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Thyroid Autoimmunity in Children and Adolescents with Type 1 Diabetes in the Annaba Department (Eastern Algeria)

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Abstract

Background : Autoimmune thyroiditis (AIT) is a comorbidity frequently encountered in children and adolescents with type 1 diabetes (T1D). It can have consequences on glycemic balance, growth, and pubertal development. Early screening for this association would reduce the severity or prevent these consequences through early management.

Objectives : The aim of our work is to determine the frequency of AIT in children and adolescents with type 1 diabetes aged 5 to 18 at the Annaba University Hospital.

Materials and method : The study is longitudinal and descriptive, involving 227 children and adolescents with T1D in whom regular screening for thyroiditis was conducted. We also studied 103 healthy children. The parameters studied were antithyroid antibodies (anti-TPO and anti-TG AB), TSH, and thyroid ultrasound.

Results : The average age of diabetic children was 10.64 ± 3.47 years with an average duration of evolution of 2.87 ± 2.88 years. The frequency of autoimmune thyroiditis associated with T1D compared to controls was 11.45% vs 2.9%. The seropositivity rates of antithyroid antibodies were 10.1% for anti-TPO antibodies, 6.6% for anti-TG antibodies, and 5.3% for both associated antibodies. The risk factors for association found were female gender (p=0.01) and older age at diabetes diagnosis (p=0.0008, OR=2.54). Dysthyroidisms represent a proportion of 34.6% with 4 cases of hypothyroidism and 5 cases of subclinical hypothyroidism.

Conclusion : The association of AIT with T1D is relatively frequent. Its systematic screening is fundamental in all diabetic children, at the diagnosis of diabetes, and during the course of the disease.

Keywords: anti-TG antibodies, anti-TPO antibodies, autoimmune thyroiditis, TSH, type 1 diabetes

Introduction

Type 1 diabetes (T1D) represents 7 to 12% of diabetes cases diagnosed in developed countries; and more than 90% of childhood and adolescent diabetes [1]. It is a common chronic disease in children and adolescents ; it is considered by the WHO as the global epidemic of the 21st century. Algeria is classified as a contry with very high incidence (34.8 per 100.000 child per year), it ranks 6th in the TOP 10 [1]. T1D is an autoimmune disease, resulting from the destruction of the β Langerhans cells of the pancreas. It is often associated with other autoimmune disorders such as celiac disease, Addison's disease, Graves' disease, pernicious anemia, autoimmune hepatitis, vitiligo, and more frequently autoimmune thyroiditis or Hashimoto's thyroiditis [2]. This latter association between T1D and autoimmune thyroiditis has been well established. It is explained by the presence of

common genetic markers and immunological factors [3].

Autoimmune thyroiditis (AIT) represents the most frequent cause of acquired hypothyroidism in children and adolescents. Its diagnosis is often delayed in a diabetic patient due to the frequency of asymptomatic subclinical forms ; however, the disease can present with a goiter or signs of hypothyroidism [3]. The assessment of statural growth and pubertal development is imperative in any pediatric examination, especially since it involves diabetic children and adolescents, in order to detect shorter stature and/or pubertal delay. AIT can present in various forms, and in decreasing order of frequency, euthyroidism is dominant, followed by subclinical hypothyroidism, then hypothyroidism, and hyperthyroidism. Screening for AIT in children with T1D is therefore justified. Its interest stems from the consequences that thyroiditis can have on glycemic control, children's height and weight growth, and their pubertal development [4]. It is performed by measuring circulating antithyroid antibodies : antithyroglobulin and antithyroperoxidase. The diagnosis of thyroiditis must be confirmed by hormone levels and thyroid ultrasound.

The frequency of positivity of anti-thyroid antibodies in children and adolescents in the general population ranges from 1.2% to 21.4% [5,6], while it is higher in diabetic children, ranging from 3.9% to 50% in different countries around the world [6-9].

In Tunisia, a frequency rate of thyroiditis 9% was reported among children with T1D [10] ; however, in Algeria, only one study including adolescents and young adults from Western Algeria showed a frequency rate of 15.46% [11].

The expert societies « ADA and ISPAD » recommend systematic screening for thyroiditis at the onset of diabetes, then every two years or more frequently if there are signs of the disease [2,12]. The aim of screening is the early management of diabetic children with thyroiditis. The severity of the consequences of thyroiditis in diabetic patients, which could be reduced by early management [13], as well as the disparity in its frequency worldwide [6-9], raise questions about its situation in Algeria and within the Annaba province. This motivated our study, which aims to determine the frequency of autoimmune thyroiditis in children and adolescents aged 5 to 18 years with type 1 diabetes and the risk factors of this association at the University Hospital of Annaba (Algeria).

Materials And Method

The study involved 227 children and adolescents aged 5 to 18 years with type 1 diabetes.
Given the absence of published Algerian studies in children, the sample size was calculated by referring to the study by Sakly and collaborators in Tunisia, where a frequency of thyroiditis of 9% was reported in children with type 1 diabetes [10].

A control group composed of children and adolescents of the same age range as the diabetic children, who were hospitalized for another acute pathology (meningitis, urinary infection, cellulitis, ethmoiditis...). It is recruited during patient check-ups. This group (103 cases) will allow us to estimate the frequency of thyroiditis in the general pediatric population.

Inclusion Criteria

Our study included for both cases and control populations all children and adolescents aged 5 to 18 years. Thyroiditis is rare in diabetic children before the age of 5 years [14].

All patients were diagnosed during their hospitalization at the pediatric clinic as T1D requiring insulin therapy according to ADA criteria.

Exclusion Criteria

Control group and diabetic group

1. Children under the age of 5
2. Children known for thyroiditis
3. Children who refused the blood draw or to participate in the study

Control group : Children with a personal or family history of type 1 diabetes or other autoimmune diseases, a recent acute illness, corticosteroid treatment that may affect thyroid function or size, cancer, or a chronic illness.

Study setting

Study involving 227 T1D patients (184 known T1D children and 43 newly diagnosed diabetics), spanning three years, with regular annual screening and taking place at the specialized pediatric diabetology consultation within the Sainte-Therese pediatric clinic

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at the Annaba University Hospital. The study of the controls took place at the same location.

Materials

Antithyroid antibodies and thyroid function were performed at the immunology and biochemistry laboratories of the Annaba University Hospital. The search for anti-thyroperoxidase (anti-TPO) antibodies and anti-thyroglobulin (anti-TG) antibodies was conducted for all subjects in both populations (diabetic and control). The method used for the measurement of anti-TPO antibodies and anti-TG antibodies, thyroidfunction (TSH, FT3, FT4) is immunochemiluminescence, from ECLIA (electrochemiluminescence immunoassay).

The blood samples being taken in dry tubes, after centrifugation, the serums are stored at -20°c or -80°c until analysis. Thyroid ultrasound was performed by the same radiologist for almost all patients with positive antibodies. It allows for confirmation of the diagnosis in the majority of cases by showing a characteristic ultrasound appearance : diffuse and heterogeneous hypoechogenicity, presence of pseudonodules, and gland hypertrophy. The radiologist calculates the thyroid volume from the measurements of the depth (d), width (w), and length (l) of each lobe. The thyroid volume is the sum of the volumes of the two lobes. Children with positive anti-TPO and/or anti-TG antibodies are considered cases of autoimmune thyroiditis. The positivity threshold for anti-TPO antibodies is > 34 IU/mL and that for anti-TG antibodies is > 115 IU/mL, while TSH values vary with age from 0.51 to 5.97 µIU/mL. The diagnosis is often confirmed by the presence of characteristic ultrasound abnormalities, namely a goiter, a heterogeneous hypoechoic appearance of the thyroid gland, and the presence of pseudonodules.

1. Hypothyroidism is defined as elevated TSH and low FT4.
2. Subclinical hypothyroidism corresponds to elevated TSH and normal FT4.
3. Hyperthyroidism corresponds to low TSH and high FT4.

Statistical study

The data entry and analysis were done using the software: Epidata 3.1 and Excel 2019. The statistical tests used for comparing the different subgroups are: the Chi-square test, Fisher's exact test, the Student's test, and the Kruskal-Wallis test (n < 30). Also, epidemiological association measures (odds ratio : OR).The significance threshold (probability value) was set at 0.05 in all cases.

Results

Study of the frequency of AIT in children with T1D and controls

a. Overall frequency of AIT

Our study population includes 227 children and adolescents with T1D, of whom 125 are girls and 102 are boys, with an average age of 10.64 ± 3.47 years and an average duration of evolution of 2.87 ± 2.88 years (table 1). The frequency of positivity of antithyroid antibodies is 11.45%, which is 26 cases, anti-TPO antibodies were positive in 10.10% of cases, and anti-TG in 6.6% of cases (table 2). However, among the controls, we collected 3 cases with positive antithyroid serology, which is a frequency of 2.9%. Diabetics have a four times higher risk of having positive antithyroid antibodies compared to controls (OR=4.3 ; p=0.0129).

b. Positivity of antithyroid antibodies at the onset of T1D

The frequency of antibody positivity among known diabetics is 11.96%, and among newly diagnosed patients at the onset of diabetes (n=43), 9.3% had positive antibodies (p=0.62).

c. Positivity of anti-TPO and anti-TG antibodies

The positivity of anti-TPO antibodies alone represents 4.8%, and that of anti-TG antibodies alone is 1.32%, while both antibodies are simultaneously positive in 5.3% of cases. 88.5% of cases of AIT are detected only by anti-TPO and 57.7% by anti-TG. The comparison of the positivity of the two antibodies demonstrated a higher frequency of positivity for anti-TPO compared to anti-TG with a significant difference (p=0.02).

Study of the profile of the seropositive T1D group (AIT+T1D) and comparison with the seronegative group and the controls

a. Frequency of AIT according to age and gender

The distribution of AIT cases associated with T1D showed that the majority, 61.5% of the cases, were aged between 10 and 15 years ; 30.8% were between 5 and 10 years old, and only 7.7% were over 15 years old. The average age of AIT associated with T1D was 10.89 ± 3.30 years with extremes of 5 and 17 years. A

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clear female predominance was noted, accounting for 69% with a sex ratio of 0.44.

b. Study of association risk factors

Our study showed a frequency of thyroiditis associated with T1D in the age range [10-15 years [with a rate of 61.5%. The positivity of anti-TG antibodies is significantly more frequent in girls than in boys 10.4% vs 2% (p=0.01); however, there is no significant difference between the two sexes for anti-TPO. We tested the association between anti-TG antibodies (the dependent outcome variable) and anti-TPO antibodies, sex, age, anti-GAD antibodies, and the age of onset of diabetes (independent variables) in the children. We observed a significant association between anti-TG antibodies and anti-TPO antibodies as well as gender (p=0.0012 and p=0.04 respectively) and no significant association for the other factors (age, duration of evolution, and anti-GAD antibodies : table 3).

Another multivariate analysis by logistic regression showed that as the age of onset of diabetes increases by one year, the risk of antibody positivity significantly increases, it is multiplied by 2.5 (p=0.0008, OR=2.54). Regarding the other factors, we did not find a significant association with antibody positivity table 4).

c. Frequency of thyroid disorders

Among seropositive diabetics, 9 patients, or about one-third, had elevated TSH (34.6%), and two-thirds were in euthyroidism (65.4%). Among the cases of dysthyroidism, 4 were in hypothyroidism and 5 in subclinical hypothyroidism. Comparatively, among seronegative T1D patients, we reported one case of subclinical hypothyroidism and another of Basedow's disease. The risk of dysthyroidism is multiplied by 10 in cases of T1D associated with AIT versus T1D not associated with AIT, with respective frequencies of 34.6% and 1% (RR=10.4. P<0.0001).

The positivity of both antithyroid antibodies (anti-TPO and anti-TG) was identical in cases of hypothyroidism and HSC ¾ (75%) and 5/5 (100%) respectively ; whereas in cases of euthyroidism, anti-TPO were positive in 15 out of 17 cases and anti-TG were positive in only 7 out of 17 cases. We conclude that positive anti-TG antibodies are more frequent in cases of dysthyroidism compared to cases of euthyroidism (p=0.048). This is not the case for positive anti-TPO antibodies, which are found in AIT regardless of thyroid status (p=0.5).

The positivity of antithyroid antibodies is significantly associated with an increase in TSH (p<0.0001 figure 1).

d. Clinical and ultrasound signs of AIT

The most frequently observed ultrasound abnormality in AIT was the heterogeneous hypoechoic aspect in 15 children (78.95% of cases). In hypothyroidism and HSC, the ultrasound is always pathological with a characteristic heterogeneous hypoechoic pseudo-nodular aspect (p=0.04 and p=0.01 respectively). A normal ultrasound was frequent in less than half of the cases of euthyroidism. Clinically, AIT was silent or pauci-symptomatic in 17 cases (65.4%) and symptomatic in 9 cases, or 34.6%.

Discussion

Through our study, we were able to draw some conclusions specific to our population. Autoimmune thyroiditis exists in children with type 1 diabetes in Annaba with a frequency of 11.45% versus 2.9% in controls. Thyroiditis can be discovered both at the diagnosis of diabetes (9.3%) and secondarily during the progression of T1D (11.96%). A female predominance is noted, and 61.5% of cases were between 10 and 15 years old. The search for the two antithyroid antibodies (anti-TPO and anti-TG) is fundamental for the diagnosis of thyroiditis. The seropositivity rates of antithyroid antibodies were 10.1% for anti-TPO antibodies, 6.6% for anti-TG antibodies, and 5.3% for both associated antibodies. Dysthyroidisms represent a proportion of 34.6% of AIT cases.

Limitations of the study

Our data is similar to that of other national and international studies ; however, like the majority of works, ours also has limitations. Our study involved a sample size of diabetics comparable to the majority of series. However, for the controls, the sample is relatively small due to the exclusion criteria for the hospitalized patient population, namely age under 5 years, treatment with corticosteroids, as well as chronic diseases and oncology. Knowing that more than two-thirds of hospitalizations in the older children's ward of our clinic (patients over 5 years old) consist of chronic diseases and cancers.

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Study of the frequency of AIT in children with T1D and controls

a. Frequency of AIT in children with T1D

More frequent in diabetic subjects than in the general population, autoimmune thyroiditis represents a real public health problem when associated with T1D. Its frequency varies considerably around the world from 3.9 to 50% [8,9]. The screening for thyroiditis in our diabetic population at the Annaba University Hospital, conducted through the measurement of antithyroid antibodies, revealed 26 positive cases among 227 children and adolescents with T1D, resulting in a frequency of 11.45%. This rate is considered high. It shows that AIT is not solely an adult pathology ; but it also affects children and adolescents. It reflects furthermore, the reality that an autoimmune pathology can be associated with another autoimmune disease. This should encourage regular screening for the condition.

Our study stands out as the first work conducted on the subject in children, in the Annaba region and in Algeria. In the Maghreb, the majority of series have involved children with adults and therefore show higher rates than ours : 24.3% in Libya [15] ; while, the pediatric study by Sakly among 166 Tunisian children with T1D, showed a lower rate and close to ours, at 9% [10]. In Africa, there is few publications on the subject in children. A small series of 69 children and adolescents in Uganda showed a rate of 7.3% of positive anti-TPO antibodies [16]. The low prevalence of AIT observed in African countries compared to Caucasians is explained by the frequency of the idiopathic form of type 1 diabetes. This non-autoimmune form is rarely accompanied by other autoimmune diseases such as autoimmune thyroiditis.

In the Middle East, a positivity rate of 12% for anti-TPO antibodies, close to ours, has been reported in Egypt [17]. Moreover, the Iranian study conducted by Ardestani and al. showed a much higher frequency 21.7% than ours [18]. In the same way, in Kuwait ; a country known for its high incidence of type 1 diabetes ; a very high rate (34.5%) of positive thyroid antibodies was reported by Al Khawari. This point further demonstrates the strong genetic association of these two autoimmune diseases. This is how the DR3 DQ2 haplotype involved in the AIT/T1D association was found to be elevated in T1D children in Kuwait [19].

In Europe, one of the largest studies on thyroiditis, that of Kordonouri with a multicenter study (Germany and Austria) of a cohort of 7097 children and adolescents with type 1 diabetes (T1D) aged 0.3 to 20 years, the positivity of antithyroid antibodies was 21.6%, which is higher than ours [20]. Compared to our results, an identical frequency (11.4%) was noted in France [21]. In Turkey, a high frequency was observed in children with T1D as well as in their siblings, with rates of 38.6% and 21.4% respectively. The explanation for these high rates, as suggested by the authors of this study, is the systematic excessive iodine supplementation dictated by the goiter control program in the country three years before the study was conducted [6].

In the USA, Burek and al reported the highest frequency of 50% among white children, and a lower rate of 16% among African Americans [9]. This ethnic difference has been explained by a naturally reduced tendency towards organ-specific autoimmunity in this population and by a mixture of T1D susceptibility genes from both races. Conversely, a meta-analysis showed no correlation between race and the frequency of anti-TPO antibody positivity in T1D [22].

This disparity in frequencies across the world can be explained by differences in the size of the studied populations, the variable sex and age of diabetic patients, as well as the duration of their diabetes. The role of genetic predisposition factors has been demonstrated ; according to Burek, there is a genetic predisposition to AIT with an incomplete penetrance dominant trait inherited from the father or the mother [9]. Also, environmental factors, especially iodine supplementation, are implicated. This is the case in several countries that have seen a decrease in the incidence of goiter and an increase in the incidence of AIT after the implementation of iodine supplementation programs [6,23]. Finally, the diagnostic methods used were different, several authors have used anti-TPO antibodies alone. Moreover, the improvement and the performance of screening techniques in recent years have increased the frequency of antibody positivity [24].

Type 1 diabetes and autoimmune thyroiditis are closely linked as they share similar etiopathogenic mechanisms with common genetic factors [3]. Their association is increasingly being sought with varying frequencies. The relatively high frequency in our

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series can be explained by the previous lack of awareness among pathology practitioners and the recommendations of learned societies ; anti-TG antibodies were rarely requested. We would also like to emphasize that the iodine status in the Annaba region is not known. The role of iodine excess in the pathogenesis of AIT has been demonstrated by several authors. It increases the antigenicity of thyroglobulin and stimulates the myeloperoxidase activity of macrophages with the release of intermediate reactants that damage the membrane of thyrocytes, leading to their necrosis [25].

The simultaneous search for both antibodies is essential for the diagnosis of thyroiditis to avoid underestimating its frequency [26]. 88.5% of cases are detected solely by anti-TPO and 57.7% by anti-TG. Moreover, some authors have reported higher seropositivity rates for anti-TG antibodies than for anti-TPO antibodies : 28% vs 17.3% [27].

b. Frequency of AIT in controls

Diabetics have a four times higher risk of having positive antithyroid antibodies compared to controls (OR=4.3 ; p=0.0129). Several case-control studies, including Sakli in Tunisia, found a rate close to ours (5.5%) [10]. For Ardestani, the frequency of thyroid autoimmunity in the pediatric population was higher with a rate of 8.09% [18].

c. Frequency of AIT at the onset of diabetes

The frequency of AIT at the onset of diabetes was 9.3%, a rate close to the frequency in known T1D cases 11.96% (p=0.62) and thus close to the overall frequency of 11.45%. The frequency of AIT at the onset of diabetes varies between 3% and 55% according to different studies [21,28,29]. In Albania, the frequency at the time of diabetes diagnosis was higher compared to that after the diagnosis 11.8% vs 3.3% [30].

d. Study of association risk factors

Our study showed a frequency of thyroiditis associated with T1D of 61.5% in the age group [10-15 years [. Kordonouri and Kakleas confirmed the increase in frequency with age, which reaches its maximum in the 15 to 20 years old age group [7, 20].

The predominance of AIT in girls has been noted in most series [7,10,15,20]. Positive anti-TG antibodies are significantly more frequent in girls than in boys (p=0.01), Sharifi also reported female predominance in cases of positive anti-TG antibodies [31]. This female predominance can be explained by the role of sex hormones in the development of antibodies in T1D patients.

Our results showed that increasing the age of onset of T1D by one year multiplies the probability of antibody positivity by 2.5 (p=0.008). Our finding agrees with those of kakleas [7] and Hwang, this later noted that the older age at the onset of diabetes is a risk factor for antibody positivity (p=0.032) [28].

e. Frequency of dysthyroidisms

The frequency of thyroid disorders in the seropositive group was significantly higher compared to the seronegative patients : 34.6% vs 1%, (P<0.0001). Autoimmune thyroiditis is the main cause of acquired hypothyroidism in diabetic children. Our results are in agreement with those of previous studies [18,32]. The risk of elevated TSH levels in seropositive T1D patients is multiplied by 16 in the presence of positive anti-TPO antibodies versus negative anti-TPO antibodies for Sharifi [31]. A recent study conducted in India (2024) showed a significant difference between the average TSH levels in the association of diabetes with thyroiditis versus diabetes without thyroiditis (p=0.001) [33]. The positivity rate of both antithyroid antibodies at the same time in our series was identical in cases of dysthyroidism (8/9 cases having both antibodies positive). While in cases of euthyroidism, anti-TPO antibodies were positive in the vast majority of cases (15/17 : 88.2%) and anti-TG antibodies were positive in only 7 out of 17 cases (41.2%). This demonstrates interest of anti-TG antibodies, which seem more specific than anti-TPO in dysthyroidism (p=0.04), and the precocity of anti-TPO since they are found in the initial phase of the disease (euthyroid state) [34].

Conclusion

The association of autoimmune thyroiditis and type 1 diabetes is a reality in children and it is frequent in the department of Annaba. Screening for autoimmune thyroiditis remains essential. Thyroiditis can be discovered both at the diagnosis of diabetes and secondarily during the progression of T1D. The risk factors for thyroid autoimmunity found are older age, especially during the peri-pubertal period, older age of diabetes onset, and female gender.

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The search for the two antithyroid antibodies (anti-TPO and anti-TG) is fundamental for the diagnosis of thyroiditis ; their combined use in screening avoids underestimating the real frequency of the disease.

Conflicts of interest : The authors of this article declare no conflict of interest.

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Tables And Figures

Table 1 : Clinical characteristics of the studied diabetic population (N= 227)

Parameters	Result
Mean age (years)	10,64 ± 3,47
Sex ratio boys/girls	0,82
Mean age at diagnosis of T1D (years)	7,82 ± 3,61
Mean duration of diabetes (years)	2,87 ± 2,88
Average height (SD)	- 0,22 ± 1,18
Average BMI (SD)	0,035± 1,22
Pubertal/pre-pubertal status	111/116
Mean HbA1C (%)	8,58 ± 1,48
Average insulin dose /Kg/day (IU)	0,87 ± 0,23

Table 2: Frequency of positivity of antithyroid antibodies in T1D

Antibodies	Anti TG AB		Anti TPO AB		Anti TPO and/or anti-TG AB	
	Number	%	Number	%	Number	%
Negative	212	93,4	204	89,9	201	88,55
Positive	15	**6,6**	23	**10,1**	26	**11,45**
Total	227	100,0	227	100	227	100
P			0,17			

Table 3: Multivariate analysis of risk factors for positive anti-TG AC vs negative anti-TG

Variable	OR	IC à 95 %	P
Age	0,92	0,69 à 1,22	0,5657
Gender (G/B)	**9,76**	3,58 à 184,64	**0,0486**
Age of onset of T1D	1,39	0,95 à 2,02	0,0851
Duration of T1D	1,26	0,58 à 2,75	0,5569
Anti-GAD AB	3,04	0,40 à 22,97	0,2810
Anti-TPO AB	**25,72**	3,58 à 184,64	**0,0012**

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Table 4: Correlation of positive anti-TPO and/or anti-TG antibodies versus negative antibodies and risk factors

Variable	OR	IC à 95 %	P
Age	1,88	0,62 à 5,73	0,2621
Gender (G/B)	1,30	0,40à 4,21	0,6615
Age of onset of T1D	**2,54**	**1,47 à 4,37**	**0,0008**
Duration of evolution	1,12	0,70 à 1,79	0,6278
Anti-GAD AB	1,43	0,42 à 4,89	0,5684

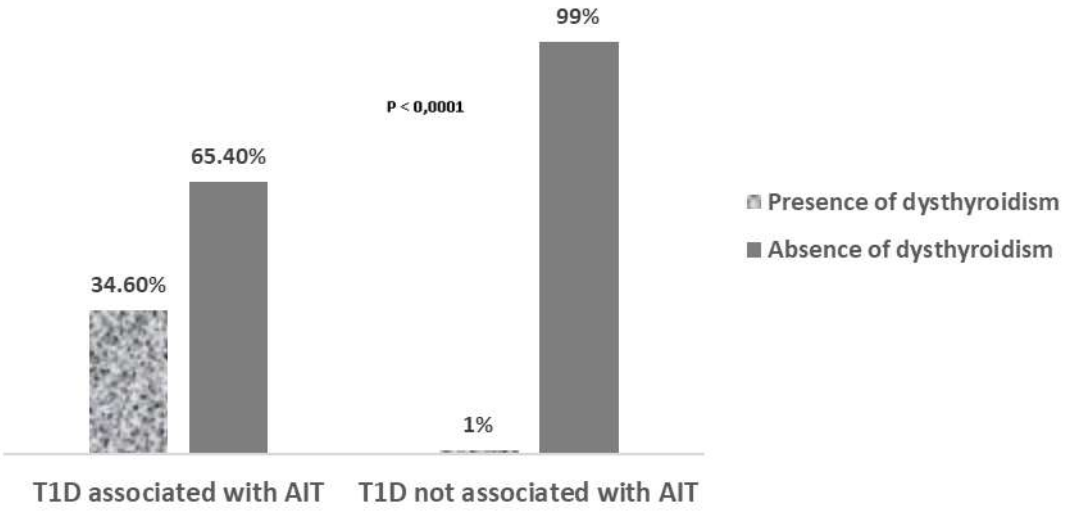

Figure1 : Frequency of thyroid dysfunction in both groups

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