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ORIGINAL ARTICLE

Immunological and genetic profile of a group of Algerian patients with type 1 diabetes

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KEYWORDS

Type 1 Diabetes;
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Autoimmune Thyroid Disease;
Vitamin D;
HLA.

Abstract

Introduction: The aim of this study is to investigate the prevalence of autoimmune markers and vitamin D dosage in patients with T1D, and to study the association between HLA class II genes and T1D. **Methods:** The study was carried out firstly on 54 patients who were tested for antibodies to insulin (IAA), glutamic acid decarboxylase 65 (GADA) and insulinoma-2 antigen (IA-2A). Patients with at least one positive autoantibody (Ab) then underwent further testing for autoantibodies to thyroid peroxidase (TPOAb), thyroglobulin (TGAb), tissue transglutaminase (tTG IgA/IgG), serum 25-hydroxy vitamin D [25(OH)D] and screening for the HLA-DR/DQ haplotypes. **Results:** We found that GADA was the most common islet Ab (90%), followed by IA2-A (36.7%) and then IAA (12.5%). 16.7% of the T1D patients were positive for tTG IgA/IgG Ab compared to no positive individuals in the control group ($P=0.02$). There was also a significant difference in 25(OH)D dose (ng/ml) between the T1D and control groups (25.96 ± 8.32 ; 17.47 ± 8.96 , $P=0.0003$). No significant differences were observed between the T1D group and the control group in the positivity of TPOAb (23.3% vs 6.7%; $P=0.071$), TG Ab (6.7% vs 0%; $P=0.150$), and both (23.3% vs 6.7%; $P=0.071$). HLA DRB1*03 (DR3), DRB1*04 (DR4), DQB1*02:01 (DQ2) and DQB1*03:02 (DQ8) were highly expressed in the T1D group compared to healthy controls (83.3% vs. 31.4%, $P<10^{-6}$), (46.7% vs. 26.4%, $P=0.028$), (66.7% vs. 39.3%, $P=0.006$) and (63.3% vs. 19.3%, $P<10^{-5}$) while HLA DR7 and HLA DQ6 were weakly expressed (3.3% vs. 17.9%, $P=0.045$) and (6.7% vs. 32.9%, $P=0.004$). **Conclusion:** People with T1D are prone to other autoimmune diseases. Low vitamin D levels are associated with an increased risk of developing T1D. HLA DR3, DR4, DQ2 and DQ8 alleles are significantly associated with T1D, whereas HLA DR7 and DQ6 alleles are protective against T1D in Algerian T1D patients.

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Introduction:

Type 1 Diabetes (T1D) accounts for 5–10% of diabetes and is due to cell-mediated autoimmune destruction of the pancreatic β -cells (1–3). It usually manifests in childhood but can occur at any age (2).

Multiple autoantibodies increase the risk of developing clinical T1D (2). Autoimmune markers play a significant role in T1D (4). They include islet cell autoantibodies, autoantibodies to glutamic acid decarboxylase 65 (GADA), insulin (IAA), the tyrosine phosphatases islet antigen 2 (IA-2A), and zinc transporter 8 (2,5). The presence of one or more anti-islet autoantibodies is a defining feature of T1D, with 90% of newly diagnosed patients being positive for at least one of them at the time of diagnosis (5,6).

Latent autoimmune diabetes in adults (LADA) is slowly evolving autoimmune diabetes in adults, often without the typical symptoms seen in T1D and characterized by the presence of at least one diabetes-associated autoantibody, adult-onset diagnosis, and preserved beta cell function at the time of diagnosis (3).

T1D is a complex autoimmune disease involving a complex interaction of genetic and environmental factors. For this reason, our study will focus on the usefulness of islet autoantibody testing in the diagnosis of T1D. We will then investigate the immunological status of autoimmune thyroid disease (AITD) and celiac disease (CD), as well as the dosage of vitamin D in patients with T1D.

Finally, we will study the association between HLA class II genes and T1D.

Material and methods:

1- Study Populations and methods:

A- Patients:

The study was carried out firstly on 54 patients between children and adults. The patients were sent to our medical immunology laboratory in the period from December 2022 up to August 2023 for the dosage of islet autoantibody: IAA, GADA, and IA-2A; in the context of confirmation of a diagnosis of T1D or in patients showing a diagnostic difficulty between T1D (including LADA) and other types of diabetes.

All of patients had biological confirmation of hyperglycaemia (either fasting blood glucose level or HbA_{1c}). They were also recently diagnosed diabetics (Diabetes developed within 1 year; average of 3.21 ± 3.97 months).

First, all serum samples were tested for GADA, IA-2A, and IAA. Then, patients with at least one positive autoantibody (to ensure the autoimmune origin of the T1D) received further tests of:

- Serum markers specific for other autoimmune diseases (AID):
 - ✓ Autoimmune thyroid disease (AITD): Autoantibodies against thyroid peroxidase (TPOAb), thyroglobulin (TGA_b), of which patients who returned positive for one of them benefited from the TSH, T₃ and T₄ assays
 - ✓ Celiac disease (CD): IgA/IgG autoantibodies against tissue transglutaminase (tTG) then determination of tTG IgA for those returning positive.
- Serum 25-hydroxy vitamin D [25(OH)D] measurement as well as a screening for the HLA-DR/DQ haplotypes.

Note: For IAA, positivity was retained only if the patient is not yet on insulin therapy or on insulin for just 2 weeks. It is worth reminding that autoimmunity to insulin cannot be distinguished from antibodies to exogenous insulin appearing roughly two weeks after the first insulin injection in T1D cases (4,5).

B- Control population:

The control population was composed of 30 healthy subjects between children and adults, non-diabetics, without any personnel or family histories of AID and had not taken vitamin D supplements within the last six months (Table1).

- For the genetic susceptibility study, the control population consisted of 140 healthy unrelated adult subjects with no chronic or autoimmune disease and no family history of AID (7).

Table 1. Demographical, clinical and biological characteristics of diabetic patients and healthy control.

Variable	Patients with diabetes (n=54)	Control Group (n=30)
Age (years) mean $\pm$ SD [extremes].	23.13 $\pm$ 12.45 [2-47]	20.86 $\pm$ 9.36 [4-40]
Under age 18	19	11
Over 18	35	19
Gender		
- Male, n (%)	34 (62.96%)	15 (50%)
- Female, n (%)	20 (37.04%)	15 (50%)
Diabetes duration (months) mean $\pm$ SD	3.21 $\pm$ 3.97	//
HbA_{1c} (%) at diagnosis (mean $\pm$ SD) [extremes]	11.26 $\pm$ 2.54 [6-18]	//
fasting blood glucose level at diagnosis (mean $\pm$ SD) [extremes]	3.46 $\pm$ 1.97 [1-15]	//

SD, Standard deviation.

2- Methods:

✓ The search for IA-2A and GADA has been realised by simple sandwich ELISA technique (EUROIMMUN a PerkinEimer company) while the search for IAA was carried out using the chemiluminescence technique (Maglumi X3, Snibe).

✓ TPOAb, TSH, T3 and T4 were measured by chemiluminescence technique (Immilit 2000 XPi, SIEMENS Healthineers) except for TGAb which was measured by chemiluminescence technique (Cobas e 411 Roche).

✓ The tTG IgA/IgG and tTG-IgA tests were performed using the Elisa technique.

✓ The determination of 25(OH)D was carried out by chemiluminescence technique (YHLO iFlash I800).

✓ The Screening for the HLA-DR/DQ haplotypes was performed using Polymerase Chain Reaction-Sequence Specific Primer (PCR-SSP) using the ONE LAMDA kit. This step was carried out after having previously extracted the DNA using the Salting out technique and checking its purity. The final step was the detection of the amplicons after Agarose gel electrophoresis.

3- Statistical analysis:

The study of the normality of the distribution of the variables as well as the overall statistical analysis were performed using IBM SPSS Statistics V 21.

The χ^2 test was used to compare categorical variables between the groups while t-test was used to compare two continuous variables. Significance was accepted when $P < 0.05$.

An OR of 1.0 indicates no disease risk; OR values greater than 1 indicate disease susceptibility, and OR values less than 1 indicate protection from disease.

Results:

1- Search for islet autoantibodies:

The dosage of islet autoantibody defined two types of groups:

The first group is composed of patients who showed at least one positive islet autoantibody, with a total of 30 patients (55.56%). This group is marked GAb+.

The results of this study showed that GADA was the most common islet autoantibody found in patients with a frequency of 90% (27 patients). IA-2A+ was in second place with 36.7% (11 patients) and finally IAA+ with a frequency of 12.5% (2 patients out of 16 patients who had not received insulin or had received insulin for less than 2 weeks). (figure1)

The second group consists of 24 patients (44.4%) with negative islet autoantibodies. This group is called GAb-.

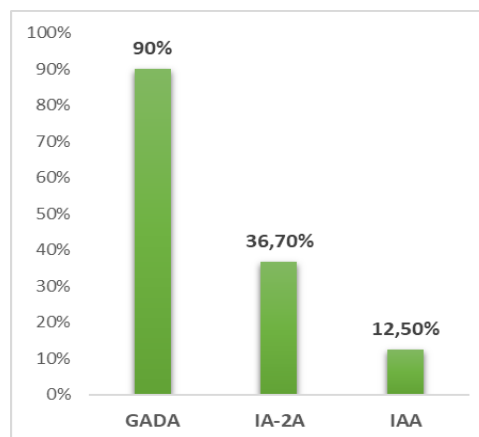


Figure 1. Frequency of islet autoantibody.

For the rest of study, we qualify the G1Ab+ by T1D group (representing diabetes diagnoses based on clinical manifestations with autoantibody positivity). The GAb- could be a possible combination of T1D (patients with unmeasured autoantibodies) and non-autoimmune diabetes. Thus, we focus our analysis only for T1D group.

2-Comparison between T1D group (GAb+) and controls:

A. Immunological markers and measurement of 25(OH)D :

The analysis of our results showed that 16.7% (5 patients) of the T1D patients were positive for tTG IgA/IgG Ab compared to no positive individuals in the control group ($P = 0.02$). Their age varied from 2 to 22 years (mean age = 8.8 ± 7.91 years) with a sex ratio of M/F = 2/3. 4 of these 5 patients were again positive for tTG IgA Ab.

We also found that although the control group presented a mean Vit D level below the normal value (25.96 ± 8.32 ; normal value [30-100] ng/mL), this value remains much higher than that found in diabetics patients (17.47 ± 8.96); $P = 0.0003$.

No significant difference was observed between the T1D group and the control group in the positivity of TPOAb, TG Ab and both.

Of these patients with positive results for thyroid autoimmunity markers, 2 had abnormal TSH, T3, and T4 levels.

The remaining characteristics are detailed in Table 3.

Table 3: Immunological profile and vitamin D dose in diabetic and control subjects

Immunological parameters	DT1 (n=30)	Control Group (n=30)	P value
tTG IgA/IgG	5 (16.7%)	0 (0%)	0.020
TPO Ab	7(23.3%)	2(6.7%)	0.071
TG Ab	2 (6.7%)	0(0%)	0.150
TPO Ab +TG Ab	7 (23.3%)	2(6.7%)	0.071
25(OH)D ng/mL (Mean ± SD)	17.47 ± 8.96	25.96 ± 8.32	0,0003

B. Immunogenetic study :

The results of the HLA typing of the patients and the control group are shown in the Table4.

The combined expression of HLA DR3 and HLA DQ2 alleles had a frequency of 19 (63.33%).

The combined expression of HLA DR4 and HLA DQ8 (Q3) alleles had a frequency of 13 (43.33%).

There was only one homozygote (3.33%) for DR4-DQ8, 3 homozygotes (10%) for DR3-DQ2 and 4 heterozygotes (13.33%) for DR3-DQ2/DR4-DQ8.

Table4: Association of established type 1 diabetes (T1D) loci with control group:

HLA DR	Diabetics: n (%) N= 30	Control group: n (%) N= 140	P value	OR	95% CI ^a
DR1	3 (10%)	27(19.3%)	0.226	/	/
DR2	0 (0%)	31 (22.1%)	----	0	/
DR3	25 (83.3%)	44 (31.4%)	<10⁻⁶	10.909	3.917-30.385
DR4	14 (46.7%)	37 (26.4%)	0.028	2.436	1.084-5.474
DR5	0 (0%)	39 (27.9%)	-----	0	/
DR7	1(3.3%)	25 (17.9%)	0.045	0.159	0.021-1.220
DR8	0 (0%)	10 (7.1%)	0.131	/	/
DR9	2 (6.7%)	6(4.3%)	0.576	/	/
DR11	8 (26.7%)	18 (12.9%)	0.057	/	/
DR13	3(10%)	10 (7.1%)	0.593	/	/
DR14	0 (0%)	2(1.4%)	0.510	/	/
DR15	1 (3.3%)	21(15%)	0.084	/	/
DR16	3(10%)	17(12.1%)	0.741	/	/

HLA DQ	Diabetics: n (%) N= 30	Control group: n (%) N= 140	P value	OR	95% CI ^a
DQ1	0(0%)	72 (51.4%)	----	0	/
DQ2	20 (66.7%)	55(39.3%)	0.006	3.091	1.346-7.09
DQ8(3)	19 (63.3%)	27 (19.3%)	<10⁻⁵	7.229	3.08-16.96
DQ4	3 (10%)	15 (10.7%)	0.908	/	/
DQ5	8 (26.7%)	18 (12.9%)	0.057	/	/
DQ6	2(6.7%)	46 (32.9%)	0.004	0.146	0.033-0.639
DQ7	8(26.7%)	25 (17.9%)	0.486	/	/
DQ9	0 (0%)	7(5%)	-----	0	/

OR—odds ratio; a95% confidence interval for the OR.

Note: The 5 patients who were positive for tTG IgA/IgG Ab had the following haplotypes: DR4-DQ8 (1 patient), DR3-DQ2 (2 patients), homozygous for DR3-DQ2/DR3-DQ2 (1 patient) and heterozygous for DR3-DQ2/DR4-DQ8 (1 patient).

The 7 patients who were positive for TPOAb and/or TG Ab had the following haplotypes: DR4-DQ8 (1 patients), DR3-DQ2 (2 patients), DRX-DQ8 (X different from 4) (1 patient), DR4-DQX (X different from 8) (1 patient), DR3-DQ8/DR4-DQ8 (1 patient) and heterozygous for DR3-DQ2/DR4-DQ8 (1 patient).

Discussion**1- Islet autoantibodies in T1D:**

Measuring islet autoantibodies is the simplest method of determining diabetes autoimmunity in both children and adults (5). They are today the only biomarkers that can distinguish LADA from phenotypically T2D (8).

In this study, we found that GADA were the most common (90%), followed by IA2-A (36.7%) and then IAA (12.5%).

The prevalence of islet antibodies at onset varies in different countries and ethnic groups (5) and is as follows: GADA (70%-80%), IA2-A (50%-70%), IAA (30%-50%) (9).

Although the rate of loss of autoantibodies varies, studies tend to agree that GADA are the most common prevalent, followed by anti-IA-2A autoantibodies (10), while anti-ZnT8A are the least common after diagnosis (11). Loss of autoantibodies is related to the duration of diabetes, age at diagnosis and genetics. Several studies suggest that GADA levels peak after diagnosis or remain stable, while IA-2A and ZnT8A levels decrease (5). In addition, the prevalence of IAA is known to decrease with increasing age at diagnosis (12).

2-T1D and Celiac disease:

T1D patients have a higher risk of developing other AID. T1D and celiac disease (CD) are among the most recognized related autoimmune disorders, as they share a common genetic background (2).

In our study, 16.7% (5 patients) of T1D patients were positive for tTG IgA/IgG Ab compared to no positive individuals in the control group (P =0.02). Worldwide, the coexistence of CD and T1D is variable, with prevalence rates of 1.6% in France, 2.4% in Finland and 11.1% in northern India. T1D usually precedes CD when both diseases are present in the same patient (13). In most cases, CD is asymptomatic. For this reason, expert clinical practice guidelines recommend screening all

children and adolescents with T1D (as high-risk individuals), sooner after diagnosis, and again at 2 and 5 years after diagnosis of T1D if the initial screening is negative (2,13,14)

Initial tests include tissue anti-transglutaminase (anti-tTG) and IgA; the anti-tTG test has very high sensitivity and specificity. In cases of IgA deficiency, testing for IgG-tTG and/or IgG deaminated gliadin is recommended. Anti-endomysial antibodies are highly sensitive and specific, but are not recommended for initial screening due to the cost and complexity of the test (13).

3- T1D and Autoimmune thyroid disease:

T1D and autoimmune thyroid disease (AITD) are common autoimmune diseases that often co-occur together (15). T1D is the main cost driver in this association (16). This close relationship is primarily attributed to a shared genetic background (15,17).

AITD includes Graves' disease (GD) and Hashimoto's thyroiditis (HT). The autoimmune condition is marked by TPOAb and TGAb (18). The prevalence of thyroid autoantibodies in patients with T1D ranged from 7% to 35% (19), and up to 50% of such patients may develop AITD (15,20).

In the present study, although we found that the percentage of patients testing positive for TPOAb and TGAb was higher in the diabetic group than in the control group (23.3% vs. 6.7%), the difference was not significant ($P > 0.05$). This does not exclude the possibility of other patients developing long-term auto-Antibody, as the population studied had diabetes for less than one year. According to Frommer et al, long-term follow-up suggests that 30% of T1D patients will develop AITD. Furthermore, the study population had a mean age of 19.43 ± 13.57 years, whereas AITD peaks in the fourth decade for GD or the fifth and sixth decades for HT (15).

4-Vitamin D and T1D Risk:

In the current study, a significant difference in 25(OH)D dosage was found between the diabetic group and the control group (mean (ng/mL) = 17.47 ± 8.96 vs 25.96 ± 8.32 ; $P = 0.0003$). This finding is in line with other studies showing that Vitamin D deficiency is more common in individuals with T1D, including those who have been recently diagnosed (21,22).

Vitamin D plays a role in modulating the developing immune system and maintaining self-tolerance (22,23). It has been shown that vitamin D could prevent cytokine-induced apoptosis of human pancreatic islets. Vitamin D may also have non-immunological effects on the pancreas by directly influencing beta-cell function. However, the exact mechanisms underlying the association

between vitamin D deficiency and T1D, as well as the interactions between genetic and environmental factors, are not fully understood (21). Further studies focusing on the molecular mechanism underlying this association are needed (22).

5-HLA genes in T1D:

Genetic studies have shown that the hereditary predisposition to T1D is multigenic (5,23). Class II HLA genes play the most important role in this process and are thought to account for around 40-50% of the genetic risk (23).

In this study, a higher frequency of HLA DRB1*03(DR3), DRB1*04(DR4), DQB1*02:01(DQ2), and DQB1*03:02(DQ8) alleles was found in diabetic patients, in comparison to the healthy group ($P < 0.05$). This supports previous findings in the literature (6,13,24).

The HLA haplotypes DR4-DQ8 (DRB1*04 - DQB1*0302) and DR3-DQ2 (DRB1*0301-DQB1*0201) increases significantly the likelihood of T1D (2,4,6,12,13), with DR3-DQ2/DR4-DQ8 heterozygosity increasing the risk by more than 30 times, a significantly higher risk than homozygosity for either haplotype (25). Indeed, these haplotypes are found in our patients.

In contrast, HLA DR7 and HLA DQ6 are associated with a strong and sometimes dominant reduction in the risk of T1D (24-26). They were weakly expressed in our patients compared to controls ($P < 0.05$). Other protective haplotypes have been identified worldwide (24,25), but no difference was found for the other haplotypes in our study. This may be due to the ethnic specificity of our population. In fact, significant differences in the distribution of prodiabetogenic, neutral and protective allele subtypes have been found in different populations, which may explain the wide variation in diabetes in different parts of the world (23,24).

The main function of Class II HLA genes is to present foreign and self-derived antigens to immune cells, which activate the immune system and control T cell selection (23,27). Genetic variation, particularly in HLA-DQB1, has been suggested to affect the affinity and stability of the antigen binding. Less efficient binding of pancreatic antigens might cause autoreactive T cells to escape negative selection in the thymus, which could induce an autoimmune reaction towards pancreatic beta-cells (27).

In our study, the haplotypes of the 5 patients with positive IgA/IgG tTG are in agreement with those described in the literature (2,13)

HLA haplotypes DR4-DQ8 and DR3-DQ2 are associated with an increased risk of both CD and

T1D. Nevertheless, this genetic predisposition alone is not sufficient to develop the disease (2). Environmental factors, viruses, diet, intestinal mucosal permeability, and the microbiome, play a role in their development (13). This could explain why not all diabetics with high-risk HLA were tested positive for CD markers in this study.

Same as for CD, the HLA antigens DQ2 and DQ8, linked with DR3 and DR4, play a major role in the common genetic predisposition to both T1D and AITD (15). This is consistent with our findings in patients with positive thyroid immunity markers. The mechanism by which HLA class II variants may be involved in the common etiology of T1D and AITD is that HLA class II molecules have a similar pocket structure that fits both islet cell peptides and thyroid-derived peptides (28) or facilitates the binding of T cell receptors to the peptide-MHC II complex (29).

Limits:

Our study has limitations. First, ZnT8A was not tested, although insulin and ZnT8 antibodies are not available in most clinical settings (6).

In addition, seroconversions for IAA and ZnT8A peak before the age of 2 years, with ZnT8A occurring least frequently after diagnosis, whereas our study population had a mean age of 23.13 (± 12.45) years.

Secondly, for IAA, positivity has been retained only if the patient is not yet on insulin therapy or has been on insulin for only 2 weeks. This may not reflect the true prevalence of IAA in our study population. And as mentioned below, IAA showed the most frequent reverse seroconversions and fluctuations.

So the likelihood of our results being biased by these limitations is very small indeed.

Conclusion:

In conclusion, clinical features alone may not be sufficient to distinguish T1D from other types of diabetes. Additional factors such as autoantibody status and genetic risk scores (GRS) are important for accurate classification.

To confirm T1D, it would be ideal to test for all islet autoantibodies as soon as possible after the onset of diabetes.

One of the potential clinical uses of the T1D GRS will be to help classify people with diabetes when clinical features are discordant with autoantibody test results.

People with T1D are also susceptible to other autoimmune diseases. Regular short and long term monitoring is recommended for these patients in order to diagnose them as early as possible and take steps to prevent complications.

Further research is needed to assess the impact of vitamin D on the development and progression of T1D, and to better understand the mechanisms involved in the association between T1D and other autoimmune diseases.

Conflicts of Interest

The authors declare no conflict of interest.

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