islets of Langerhans which results in complete insulin deficiency. Antipancreatic autoantibodies are therefore witnesses to cell destruction releasing “antigenic material.” Five types of antibodies are in common use. They are directed against enzymes or membrane proteins or cytoplasmic: glutamic acid decarboxylase antibodies (GADA), tyrosine phosphatase antibodies (IA2A), insulin autoantibodies (IAA), islet cell antibodies (ICA),[1] and the zinc transporter antibodies (anti-ZnT8 antibody).

Patients with T1DM may also develop organ-specific multiple autoimmunity in the context of autoimmune polyendocrine syndrome (APS) type 1 or 2. The most frequently encountered associated autoimmune disorders in T1DM are autoimmune thyroid, followed by celiac and autoimmune gastric disease and other rare autoimmune diseases.

Etiological diagnosis of diabetes and screening for autoimmunity associated with T1DM requires better knowledge of the prevalence of antibodies. There are limited previous studies on the prevalence of associated autoimmunity in T1DM.

OBJECTIVES
The present study reports on the prevalence of pancreatic autoimmunity and of all associated autoimmune disorders in T1DM and suggested screening and follow-up strategies for early detection and management.

METHODS
The study was conducted at the Department of Endocrinology of the Military Hospital Moulay Ismail in Meknes Morocco from January 2016 to December 2018. All T1DM patients consulting during the study period were included. The only criterion for noninclusion was the absence of biological confirmation of type 1 diabetes based on the positivity of antipancreatic auto antibodies.

The information collected concerned age, gender, autoimmunity signs (personal and family antecedent of autoimmunity and research vitiligo at inspection), and duration of diabetes. At the biological level, the antibody test concerned antipancreatic antibodies (GADA, IA2A and ICA) and specific antibodies to organs: the thyroid (anti thyroid peroxidase [anti TPO]), anti thyroglobulin [anti TG], anti thyroid stimulating hormone receptor antibody [TRAb]), the intestine (IgA anti-tissue transglutaminase antibody [anti-TTG]), the adrenal gland (anti-21 hydroxylase antibody or adrenocortical antibodies [ACA], and the stomach (anti gastric parietal cell antibody [GPCA] and anti-intrinsic factor antibody [IFA]).

All the study participants signed informed consent, as recommended by an ethics committee.

Statistical analysis
Data were plotted on a table in the Excel 2010 program. Statistical Package for the Social Sciences (SPSS), Version 23.0. Armonk, NY: IBM Corp. was used for the statistical analyses. The results were given as percentages and mean standard error otherwise as median. A probability level of a random difference of \( P \leq 0.05 \) is considered significant.

RESULTS
A total of 54 patients were included in the study, 40 men and 14 women. Patients age ranged between 8 and 55 years, with an average of 26 years at the time of the consultation and 18 years at the time of diagnosis of diabetes. Twenty-five percentage of our patients have a recent discovery of diabetes, and the average duration of diabetes was 8 years. According to the clinical data, vitiligo and antecedent (personal or family) of autoimmunity were found in four and six patients, respectively. The distribution results of the different antipancreatic auto antibodies is shown in Table 1. The GADA, IA2A, and ICA were present in 40, 12, and 2 patients, respectively. Extrapancreatic antibodies were detected in about half of the patients, namely revealed the presence of anti-TPO, anti-TG, TRAb, and anti-tTG in 11, 3, 5, and 6 of these cases, respectively. The other antibodies ACA and GPCA were positive in only one case, while the IFA was negative in all patients. Table 2 shows the results details of the autoimmunity parameters prospection in the studied population.

DISCUSSION
Pancreatic autoimmunity
The immune destruction of pancreatic beta cells is associated with various antigens. Antibodies against some of these antigens are used in clinical practice to assist in the diagnosis of diabetes type and they are considered well predictors of the disease.[2] Moreover, the assay of these antibodies detection can be used for other purposes such as family screening or the autoimmunopolyendocrine syndrome.[3] These include GADA, ICA, IA2A, IAA, and anti-ZnT8 antibodies.[2-4] The ICA is characteristic of

Mots-clés: Auto-immunité, maladie cœliaque, thyroïdite, diabète de type 1
the onset of T1DM,[5] and its serum levels decrease each year after diagnosis.[6] The anti-ZnT8 antibodies come later than the GADA and IAA.[2] IAA has a little value after onset of insulin therapy.[5-7] In our study, IAA was not measured because all patients took insulin prior to admission as well as anti-ZnT8 antibodies because of lack of availability. GADAs are detected in 70%–80% of patients with T1DM long before the clinical manifestations of the disease and remain positive for a long time after. This antibody targets glutamic acid decarboxylase (GAD), an enzyme protein with a molecular weight of 64,000 Da, essential in the synthesis of γ-aminobutyrate in pancreatic cells. GAD enzyme is also located in the brain, the stomach, and the thyroid gland in the form of two isomers, GAD65 and GAD67. GAD-65 is the antigenic target for T1DM.[9] Loss of immune tolerance on GAD65 coincides with the onset of insulitis and the detection of GADA.[9,10] These findings indicate a significant involvement of GAD antigen in the triggering of the autoimmune process in patients with T1DM.[11] Our series are consistent with the data from the literature. Indeed, the enregistered prevalence of GADA was 74% and 89% to discovery of diabetes.

Hence, we retain that GADA is considered the ideal marker for patients who have T1DM for a long time and are treated with insulin because its presence remains positive for many years after diagnosis.

Extrapancreatic autoimmunity

Regarding the autoimmune field, vitiligo retains the first place in Tunisian[12] and Indian[13] studies as well as in our, even at variable rates. Tunisian series reported a higher rate of pathology family autoimmunity compared to our study.

**Table 1: Prevalence of antipancreatic antibodies from the study patients**

| Antibodies             | Prevalence (%) |
|------------------------|----------------|
| GADA                   | 74.0           |
| IAA                    | 22.0           |
| ICA                    | 3.7            |
| GADA and IAA           | 14.8           |

GADA=Glutamic acid decarboxylase antibodies, IAA=Tyrosine phosphatase antibodies, ICA=Islet cell antibodies

**Table 2: Prevalence of extrapancreatic antibodies of the study patients**

| Antibodies             | Prevalence (%) |
|------------------------|----------------|
| Anti-TPO and anti-TG   | 26.7           |
| TRAb                   | 9.0            |
| anti-TG (IgA)          | 11.1           |
| ACA                    | 1.9            |
| GPCA                   | 1.9            |
| IFA                    | 0.0            |

Anti-TPO=Anti-thyroid peroxidase antibody, anti-TG=Anti-thyroglobulin antibody, TRAb=Anti-thyroid-stimulating hormone receptor antibody, anti-TG=Anti-tissue transglutaminase antibody, ACA=Adrenocortical antibodies, GPCA=Anti-gastric parietal cell antibody, IFA=Anti-intrinsic factor antibody

**Thyroid autoimmunity**

The prevalence for thyroid autoantibodies in individuals with T1DM varies in different countries and ethnic groups from 7% to 35%.[14] Our study found prevalence rates of 26% for anti-TPO and anti-TG. It is not known whether these antibodies are directly responsible for the pathogenesis of thyroid disease or are the result of destruction mediated by T-cell infiltration in the thyroid.[15] In international studies, the prevalence of anti-TPO and/or anti-TG in patients with T1DM ranged from 7% to 36%. Kawasaki found a prevalence of anti-TPO of 36% and Kahaly and Hansen and Porandalaa et al. found prevalence rates for anti-TPO in 29% and 17% of the patients, respectively.[15-17] In the study of Taylor, anti-TPO was positive in 12% of the patients.[18] Kota et al. and Levin et al. obtained the lowest prevalence of 8% and 7% for anti-TPO, respectively, after the diagnosis of T1DM[13,19] [Table 3].

Furthermore, in T1DM patients, the prevalence of thyroid auto-antibodies increases with female gender, increasing age and diabetes duration.[20,21] In these studies, female adolescents with T1DM are three times more prone to develop positive anti-TPO, compared to males. Indeed, in animal models and patients with T1DM, estradiol has been found to accelerate the progression of autoimmune disease by interfering in the T helper type 2 cell pathway, while androgens had a protective effect.[22,23] Furthermore, the highest prevalence of thyroid auto-antibody positivity was observed around puberty (14–15 years) and after 3–4 years of diabetes duration. The higher prevalence of thyroid autoimmunity found in our series compared to the literature can be explained by the

**Table 3: Prevalence of thyroid autoimmunity in type 1 diabetes mellitus in different studies**

| Studies                  | Prevalence of thyroid autoimmunity (%) |
|--------------------------|----------------------------------------|
| Kawasaki[15]             | 36.0                                   |
| Kota et al.[13]          | 8.0                                    |
| Levin et al.[19]         | 7.4                                    |
| Kahaly and Hansen[16]    | 29.0                                   |
| Porandalaa et al.[17]    | 16.6                                   |
| Taylor[18]               | 12.3                                   |
| Our series               | 26.0                                   |

**Table 4: Prevalence of celiac disease in Type 1 diabetes mellitus in different studies**

| Studies                  | Prevalence of celiac disease (%) |
|--------------------------|----------------------------------|
| Graja et al.[12]         | 6.4                               |
| Eisenbarth and Gottlieb[25] | 35.0                          |
| Kota et al.[13]          | 6.9                               |
| Rewers et al.[26]        | 16.4                              |
| Tiberti et al.[27]       | 12.8                              |
| Bhadada et al.[28]       | 9.2                               |
| Djurić et al.[29]        | 7.4                               |
| Taylor[18]               | 24.6                              |
| Our series               | 11.1                              |
higher age of our patients (the average was 30 years) and by the higher duration of the diabetic disease (average duration of diabetes was 10 years). However, most of our patients were male (given the method of recruiting in a military hospital), which has a lowering effect according to literature and so it is in opposition with our results showing an increased prevalence.

**Celiac disease**
Celiac disease is an autoimmune disease, found in 0.2%–5.5% of children in the general population, with the lowest incidence in Germany and the highest in Algeria.[24] Several studies demonstrated the greater prevalence of the disease in patients with T1DM; it fluctuates between 6% and 35%.[12,13,18,25-29] Our study found prevalence rates of 11% for anti-tTG [Table 4], which stands in this scope.

Eisenbarth and Gottlieb. showed that 35% of the patients with T1DM had anti-tTG. In the studies of Rewers et al. and Tiberti et al., the prevalence rates for anti-tTG were 16% and 13%, respectively.[25-27] However, the lowest prevalence was recorded in Graja et al.’s study.[12]

The high prevalence of the presence of anti-tTG is associated with younger age at diagnosis, longer duration of T1DM, and the ethnic origin (Finland, United States, South America, Middle East, Northern India, and North Africa).[27,30] Consistent with these findings, the high prevalence in our series can be explained by our study context, where all patients are from Moroccan origin, the average age at discovery of T1DM was 18 years, and its average duration was sufficiently long (10 years).

Our results suggest a systematic screening for these antibodies, which is in agreement with the recommendations of learned societies, particularly the American Diabetes Association, which suggests it, through Expert consensus.

**Addison’s disease**
The association of Addison’s disease (AD) and T1DM is not common and indeed has been found to be 0.8%–2%.[13,15,18,31] [Table 5].

In childhood diabetes, two previous studies[34,35] reported no patient with ACA positivity among 144 and 461 children and adolescents, respectively, with T1DM. The prevalence of ACA antibodies in adult T1DM patients has been found to be 0%–4%.[32-31] Our study found one case of AD who has a positive ACA with the prevalence of 1.9%.

Given the low number of patients in our series and the rarity of the association, we do not think that we had a case and this is probably explained by the high prevalence of thyroid autoimmunity (26.7%). Indeed, T1DM and co-existent autoimmune thyroid disease had a high prevalence of ACA; it was found that approximately 70% of the T1DM population sample with positive ACA were also affected by thyroid autoimmunity.

**Biermer's anemia**
Finally, with regard to gastric autoimmunity associated with T1DM, we found only one case with asymptomatic positive anti-parietal cell antibodies (APCA) (1.9%). Indeed, in adult patients with T1DM, the prevalence rate of APCA is 2%–30%[12,13,32,33] [Table 5], while in T1DM children and adolescents, the values are 5.3%–7.5%, while the prevalence rate is 2.5% in nondiabetic adults in their third decade of life.[20,26]

This disparity in prevalence is explained by several factors, such as age, gender, or diabetes duration in the development of APCA.[12] The presence of APCA has been associated with older age of T1DM patients, longer diabetes duration,[36,37] and female gender.[38] However, in our study, we found no explication of the low prevalence of gastric autoimmunity.

**Conclusion**
In our context, the GADA and the IA2A are the best diagnostic test, they will allow the diagnosis of T1DM in more than 80% of cases. These results will be discussed again by looking for anti-ZnT8 antibody which have a higher prevalence than IA2A in the literature. Regarding extrapancretic autoimmunity, our results recommend that all Moroccan patients with T1DM should be investigated for the presence of thyroid and celiac autoimmunity at the time of diabetes diagnosis and annually thereafter. The other autoimmunities should be screened in presence of more indicator, especially in the presence of a relevant family history, or in the association with more autoimmunity affections (APS).

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**Conflicts of interest**
There are no conflicts of interest.

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